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[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Catalytic Dehydrogenation of Hydroaromatic Compounds in Benzene. II

BY HOMER ADKINS AND JAMES W. DAVIS[1]

The study of the aromatization of hydroaromatic compounds with benzene as a hydrogen acceptor[2] was continued with twelve variously substituted compounds as listed in Table I. The data on three of these compounds, *i. e.*, 2-methyl-1-ethyl-3,4-dihydronaphthalene, 2-methyl- and 2-ethyldecalin show that the corresponding naphthalene may be prepared from them in yields of more than 90% of the theoretical with a platinum catalyst. Attempts to aromatize alcohols, *i. e.*, 2-decalol and 2-methyl-1-ethyl-1,2,3,4-tetrahydro-1-naphthol, without loss of oxygen were not so successful. The highest yield of 2-naphthol over any catalyst was only 18–20% from 2-decalol or 2-decalone over a platinum catalyst, while the hydrocarbon 2-methyl-2-ethyl-naphthalene was obtained in 91% yield from the tetrol without any evidence of a phenol. However, a 65% yield of thymol from menthol was obtained[2] over a nickel catalyst.

The dehydrogenation of compounds with quaternary carbon atoms in the rings to be aromatized required more drastic conditions than for simple dehydrogenation. Data for the reaction of six such compounds are given in Table I. Three tetralins carrying two methyls, I, a methyl and an ethyl or a methyl and a phenyl group in the 1,1-position all gave 1-methylnaphthalene, II, but in rather low yields. The nickel on kieselguhr catalyst gave migration rather than elimination of the alkyl group so that 1,2-dimethylnaphthalene, III, was produced from the 1,1-dimethyltetralin. There was a similar migration of a carbon linkage in the aromatization of 1,1-spirocyclopentyl-1,2,-3,4-tetrahydronaphthalene, IV, to phenanthrene,

TABLE I

DEHYDROGENATION OF HYDROAROMATIC COMPOUNDS[a]

Compound	G. catalyst	Temp., °C.	
1,1-Dimethyl-1,2,3,4-tetrahydronaphthalene	0.5 Pt	350	25% 1-Methylnaphthalene 61% No reaction
	3 Ni (CrO)	370	38% 1-Methylnaphthalene 50% No reaction
	3 Ni (k)	350	35% 1,2-Dimethylnaphthalene 35% No reaction
1-Methyl-1-ethyl-1,2,3,4-tetrahydronaphthalene	3 Ni (CrO)	375	35–55% 1-Methylnaphthalene 27% No reaction
1-Methyl-1-phenyl-1,2,3,4-tetrahydronaphthalene	3 Ni (k)	350	12% 1-Methylnaphthalene
1,1-Spirocyclopentyl-1,2,3,4-tetrahydronaphthalene	3 Ni (k)	350	25–40% Phenanthrene
12-Methyl-1,2,3,4,5,6,7,8-octahydrophenanthrene	1 Pt	350	65% Phenanthrene
2-Methyl-12-isopropyl-1,2,3,4,5,6,7,8-octahydrophenanthrene	2 Ni (CrO)	350	50% 2-Methylphenanthrene
2-Methyldecalin	1 Pt	350	91% 2-Methylnaphthalene
2-Ethyldecalin	0.25 Pt	350	94% 2-Ethylnaphthalene
2-Methyl-1-ethyl-1,2,3,4-tetrahydro-1-naphthol	2 Ni (k)	300	66% 2-Methyl-1-ethylnaphthalene
1-Methyl-2-ethyl-3,4-dihydronaphthalene	0.25 Pt	300	91% 1-Methyl-2-ethylnaphthalene
2-Decalol	1 Pt	275	18% 2-Naphthol
2-Decalone	1 Pt	275	20% 2-Naphthol 33% Naphthalene

[a] The dehydrogenations were made on about 5 g. of compound, in 20–40 ml. of benzene for 10–12 hours, in chrome vanadium steel vessels having voids of 62 ml. (platinum catalysts) or 270 ml. (nickel catalysts).

V. A methyl or isopropyl group in an angular position of octahydrophenanthrene was eliminated

(1) Allied Chemical and Dye Corporation Fellow, 1941–1942.

(2) (a) Adkins, Richards and Davis, THIS JOURNAL, **63**, 1320 (1941); (b) Adkins, Rae, Davis, Hager and Hoyle, *ibid.*, **70**, 381 (1948).

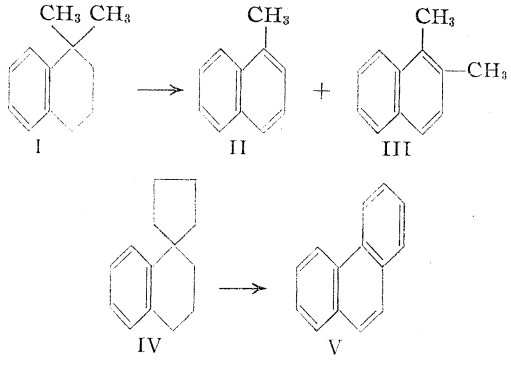
TABLE II

PROPERTIES OF COMPOUNDS

(a) Picrates, (b) trinitrobenzene derivatives, (c) styphnates

Compound	M. p., °C.	Mol. form.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1-Methylnaphthalene	−22	(n^{20}D 1.6180)				
(a)[3]	141–142					
(b)	153–154	$C_{17}H_{13}N_3O_6$	57.46	57.63	3.69	3.77
2-Methylnaphthalene	37–38	(n^{25}D 1.6086)				
(a)[4]	115–116					
(b)[4]	123					
1,2-Dimethylnaphthalene	(B. p. 139–140 (15 mm.), $n^{16.6}$D 1.6105)					
(a)[5]	129.5–130.5					
(b)[6]	147–148					
(c)[6]	142–143					
1-Ethylnaphthalene	−15	(n^{15}D 1.6089)				
(a)[7]	98.5					
2-Ethylnaphthalene	−7.5	(n^{15}D 1.6028)				
(a)[8]	76–77					
(b)	88–89	$C_{18}H_{15}N_3O_6$	58.53	58.44	4.08	3.97
1-Methyl-2-ethylnaphthalene	B. p. 140–145 (11 mm.)					
(a)[9]	97					
(b)	98.5–99.5	$C_{19}H_{17}N_3O_6$	59.52	59.69	4.47	4.52
(c)[9]	114					
2-Methyl-1-ethylnaphthalene	B. p. 135–145 (11 mm.)					
(a)[9]	110–111					
(b)	117.5–119.5	$C_{19}H_{17}N_3O_6$	59.52	59.60	4.47	4.49
(c)[9]	141					
2-Methylphenanthrene	55–56					
(a)	118–119					

and a phenanthrene formed under the standard conditions for aromatization.



Experimental Part

The conditions and procedures used for the reactions referred to in the table were essentially the same as those described in the earlier paper. The physical properties and analyses for certain compounds are given in Table II. 2-Decalol, b. p. 140–143° (28 mm.), n^{25}D 1.4958–1.5000, was prepared by the hydrogenation of 2-naphthol over Raney nickel at 200°. The alcohol (40 g.) was oxidized to 2-decalone (24 g.) (b. p. 123.5–125 (27 mm.), n^{25}D 1.4885–1.4905) by the procedure described for the preparation of menthone.[10,11] 2-Methyldecalin[12] (b. p. 203–205°, n^{25}D 1.4712) and 2-ethyldecalin[13] (b. p. 85–87 (7 mm.), n^{25}D 1.4727) were prepared by hydrogenation at 200° over Raney nickel, from 2-methylnaphthalene and methyl 2-naphthyl ketone, respectively. 1,1-Dimethyl-1,2,3,4-tetrahydronaphthalene, (b. p. 94–95 (12 mm.), n^{25}D 1.5262); 12-methyl-1,2,3,4,5,6,7,8-octahydrophenanthrene (b. p. 150 (13 mm.), n^{25}D 1.5510); and 2-methyl-12-isopropyl-1,2,3,4,5,6,7,8-octahydrophenanthrene (n^{25}D 1.5435) were prepared as described.[14,15,16] Other procedures described below were in general patterned after those of Brunner and Grof[9] or of Bogert, Davidson, Apfelbaum and Perlman.[14,15]

1-Methyl-1-ethyltetralin.[14]—One hundred and sixty grams of 3-phenylpropyl bromide in 300 ml. of dry ether was added to 20 g. of magnesium over a period of fifty minutes. The mixture was refluxed for fifty minutes, and then 72 ml. of methyl ethyl ketone in 72 ml. of dry ether was added over a period of twenty minutes. After thirty minutes of refluxing, the addition product was hydrolyzed with saturated ammonium chloride solution. The ether solution was washed twice with water, dried over anhydrous sodium sulfate and the product (125 g.) distilled at 154–163° (23 mm.), n^{25}D 1.4970–1.5050.

Eighty-five grams of the alcohol so obtained was cooled to 15° and 85 ml. of cold, concentrated sulfuric acid was added dropwise while the mixture was stirred vigorously

(3) Darzens and Levy, *Compt. rend.*, **199**, 1131 (1934).
(4) Barbot, *Bull. soc. chim.*, **47**, 1314 (1930).
(5) Schroeter and Lichtenstadt, *Ber.*, **51**, 1601 (1918).
(6) Kloetzel, THIS JOURNAL, **62**, 1708–1713 (1940).
(7) Froschl and Harlass, *Monatsh.*, **59**, 280 (1932).
(8) Levy, *Compt. rend.*, **192**, 1397 (1931).
(9) Brunner and Grof, *Monatsh.*, **64**, 78–79 (1934).
(10) "Organic Syntheses," Coll. Vol. 1, p. 333, John Wiley and Sons, Inc., New York, N. Y., 1941.
(11) Leroux, *Compt. rend.*, **141**, 46 (1900).
(12) Weissenberger, *Z. anorg. allgem. Chem.*, **153**, 33 (1926).
(13) Levy, *Compt. rend.*, **192**, 1397–1399 (1931).
(14) Bogert, Davidson and Apfelbaum, THIS JOURNAL, **56**, 961 (1934).
(15) Perlman, Davidson and Bogert, *J. Org. Chem.*, **1**, 288 (1936).
(16) Orcutt and Bogert, *ibid.*, **4**, 543 (1939).

and the temperature kept below 25°. Ten minutes after all the acid had been added, the mixture was diluted with water and ether. The ether solution was washed with a sodium carbonate solution, dried and distilled from sodium. The yield was 48.6 g., b. p. 125.5° (23 mm.), $n^{25}D$ 1.5250–1.5260. The product was redistilled from sodium through a modified Widmer column to give 34 g., b. p. 127–127.5° (23 mm.), $n^{25}D$ 1.5255.

Anal. Calcd. for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.55; H, 10.35.

1-Methyl-1-phenyltetralin.[14]—A Grignard reagent was prepared as before from 125 g. of 3-phenylpropyl bromide in 225 ml. of ether and 72 ml. of acetophenone in 70 ml. of dry ether added over a period of twenty minutes. After one hour of refluxing, the addition compound was hydrolyzed with dilute sulfuric acid and the ether solution washed with water. The low boiling material was removed by distillation, and the crude alcohol cyclized as described above. There was obtained 73.2 g. or a 55% yield; b. p. 141–147° (2 mm.), $n^{25}D$ 1.5850–1.5855. The product was redistilled from sodium to give 67 g., b. p. 129–131° (1 mm.), $n^{25}D$ 1.5853, d^{25}_4 1.042. M_D calcd.: 71.32. Found: 71.6. *Anal.* Calcd. for $C_{17}H_{18}$: C, 91.83; H, 8.17. Found: C, 91.60; H, 8.23.

1,1-Spirocyclopentyltetralin.[15]—A Grignard reagent was prepared as before from 160 g. of 3-phenylpropyl bromide and 71 ml. of cyclopentanone in 70 ml. of dry ether was added over a period of thirty minutes. After one hour of refluxing, the addition product was hydrolyzed with saturated ammonium chloride solution; the ether solution was washed with water, dried and distilled. The alcohol so obtained boiled at 150–170° (25 mm.), $n^{25}D$ 1.5200. The alcohol was cyclized by treatment with an equal volume of cold concentrated sulfuric acid as for methylethyltetralin. The tetralin was distilled from sodium through a modified Widmer column. The yield was 23.1 g., b. p. 158° (24 mm.), $n^{25}D$ 1.5535. *Anal.* Calcd. for $C_{14}H_{18}$: C, 90.25; H, 9.75. Found: C, 89.91; H, 9.74.

2-Methyl-1-tetralone.[9]—Nineteen and one-half grams of potassium was powdered in 500 ml. of xylene in a 1 l. three-necked flask fitted with a dropping funnel, a reflux condenser and a Hershberg stirrer. The mixture was cooled and 87 g. of diethyl methylmalonate was added over a period of ten minutes. After one hour, 93 g., of β-phenethyl bromide was added and the mixture was refluxed and stirred for twelve hours in an oil-bath at 150–160°. The xylene solution was washed with water, dried and distilled, and there was obtained 85 g. of diethyl methyl-β-phenethylmalonate, b. p. 188–192° (17 mm.), $n^{25}D$ 1.4818–1.4820.

Ninety-three grams of this ester was hydrolyzed by refluxing it ninety minutes with 56 g. of potassium hydroxide in 200 ml. of 50% aqueous alcohol. After water was added and the alcohol was distilled off, the solution was acidified to congo red with concentrated hydrochloric acid. The solid acid which precipitated was dissolved in ether and the aqueous solution was extracted with ether. The ether solutions were combined, washed with water, dried with anhydrous sodium sulfate and the ether distilled. The acid was heated to 180° and distilled after carbon dioxide ceased to be evolved. The yield of γ-phenyl-α-methylbutyric acid was 48.9 g. or 82%, b. p. 176–178° (17 mm.), $n^{25}D$ 1.5093–1.5100, plus 4.9 g., b. p. 178–183° (17 mm.). To 53.8 g. of this acid dissolved in 250 ml. of dry benzene was added 80 g. of phosphorus pentachloride, the solution refluxed thirty minutes, cooled, and 70 ml. of stannic chloride in 70 ml. of benzene added slowly. After twenty-five minutes the mixture was poured into 250 ml. of concentrated hydrochloric acid. The benzene solution was separated and washed with three 100 ml. portions of 10% hydrochloric acid, followed by three 100 ml. portions of a 5% sodium carbonate solution, dried and distilled. The yield (71%) was 34.2 g., b. p. 136–138° (16 mm.), $n^{25}D$ 1.5538.

2-Ethyl-1-tetralone[9] was prepared by the same method as 2-methyl-1-tetralone. From 20 g. of potassium, 94 g. of ethyl diethylmalonate and 93 g. of β-phenethyl bromide there was obtained 70 g. or 48% of diethyl ethyl-β-phenethylmalonate, b. p. 160–180° (4 mm.). A much lower yield was obtained when benzene instead of xylene was used as the solvent.

Hydrolysis and decarboxylation of 102.8 g. of this ester gave 62.5 g. of 93% of α-ethyl-γ-phenylbutyric acid, b. p. 146–161° (3 mm.), $n^{25}D$ 1.5010–1.5055. The ethylphenylbutyric acid (10.3 g.) was dissolved in 30 ml. of concentrated sulfuric acid, heated to 90° for 2.5 hours on the steam-bath, cooled, diluted with water and extracted with ether. The ether solution was washed with sodium carbonate solution, dried and the ether removed. The yield was 7.8 g. or 84%, which upon distillation gave a faintly yellow liquid, b. p. 147–148° (15 mm.), $n^{25}D$ 1.5460–1.5458. The combined yield of pure redistilled ketone from several cyclizations was 70%.

1-Ethyl-2-methyl-1-tetralol.—A Grignard reagent was prepared from 17.5 g. of ethyl bromide and 3.9 g. of magnesium in 70 ml. of ether. 2-Methyl-1-tetralone (20 g.) in 50 ml. of dry ether was added over a period of ten minutes and the solution refluxed six hours. The addition product was hydrolyzed with ice-cold dilute sulfuric acid, the ether solution washed with dilute sulfuric acid, a sodium carbonate solution and dried. The solid remaining after the distillation of the ether was recrystallized twice from acetone at about −70°. The yield of alcohol was 16.1 g. or 68%, m. p. 65–67°. *Anal.* Calcd. for $C_{13}H_{18}O$: C, 82.05; H, 9.54. Found: C, 82.27; H, 9.53.

1-Ethyl-2-methyl-3,4-dihydronaphthalene was prepared by dehydration of the filtrates from the crystallization of 1-ethyl-2-methyl-1-tetralol. The acetone was removed and the residue distilled from potassium bisulfate. The yield (26%) was 5.7 g., b. p. 125–130° (15 mm.). The crude product was redistilled from sodium to give 4.47 g., b. p. 121–127° (13 mm.), $n^{25}D$ 1.5660.

1-Methyl-2-ethyl-3,4-dihydronaphthalene.—Methylmagnesium iodide was prepared from 23 g. of methyl iodide and 3.9 g. of magnesium in 70 ml. of ether, to which was added 21.8 g. of 2-ethyl-1-tetralone in 50 ml. of dry ether and the mixture refluxed thirty minutes. The addition product was decomposed with a saturated ammonium chloride solution and the ether solution washed with water and dried. The thick oil left after the distillation of the ether did not crystallize. This oil was distilled from potassium bisulfate. The crude product below 135° (15 mm.) was redistilled from sodium. The yield was 16.6 g. or 79%, b. p. 132° (14 mm.), $n^{25}D$ 1.5658.

The m. p. of the trinitrobenzene derivative of 1,2-dimethylnaphthalene (148°) is the same as the m. p. of a mixture of 30% of the compound and 70% of the trinitrobenzene derivative of 1-methylnaphthalene. Mixtures of intermediate composition melt lower with a minimum of 147°. The mixtures containing a higher proportion of the derivative of 1-methylnaphthalene melt for 80% at 149.5°, 90% at 151° and the pure compound at 154°.

Summary

The method of aromatizing hydroaromatic compounds over nickel or platinum catalysts with benzene as a hydrogen acceptor has been applied to several substituted hydronaphthalenes and hydrophenanthrenes. Aromatization has in some cases involved the rupture of linkages to a quaternary carbon. The nickel on kieselguhr catalyst has been found to bring about aromatization through catalysis of migration as in the formation of phenanthrene from 1,1-spirocyclopentyltetralin. The platinum and nickel on nickel chromite catalysts brought about aromatization through elimination of an alkyl group on the quaternary carbon.

MADISON, WISCONSIN RECEIVED DECEMBER 10, 1948

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

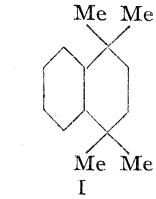
Catalytic Dehydrogenation of Hydroaromatic Compounds in Benzene. III. Compounds Containing Gem Dialkyl Groups

BY HOMER ADKINS AND DAVID C. ENGLAND

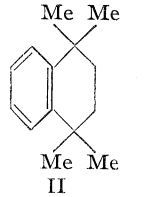
Hydroaromatic compounds may be aromatized in liquid phase in benzene with nickel, platinum or palladium catalysts, the benzene serving as hydrogen acceptor.[1,2] While gem or angular alkyls are rather stable under the conditions required for simple dehydrogenation, compounds carrying such substituents may be aromatized, with the elimination or migration of alkyl groups.[3]

The present paper is primarily concerned with the behavior of eleven hydroaromatic derivatives of naphthalene or phenanthrene which carry two alkyl groups on one of the carbon atoms of the nucleus. These compounds in benzene were heated at 350–375° in a closed chrome–vanadium steel vessel over platinum on activated carbon, nickel-on-kieselguhr and nickel-on-nickel chromite catalysts. With possibly one exception the aromatization reaction proceeded more cleanly over the platinum than over the nickel catalysts. The nickel catalysts gave aromatization with each of the eleven compounds but the isolation of the products was in general more difficult, and except for a few cases, the amounts isolated were lower.

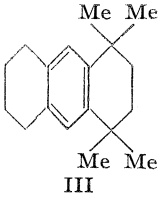
More drastic conditions are required to bring about an aromatization if a carbon-to-carbon bond must be ruptured than if only dehydrogenation is required. Thus 2,2-dimethyltetralin (V) is more difficult to dehydrogenate than tetralin itself, and 1,1,4,4-tetramethyltetralin (II) has not been dehydrogenated to any appreciable extent under the conditions employed in this work. 1,1,4,4-Tetramethyldecalin (I) was converted to the corresponding tetralin (II) in 90% yield without formation of significant amounts of methylnaphthalenes. Similarly a tetramethyloctahydroanthracene (III) was converted in 68% yield to the tetramethyltetrahydroanthracene (IV) without aromatization of the ring containing the gem methyl groups.



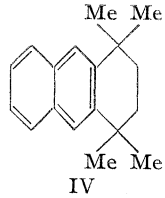
I



II

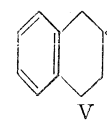


III

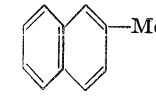


IV

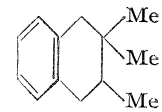
Both 2,2-dimethyltetralin (V) and 2-methyl-2-ethyltetralin were converted to 2-methylnaphthalene (VI) in yields of the order of 40%. The 2-methyl-2-ethyldecalin also gave 2-methylnaphthalene in a yield of the order of 80–85%. Similarly, one of the gem methyl groups was eliminated in 2,2,3-trimethyltetralin (VII) to give 2,3-dimethylnaphthalene (VIII) in a yield of perhaps 80%.



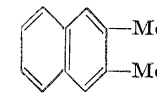
V



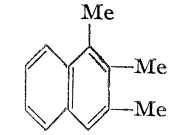
VI



VII



VIII



IX

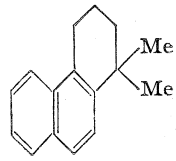
There was evidence of migration as well as elimination of a methyl group and the formation of 1,2,3-trimethylnaphthalene (IX). With a nickel-on-kieselguhr catalyst migration was the chief reaction, the yield of IX being of the order of 40%. This nickel catalyst gave a mixture of two migration products 2,3-dimethylnaphthalene (VIII) and 1,2-dimethylnaphthalene in yields of 50 and 20%, respectively, from V. It also gave the migration product 2-methyl-3-ethylnaphthalene in 30% yield from 2-methyl-2-ethyltetralin and in 20% yield from the decalin.

From 1,1-dimethyl-1,2,3,4-tetrahydrophenanthrene (X) over nickel (k) there was obtained 1,2-dimethylphenanthrene and from 1,1-diethyl-1,2,-3,4-tetrahydrophenanthrene there was evidence for the formation of 1,2-diethylphenanthrene. Thus it may be said that the platinum catalyst brings about aromatization through elimination of an alkyl group while the nickel (k) catalyst aromatizes through inducing migration of an alkyl group from a quaternary carbon atom. The nickel-on-nickel chromite catalyst is intermediate between the platinum (C) and the nickel (k) catalysts; it induces both elimination and migration of alkyl groups.

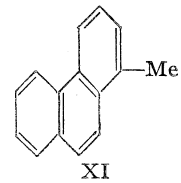
The tetrahydrophenanthrene (X) and the corresponding perhydrophenanthrene were both converted to 1-methylphenanthrene (XI) when aromatized over the platinum catalyst. Similarly the 1-methyl-1-ethyltetrahydrophenanthrene and perhydrophenanthrene lost an ethyl group and gave 1-methylphenanthrene (XI) among other products. The 1,1-diethyl-1,2,3,4-tetrahydrophenanthrene also lost one ethyl group in aromatization and so gave 1-ethylphenanthrene in fair yield and

(1) Adkins, Richards and Davis, THIS JOURNAL, **63**, 1320 (1941).
(2) Adkins, Rae, Davis, Hager and Hoyle, *ibid.*, **70**, 381 (1948).
(3) Adkins and Davis, *ibid.*, **71**, 2955 (1949).

purity. When the gem methyl groups were in the 2-position of tetrahydrophenanthrene, aromatization was accomplished, but no single product could be isolated or identified, except in the case of the nickel (k) catalyst where a migration product 1,2-dimethylphenanthrene was identified.

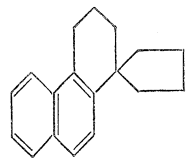


X

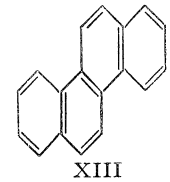


XI

1,1-Spirocyclopentano-1,2,3,4-tetrahydrophenanthrene (XII) was aromatized to chrysene (XIII) over all three catalysts to the extent of 15 to 50%. Since this conversion involves a migration of a carbon-to-carbon linkage it is not surprising that the nickel (k) catalyst gave a better yield (50%) than the platinum (C) catalyst (30%), both being superior as in other cases cited in this paper, to the nickel-on-nickel chromite catalyst which gave a 15% yield.



XII



XIII

The details as to identification, yields and purity of products are given in the experimental section. The percentage yields given above are approximations, based upon changes in refractive indices as well as weights of purified products isolated. The quantities of one to five grams used in each dehydrogenation did not permit a precise determination of the yield of each product.

The tetralins used in this work were prepared by modifications of a route described by others[4,5] through the condensation of substituted succinic anhydrides[6,7] with benzene in the presence of aluminum chloride, followed by a Clemmensen reduction,[8] ring closure with hydrogen fluoride, and another Clemmensen reduction[8] of the cyclic ketone so obtained. A similar procedure[9] using naphthalene instead of benzene was used to prepare 2,2-dimethyl-1,2,3,4-tetrahydrophenanthrene.

The 1,1-disubstituted-1,2,3,4-tetrahydrophenanthrenes were prepared in four steps from 1-chloromethylnaphthalene,[10] the first step being a Grignard reaction with ethylene oxide run in a manner analogous to the procedure described by Wilds[11] for the reaction of 1-bromonaphthalene with ethylene oxide. The resulting 3-(1-naphthyl)-1-propanol was converted to the bromide with phosphorus tribromide[12] from which the Grignard reagent was prepared for reaction with various ketones to give tertiary alcohols. These alcohols were cyclized in 85% sulfuric acid[13] to give the desired hydrocarbons.

Compounds containing more than one gem dimethyl grouping were prepared using procedures of Bruson and Kroeger.[14]

Analytical data and physical constants on compounds not previously reported are given in Tables I and II.

Experimental

Hydrogenations.—2-Methyl-2-ethyl-1,2,3,4-tetrahydronaphthalene (14.4 g., $n^{25}D$ 1.5208) was hydrogenated over Raney nickel at 225° under 3000 p. s. i. to give 2-methyl-2-ethyldecalin (14.2 g., $n^{25}D$ 1.4782, d^{25}_4 0.8880). The molecular refraction is 57.5 as compared with a calculated value of 57.8. 1,1-Dimethylperhydrophenanthrene and 1,1-diethylperhydrophenanthrene were prepared by the hydrogenation of the corresponding tetrahydrophenanthrenes over Raney nickel at 250° and 3000 p. s. i. The products of the first hydrogenations were rehydrogenated once or twice in methylcyclohexane in order to obtain the perhydrophenanthrene free of less completely hydrogenated products. 1,1,4,4-Tetramethyl-1,2,3,4-tetrahydronaphthalene (10.4 g., $n^{25}D$ 1.5192) was hydrogenated over Raney nickel at 250° under 3000 p. s. i. to give 1,1,4,4-tetramethyldecalin (10 g. b. p. 100–103° (11 mm.), $n^{25}D$ 1.4732, d^{25}_4 0.8816). The molecular refraction was thus 61.8 as compared with a calculated value of 62.4. A mixture of stereoisomers of 1,1,4,4,5,5,8,8-octamethylperhydroanthracene (m. p. 100–110° from alcohol) was prepared by the hydrogenation of the corresponding octahydroanthracene over Raney nickel at 340° for four hours at 3000 p. s. i. The hydrogenation of 1,1,4,4,7,7,10,10-octamethyl-1,2,3,4,7,8,9,10-octahydronaphthacene over Raney nickel in methylcyclohexane at 250° gave a mixture of stereoisomers of the corresponding perhydronaphthacene (m. p. 162–167° from chloroform–alcohol). 2,5-Dimethyl-3-hexyn-2,5-diol was hydrogenated at 27–75° over Raney nickel at 3000 p. s. i. to give a quantitative yield of 2,5-dimethyl-2,5-hexanediol.

Procedures of Dehydrogenation, Isolation and Characterization.—The dehydrogenations were carried out in a chrome–vanadium steel reaction vessel having a void of 270 ml. In general about 2 g. of the compound to be dehydrogenated in 5 ml. of benzene was heated for eight to twelve hours at 350–375° with 0.25 g. of a platinum-on-carbon catalyst carrying about 0.06 g. of reduced platinum. Where other conditions were used it is noted in the summary of experimental results given below. A nickel-on-nickel chromite (2 g.) and a nickel-on-kieselguhr catalyst (2 g.) were used also with all compounds, but the results are not given below in detail except in a few cases. The benzene was usually thiophene free. A little thiophene is advantageous with nickel catalysts.[2]

The products of reaction were removed from the steel vessel with ether, the catalyst separated by centrifuging, the solution decolorized with activated carbon and the solvents removed under reduced pressure. Usually a solid product was isolated by crystallization at about −80° from petroleum ether (b. p. 40–60°) using a "Dry Ice technique."[1] From the amount of solid isolated and/or the refractive index of the residue an estimate of the per cent. aromatization could be made. The formation of picrates, styphnates and trinitrobenzene derivatives served also to separate and characterize aromatic products. The hydrocarbon was conveniently recovered from these de-

(4) Clemo and Dickenson, *J. Chem. Soc.*, 255 (1937).
(5) Sengupta, *J. prakt. Chem.*, **151**, 82 (1938).
(6) Higson and Thorpe, *J. Chem. Soc.*, **89**, 1465 (1906).
(7) Inglis, *ibid.*, **99**, 544 (1911).
(8) Martin, THIS JOURNAL, **58**, 1440 (1936).
(9) Sengupta, *J. prakt. Chem.*, **152**, 9 (1939).
(10) Cambron, *Can. J. Research*, **17B**, 10 (1939).
(11) Wilds, THIS JOURNAL, **64**, 1424 (1942).
(12) Hoch, *Bull. soc. chim.*, [5] **5**, 268 (1938).
(13) Perlman, Davidson and Bogert, *J. Org. Chem.*, **1**, 295 (1936).
(14) Bruson and Kroeger, THIS JOURNAL, **62**, 36 (1940).

TABLE I

ANALYTICAL DATA AND PHYSICAL CONSTANTS

Compound	$n^{25}D$	d^{25}_4	M_D Calcd.	M_D Found	B. p. or m. p. °C.	Mm.	Mol. form.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1,1-Dimethyl-1,2,3,4-tetrahydrophenanthrene	1.6035	1.031	67.2	71.6	122–123	1	$C_{16}H_{18}$	91.37	91.53	8.63	8.58
1,1-Dimethylperhydrophenanthrene	1.4960	0.9289	69.5	69.3	103–106	1	$C_{16}H_{28}$	87.20	87.40	12.80	12.90
1,1-Methylethyl-1,2,3,4-tetrahydrophenanthrene	1.6007	1.029	71.9	74.7	144–145	2	$C_{17}H_{20}$	91.00	90.92	9.00	8.99
1,1-Methylethylperhydrophenanthrene	1.5015	0.9404	74.1	73.5	123–125	1.5	$C_{17}H_{30}$	87.12	87.42	12.88	12.78
1,1-Diethyl-1,2,3,4-tetrahydrophenanthrene	1.5990	1.027	76.4	79.1	146–147	1.1	$C_{18}H_{22}$	90.69	91.00	9.31	9.39
1,1-Spirocyclopentano-1,2,3,4-tetrahydrophenanthrene					160–164	0.5	$C_{18}H_{20}$	91.50	91.49	8.50	8.61
2,2,3-Trimethyl-1,2,3,4-tetrahydronaphthalene	1.5200	0.9325	55.3	56.8	64	0.4	$C_{13}H_{18}$	89.61	89.25	10.39	10.31
2-Methyl-2-ethyldecalin	1.4782	0.8880	57.8	57.5			$C_{13}H_{24}$	86.58	86.47	13.42	13.37
1,1,4,4-Tetramethyldecalin	1.4732	0.8816	62.4	61.8	100–103	11	$C_{14}H_{26}$	86.60	86.30	13.40	13.30
2,2-Dimethyl-1,2,3,4-tetrahydrophenanthrene					45–46.5		$C_{16}H_{18}$	91.43	91.42	8.57	8.42
1,1,4,4-Tetramethyl-1,2,3,4-tetrahydroanthracene					82.5–84		$C_{18}H_{22}$	90.75	90.81	9.25	9.29
α-Methyl-α-phenylsuccinic acid					156–158		$C_{11}H_{12}O_4$	63.45	63.45	5.81	5.76
γ-Phenyl-γ-keto-α,α,β-trimethylbutyric acid					133.5–136		$C_{13}H_{16}O_3$	70.89	71.10	7.31	7.23
γ-Phenyl-α,α,β-trimethylbutyric acid					115–120		$C_{13}H_{18}O_2$	75.70	75.76	8.78	8.97
1,1,4,4,5,5,8,8-Octamethylperhydroanthracene					100–110		$C_{22}H_{46}$	86.84	86.94	13.16	12.97
1,1,4,4,7,7,10,10-Octamethylperhydronaphthacene					162–167		$C_{26}H_{46}$	87.2	86.8	12.8	12.5

TABLE II

ANALYSIS OF (a) PICRATES AND (b) TRINITROBENZENE DERIVATIVES

Compound	M. p., °C.	Mol. form.	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
1,1-Spirocyclopentano-1,2,3,4-tetrahydrophenanthrene (a)	96–97	$C_{24}H_{23}O_7N_3$	61.92	61.87	4.99	4.91
1,1-Spirocyclopentano-1,2,3,4-tetrahydrophenanthrene (b)	125–126	$C_{24}H_{23}O_6N_3$	64.13	64.16	5.12	5.11
1,2,3-Trimethylnaphthalene (a)	141–142	$C_{19}H_{17}O_7N_3$	57.13	57.12	4.26	4.40
2,2-Dimethyl-1,2,3,4-tetrahydrophenanthrene (b)	112–115	$C_{22}H_{21}O_6N_3$	62.41	62.38	4.96	4.86
1-Methylphenanthrene (b)	160–161	$C_{21}H_{15}O_6N_3$	62.22	62.46	3.70	3.72
1,2-Diethylphenanthrene (b)	137–138	$C_{24}H_{21}O_6N_3$	64.42	64.85	4.74	4.78
2-Methyl-3-ethylnaphthalene (a)	131.5–133.5	$C_{19}H_{17}O_7N_3$	57.13	57.26	4.26	4.36
2-Methyl-3-ethylnaphthalene (b)	131–131.5	$C_{19}H_{17}O_6N_3$	59.51	59.47	4.44	4.45

rivatives by dissolving in the proper solvent (benzene for picrate and petroleum ether for trinitrobenzene derivatives) and passing through a tower packed with activated alumina. Thus, small amounts of low melting aromatic hydrocarbons were conveniently purified by preparing a higher melting derivative such as the picrate, recrystallizing to purity and recovering the hydrocarbon by passing the picrate in benzene solution through an alumina tower. The picric acid was adsorbed on the alumina and the purified hydrocarbon could be recovered by evaporation of the benzene. After determination of its refractive index and/or melting point other derivatives could be prepared.

Results of Dehydrogenations

2,2-Dimethyltetralin (1.54 g., $n^{25}D$ 1.5188) gave 1.27 g. of product $n^{25}D$ 1.5410, which after crystallization gave 0.44 g. crystals and 0.75 g. of oil $n^{25}D$ 1.5330. The crystalline product was characterized as 2-methylnaphthalene through the formation of the trinitrobenzene derivative which after three crystallizations from methanol showed a m. p. 123–125.5°. The m. p. of the derivative was not lowered when mixed with an authentic sample. Decomposition of the derivative over alumina gave a sample of 2-methylnaphthalene m. p. above 25° which gave a picrate m. p. 113–114° corresponding to that reported.[15]

2-Methyl-2-ethyltetralin (1.4 g., $n^{25}D$ 1.5170) gave a product (1.1 g., $n^{25}D$ 1.5595) which yielded 0.4 g. of crystals melting at room temperature and 0.67 g. of an oil $n^{25}D$ 1.5520. The crystals were characterized as 2-methylnaphthalene as described above.

2,2-Dimethyltetralin (2.9 g.) over the nickel (k) catalyst gave 1.03 g. m. p. 90–92° and 0.88 g. of an oil $n^{25}D$ 1.5950. The solid after four recrystallizations from methanol showed a m. p. 102–103.5° and gave a trinitrobenzene derivative m. p. 134.5–136.5°. These values correspond to those for 2,3-dimethylnaphthalene. 1,2-Dimethylnaphthalene was identified in the oil through the formation of the trinitrobenzene derivative m. p. 144–148° and comparison of it with an authentic compound. A few milligrams of the hydrocarbon was recovered from the derivative and converted to the picrate m. p. 124–128°.

2-Methyl-2-ethyltetralin and the corresponding decalin, over the nickel (k) catalyst, gave aromatic oils from which derivatives of 2-methyl-3-ethylnaphthalene ($n^{25}D$ 1.6003) were prepared. The yields of this compound were estimated to be 20–30%. The picrate m. p. 131.5–133.5°, styphnate m. p. 118–119°, and trinitrobenzene derivative m. p. 131–133.5° were unreported but a quinone mixture m. p. 64–68° prepared as by Karrer,[16] served to identify it as 2-methyl-3-ethylnaphthalene.

2-Methyl-2-ethyldecalin (2.3 g., $n^{25}D$ 1.4775) gave a product (2.1 g., $n^{25}D$ 1.5450) from which was obtained 1.53 g. of 2-methylnaphthalene (m. p. 23–25°) and 0.23 g. of oil. The 2-methylnaphthalene was characterized as described above.

2,2,3-Trimethyltetralin (1.08 g., $n^{25}D$ 1.5200) gave a product (1.0 g.) which yielded 0.77 g. of crystalline but impure 2,3-dimethylnaphthalene and a liquid (0.2 g., $n^{25}D$ 1.5720). Recrystallization of the crude 2,3-dimethylnaphthalene from petroleum ether (b. p. 40–60°) yielded 0.5 g., m. p. 95–99° and three crystallizations from methanol gave 0.2 g., m. p. 104–105°. The m. p. reported is 102°. The picrate, m. p. 123–124.5° and the trinitrobenzene derivative m. p. 137–138° were also prepared and found to agree with those reported.[17] From another run there was obtained 0.3 g. of crystalline 2,3-dimethylnaphthalene and 0.41 g. of oil $n^{25}D$ 1.5570. From the oil a picrate was prepared which after two recrystallizations from methanol melted at 138–142° and showed no lowering when mixed with the picrate of 1,2,3-trimethylnaphthalene m. p. 141–142° obtained from the nickel (k) run below. Therefore it was concluded that some of this hydrocarbon was present in the dehydrogenation product.

2,2,3-Trimethyltetralin (1 g.) over the nickel (k) catalyst gave 0.52 g. of an oil $n^{25}D$ 1.5725. A picrate m. p.

(15) Barbot, *Bull. soc. chim.*, **47**, 1317 (1930).

(16) Karrer and Epprecht, *Helv. chim. acta*, **23**, 277 (1940).

(17) Thiele and Troutman, *Ber.*, **68B**, 2247 (1935).

141–142° and the styphnate m. p. 136–139° corresponding to 1,2,3-trimethylnaphthalene were obtained.

1,1,4,4-Tetramethyldecalin (2.6 g., $n^{25}D$ 1.4732) gave 2.3 g. of a product $n^{25}D$ 1.5210. This value is similar to that of 1,1,4,4-tetramethyltetralin, $n^{25}D$ 1.5180, and identical with the product from an attempted dehydrogenation of the tetralin. There was also fair agreement in the densities, *i. e.*, d^{25}_4 0.9215 as compared with 0.9244 for the authentic tetralin.

1,1-Dimethyl-1,2,3,4-tetrahydrophenanthrene (2 g., $n^{25}D$ 1.6035) gave 1.1 g. of crystals and 0.58 g. of oil $n^{25}D$ 1.6092. After two crystallizations from petroleum ether (b. p. 60–68°) the 1-methylphenanthrene (0.47 g.) had a m. p. 115–117° and after three recrystallizations from methanol the m. p. was 118–119°. The picrate m. p. 135.5–137°, the styphnate m. p. 150.5–152°, and the trinitrobenzene derivative m. p. 160–161° were obtained. These values correspond with those of 1-methylphenanthrene and its derivatives.

1,1-Dimethyl-1,2,3,4-tetrahydrophenanthrene (2 g., $n^{25}D$ 1.6035) over the nickel (k) catalyst gave 0.6 g. of crystals which after three recrystallizations from methanol melted at 136–140°. The picrate melted at 151–153°. These values are in agreement with those reported for 1,2-dimethylphenanthrene.[18]

1,1-Dimethylperhydrophenanthrene (2.3 g., $n^{25}D$ 1.4940) gave 1.17 g. of crude 1-methylphenanthrene and 0.93 g. of oil $n^{25}D$ 1.5885. Crystallization and characterization as described above gave 0.68 g. of 1-methylphenanthrene m. p. 83–95° which was purified to 0.24 g., m. p. 116–117°.

1-Methyl-1-ethyl-1,2,3,4-tetrahydrophenanthrene (2 g., $n^{25}D$ 1.6002) gave 1 g. of a solid and 0.58 g. of an oil $n^{25}D$ 1.6138. Purification and characterization of the solid product, as described above for 1-methylphenanthrene, showed it to consist primarily of that compound. The quantities obtained were low, *i. e.*, 0.33 g., m. p. 99–107°, and 0.10 g., m. p. 117–120°.

1-Methyl-1-ethyl-perhydrophenanthrene (1.6 g., $n^{25}D$ 1.5010) gave 1.21 g. of a solid and an oil $n^{25}D$ 1.6145. Purification and characterization of the solid product as described above, indicated that 1-methylphenanthrene was produced along with other compounds in the dehydrogenation.

1,1-Diethyl-1,2,3,4-tetrahydrophenanthrene (2 g., $n^{25}D$ 1.5960) gave 0.72 g. of crystals and 0.77 g. of oil $n^{25}D$ 1.6210. 1-Ethylphenanthrene, 0.37 g., m. p. 60–61.5° was obtained by recrystallization of the product from methanol. Further recrystallization gave a sample m. p. 62.5–63° corresponding with that previously reported.[19] The above run repeated over a nickel (k) catalyst gave an oil $n^{25}D$ 1.6355. A trinitrobenzene derivative after six recrystallizations from methanol melted at 137–138° (0.1 g.). It gave the correct carbon and hydrogen analyses for the trinitrobenzene derivative of 1,2-diethylphenanthrene.

2,2-Dimethyl-1,2,3,4-tetrahydrophenanthrene (0.5 g., m. p. 45–46.5°) gave 0.4 g. of a product which formed a picrate that melted at 120–123° after being twice recrystallized from methanol. The m. p. of the picrate of 2-methylphenanthrene is 118–119°. The m. p. of a mixture of the two samples was 118–120°. Analysis of the picrate for carbon and hydrogen indicated that it was a mixture derived from a mono- and a dimethylphenanthrene. The hydrocarbon(s) recovered from the picrate over alumina showed a m. p. 65–75° which is higher than that of 2-methylphenanthrene, m. p. 53–54°.

2,2-Dimethyl-1,2,3,4-tetrahydrophenanthrene (1.06 g.) over nickel (k) catalyst gave 0.82 g. of solid. Four recrystallizations from methanol gave crystals melting at 142–143°, the reported melting point of 1,2-dimethylphenanthrene.[18]

1,1,4,4-Tetramethyl-1,2,3,4,5,6,7,8-octahydroanthracene (5 g., m. p. 88–91°) at 350° gave 4.8 g. of a solid product. Recrystallizations from ethanol gave 3.3 g. of 1,1,4,4-tetramethyl-1,2,3,4-tetrahydroanthracene m. p. 78–81° or 1.6 g., m. p. 82.5–84°. This compound reacted with 2,5-dichloro-2,5-dimethylhexane in the presence of aluminum chloride to give 1,1,4,4,7,7,10,10-octamethyl-1,2,3,4,7,8,9,10-octahydronaphthacene.

A sample of 1,1,4,4,7,7,10,10-octamethylperhydronaphthacene (2 g., m. p. 162–167°) gave upon dehydrogenation a product which after crystallization from toluene amounted to 1.2 g. of product m. p. 160–170°. After five recrystallizations there was obtained 0.05 g., m. p. 295–298° of a compound that is probably 1,1,4,4,7,7,10,10-octamethyl-1,2,3,4,7,8,9,10-octahydronaphthacene.

1,1,4,4,5,5,8,8-Octamethylperhydroanthracene resisted dehydrogenation even to the octamethyloctahydroanthracene under the conditions used in this work. This might be expected since the reverse hydrogenation was so difficult to accomplish, *i. e.*, 340° was required.

1,1-Spirocyclopentano-1,2,3,4-tetrahydrophenanthrene (0.8 g., m. p. 56–58°) gave after evaporative distillation of the dehydrogenation product 0.17 g., m. p. 200–244°. This solid could be crystallized from benzene to m. p. 250–251° and the melting point was not lowered on mixing with an authentic sample of chrysene m. p. 251–252°.

The above experiment was repeated using nickel (k) as catalyst and there was obtained after evaporative distillation 0.23 g., m. p. 240–250°.

Summary

Eleven tetralins, decalins, tetrahydrophenanthrenes and perhydrophenanthrenes carrying gem dialkyl groups have been prepared. These compounds have been aromatized in the liquid phase with benzene and platinum and nickel catalysts to substituted naphthalenes or phenanthrenes. The platinum catalyst brings about aromatization almost exclusively through elimination of an alkyl group and hydrogen, while the nickel-on-kieselguhr catalyst brings about aromatization through the catalysis of the migration of a carbon linkage. The latter catalyst, for example, brings about a rather clean transformation of 1,1-spirocyclopentano-1,2,3,4-tetrahydrophenanthrene to chrysene.

MADISON, WISCONSIN RECEIVED NOVEMBER 15, 1948

(18) Haworth, *J. Chem. Soc.*, 457 (1934).

(19) Haworth, *ibid.*, 460 (1934).

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

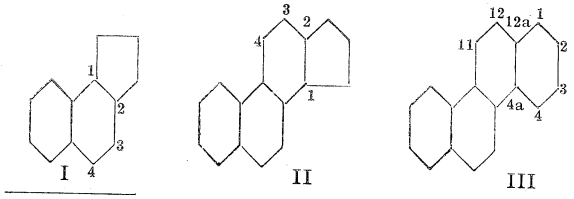
Catalytic Dehydrogenation of Hydroaromatic Compounds in Benzene. IV. Aromatization of Compounds Containing an Angular Alkyl Group

BY HOMER ADKINS AND GLENN F. HAGER[1]

The feasibility of the aromatization of a number of naphthalene, phenanthrene and chrysene derivatives containing angular alkyl groups, under conditions used for simple dehydrogenation, has been investigated, in conjunction with James W. Davis and David C. England.[2,3,4]

A summary of the experimental results obtained in the aromatization of a variety of compounds is given in Table I. The per cent. conversions, based upon the amount of compound undergoing reaction, were considerably higher than those given in the table. Except for one or two cases the amount of recovered starting material was such that 80–90% of the compound reacting went to the indicated product. 1-Methyl-1,2-cyclopentanodecalin and 2-methyl-1,2-cyclopentanoperhydrophenanthrene gave 10% yields of naphthalene and phenanthrene, respectively, in addition to 1,2-cyclopentenonaphthalene and 1,2-cyclopentenophenanthrene. No doubt small quantities of compounds not characterized were present in the various reaction mixtures.

The aromatizations were conducted under rather arbitrarily chosen conditions which were certainly not the optimum, especially from the standpoint of completeness of conversion. The aromatization of 1-methyl-1,2-cyclopentanodecalin was studied under a variety of conditions. The effect of the void in the steel vessel, of various amounts and qualities of benzene, of the addition of thiophene,[5] of ratio of catalyst to compound, of periods of reaction varying from two to twelve hours and of temperatures from 350 to 450°, were determined. The optimum conditions for yield of 1,2-cyclopentanonaphthalene over a Ni·NiCrO catalyst was found to be with equal weights (4 g.) of catalyst and organic compound, 20 ml. of pure benzene containing 40 mg. of thiophene, shaken in a 270-ml. steel vessel at 37[illegible]° for eight hours. Under these conditions the yield of 1,2-cyclopentenonaphthalene was about 63% of the theoretical as compared with 45% as given in Table I. However, at the lower temperature referred to in the table, 50% of the starting material did not react so that the efficiency of conversion was better at the lower temperature.



A series of eight compounds, related to 1,2-cyclopentenonaphthalene (I), were aromatized to that compound in good yield. These compounds listed in Table I differed from each other in their degree of hydrogenation varying from di to tetra

TABLE I

AROMATIZATION IN BENZENE

Compound	G. of catalyst	Yield of product, %
1,2-Cyclopentenonaphthalene		
1,2-Cyclopentanodecalin	1 Pd(C)[a]	55
	0.5 Pt(C)	76
	2 Ni·NiCrO	66
1,2-Cyclopentano-1,2,3,4-tetrahydronaphthalene	1 Pd(C)	55
	0.5 Pt(C)	67
	2 Ni·NiCrO	52
1-Methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene	0.5 Pt	52
	2 Ni·NiCrO	40
1-Methyl-1,2-cyclopentanodecalin	2 Ni·NiCrO	45
	0.5 Pt(C)	42
1-(*n*-Butyl)-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene	2 Ni·NiCrO	22
	0.5 Pt (C)	51
2-Methyl-1,2-cyclopentanodecalin	2 Ni·NiCrO	72
	0.5 Pt (C)	72
2-Carbethoxy-3,4-dihydro-1,2-cyclopentenonaphthalene	0.5 Pt (C)	82
2-Carbethoxy-1,2-cyclopentanodecalin	0.5 Pt (C)	69
1,2-Cyclopentanophenanthrene		
2-Methyl-1,2-cyclopentanoperhydrophenanthrene	0.5 Pt (C)	61
	2 Ni·NiCrO	30
1-Methyl-1,2-cyclopentano-1,2,3,4-tetrahydrophenanthrene	0.5 Pt (C)	67
	2 Ni·NiCrO	18
1-Methyl-1,2-cyclopentanoperhydrophenanthrene	0.5 Pt (C)	62
	1 Pd (C)	37
	2 Ni·NiCrO	24
1-Ethyl-1,2-cyclopentano-1,2,3,4-tetrahydrophenanthrene	0.5 Pt	68
	2 Ni·NiCrO	43
1-(*n*-Butyl)-1,2-cyclopentano-1,2,3,4-tetrahydrophenanthrene	0.5 Pt	60
	2 Ni·NiCrO	35
Chrysene		
4a-Methyl-1,2,3,4,4a,11,12,12a-octahydrochrysene	2 Ni·NiCrO	74
	0.5 Pt (C)	64
	1 Pd (C)	65
	2 Ni (k)	53
4a-Methylperhydrochrysene	0.5 Pt (C)	40
	2 Ni·NiCrO	40

[a] The dehydrogenations were on 3–4 g. of compound in a 270-ml. chrome vanadium steel vessel with 20–40 ml. of benzene at 350° for 8–12 hours. A glass liner was used with the palladium catalyst.

(1) Monsanto Co. Fellow 1942–1943.

(2) Adkins, Richards and Davis, THIS JOURNAL, **63**, 1320 (1941).

(3) Adkins and Davis, *ibid.*, **71**, 2955 (1949).

(4) Adkins and England, *ibid.*, **71**, 2958 (1949).

(5) Adkins, Rae, Davis, Hager and Hoyle, *ibid.*, **70**, 381 (1948).

to complete saturation. They also differed in that two of them did not carry a carbon substituent on the ring, while the others had substituents in the angular 1- or 2-positions. Two had methyl groups in the 1-position, one had a *n*-butyl group in the 1-position, two had carbethoxy groups in the 2-position, and one had a methyl group in the 2-position. There was not much difference in the yields of 1,2-cyclopentenonaphthalene from a tetralin as compared with a decalin, although the former was dehydrogenated more rapidly at 350° and could be dehydrogenated under milder conditions than the decalin. The methyl in the 2-position was more readily removed than when in the 1-position. An angular methyl group in the 1-position was more completely removed under the standard conditions than a *n*-butyl group. A carbethoxy group in the 2-position was quite readily eliminated from either the dihydronaphthalene or from the decalin.

The platinum catalyst gave somewhat better yields in most cases than did the nickel on nickel chromate catalyst. However, this is apparently due to a slower rate of aromatization over the nickel catalyst and not to the catalysis of other reactions. Palladium was also an effective catalyst. The nickel on kieselguhr catalyst was uniformly less useful for these compounds than the other catalysts mentioned so that no data for it are given.

A series of five compounds, related to 1,2-cyclopentenophenanthrene (II), were aromatized to that compound. The yields were rather good but somwhat inferior to those obtained for 1,2-cyclopentenonaphthalene discussed above. All of the compounds aromatized carried an angular methyl or ethyl or *n*-butyl group in the 1- or 2-position. There was little difference in the yield of 1,2-cyclopentenophenanthrene from tetra- as compared with perhydrophenanthrene. This is understandable since the conditions required for the elimination of an angular alkyl group are rather drastic, so that the relative ease of dehydrogenation of a tetrahydro as compared with a perhydro compound is not a significant factor in determining yields. The platinum catalyst gave on the average twice as high yields as did the nickel catalyst.

Chrysene (III) was obtained as a minor product (10%) in the aromatization of 2-methyl-1,2-cyclopentanoperhydrophenanthrene through ring expansion over the platinum catalyst. Chrysene was obtained in better yields by England[4] through ring expansion of another phenanthrene, *i. e.*, 1-spirocyclopentano - 1,2,3,4 - tetrahydrophenanthrene. An octahydro- and a perhydrochrysene, with a methyl group in the angular 4a position, gave good yields of chrysene over four different catalysts.

The methods of synthesis and properties of the compounds aromatized are given in another paper.[6] The catalysts were prepared and used as described in an earlier paper[2] except for palladium-on-carbon. This catalyst, carrying about 8% palladium, was prepared by a standard method,[7] and used in a glass liner.

Separation, Characterization and Estimation of Products

The products of reaction were removed from the reaction vessel and catalyst with ether or benzene. The products containing 1,2-cyclopentenonaphthalene were distilled in a 7-ml. modified Claisen flask at less than 1 mm. pressure. Yields were estimated from the refractive index of the distillate, assuming it to be a binary mixture of starting material and 1,2-cyclopentenonaphthalene. The validity of this assumption was justified by various experiments including the formation of various derivatives. Identification of 1,2-cyclopentenonaphthalene (b. p. 118 (0.5 mm.), $n^{25}D$ 1.6300) was effected by conversion to its picrate (m. p. 109°) and trinitrobenzene (m. p. 121°) derivatives. The products containing 1,2-cyclopentenophenanthrene or chrysene were washed with two portions of about 7 ml. of petroleum ether, b. p. 40–60°, on a sintered glass funnel at −80° by the "Dry Ice technique"[2] to separate aromatic products from starting material. The solid was then distilled evaporatively in a sublimer tube at a pressure of about 0.1 mm. Yields and purity of product were estimated from the weight and m. p. of this distillate. When the distillate contained both 1,2-cyclopentenophenanthrene (m. p. 135°) and chrysene (m. p. 251°), yields were estimated from the melting point of the mixture. The melting points for mixtures containing various proportions of chrysene are: 12.5%, 158°; 25%, 175°; 37.5%, 191°; 50%, 202°; and 75%, 226°. These aromatics were separated by fractional crystallization and identified by conversion to trinitrobenzene derivatives: 1,2-cyclopentenophenanthrene-TNB, m. p. 165° and chrysene-TNB, m. p. 188°.

Summary

Fifteen compounds, in various stages of hydrogenation, related to 1,2-cyclopentenonaphthalene, 1,2-cyclopentenophenanthrene or chrysene and in thirteen cases containing angular substituents, have been aromatized to one of the three compounds just mentioned. Fairly good yields of the aromatic compound have been obtained in benzene under pressure at 350° over platinum, palladium or nickel catalysts.

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(6) Adkins and Hager, THIS JOURNAL, **71**, 2965 (1949).

(7) Zelinsky and Turowa-Pollock, *Ber.*, **58**, 1295 (1925).

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSIY OF WISCONSIN]

Catalytic Dehydrogenation of Hydroaromatic Compounds in Benzene. V. Application to Pyrrolidines and Piperidines

BY HOMER ADKINS AND LESTER G. LUNDSTED

A catalytic method of dehydrogenating hydroaromatic compounds in benzene in the liquid phase[1] has been evaluated against representative

TABLE I

DEHYDROGENATION OF PYRROLIDINES AND PIPERIDINES[a]

Compound	°C.	Hours	Yield, %	
1-(*n*-Amyl)-pyrrolidine[5]	300	1.5	79	1-(*n*-Amyl)-pyrrole
	250	3	88	1-(*n*-Amyl)-pyrrole
1-Ethyl-2,3,4,5,-tetramethyl-pyrrolidine[3]	300	1.5	70	1-Ethyl-2,3,4,5-tetramethylpyrrole
2-Ethyl-3,4,5-trimethylpyrrolidine[3]	300	1.5	56	2-Ethyl-3,4,5-trimethylpyrrole
1-Cyclohexylpyrrolidine[4]	350	5	56	1-Cyclohexylpyrrole
1-Phenylpyrrolidine[4]	350	5	53	1-Phenylpyrrole
Indoline[4,6]	200	1	75	Indole[4]
1,2,3,4-Tetrahydrocarbazole[9]	300	3	95	Carbazole[4]
Perhydrocarbazole[4]	350	4	82	Carbazole[4]
9-Ethylperhydrocarbazole[4]	250	1.5	98	9-Ethylcarbazole[4]
2-Phenylpyrrolidine[4]	300	1.5	46	2-Phenylpyrrole[4]
2-Cyclohexylpyrrolidine[4]	300	3	16	2-Phenylpyrrole[4]
Piperidine	350	5	48	Pyridine
α-Pipecoline	350	5	62	α-Picoline
β-Pipecoline	350	5	53	β-Picoline
γ-Pipecoline	350	5	64	γ-Picoline
2,6-Lupetidine	250	5	45	2,6-Lutidine
trans-Decahydroquinoline[8]	350	5	42	Quinoline
cis-Decahydroquinoline[8]	350	5	47	Quinoline
N-Benzoyl-*cis*-decahydroquinoline[8]	350	5	57	Quinoline

[a] Three to 10 g. of the compound in 20–30 ml. of benzene with 1 to 2 g. of the Ni·NiCrO catalyst was held in a 180 ml. chrome vanadium steel vessel.

pyrrolidines, indolines, hydrocarbazoles and piperidines. A summary of the results obtained in the dehydrogenation of nineteen compounds over the nickel-on-nickel chromite catalyst (Ni·NiCrO) is given in Table I. The temperatures and time intervals required for reaction are less for the heterocyclic compounds than for the carboxylic compounds studied earlier. Several dehydrogenations were accomplished at 250–300°.

There is more tendency for the heterocyclic compounds, especially the piperidines, to go to compounds of higher molecular weight during dehydrogenations. Nevertheless the yields with eight compounds containing the pyridine nucleus averaged about 50% of the theoretical. The yields of ten compounds containing the pyrrole nucleus averaged 73%. The yields for compounds having the carbazole nucleus were almost quantitative. The yields of 1-(*n*-amyl)-pyrrole (88%), 1-ethyl-2,3,4,5-tetramethylpyrrole (74%) and 2-ethyl-3,4,5-trimethylpyrrole (69%) appear particularly attractive from a preparational standpoint since these compounds have not been available. Successful dehydrogenations were not accomplished on 1-benzoylpyrrolidene, 1-carbethoxypyrolidine, nicotine or 4-phenylpiperidine. The yield of 2-phenylpyrrole from 2-phenylpyrrolidine was 46% and from 2-cyclohexylpyrrolidine was only 16%.

The nickel-on-nickel chromite catalyst was prepared as described.[2] The compounds submitted to hydrogenation were available through methods used by others in this Laboratory.[3,4,5,6,7,8] The pipecolines and 2,6-lupetidine were made by the hydrogenation of the corresponding pyridine derivatives from commerical sources, over W-4 Raney nickel at 150–175° during an hour or two. 1,2,3,4-Tetrahydrocarbazole m. p. 118–120° was made by the Fischer indole synthesis[9] from the phenylhydrazone of cyclohexanone in a yield of 86%.

The products of reaction indicated in Table I were isolated by conventional methods of distilla-

TABLE II

PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR VARIOUS COMPOUNDS

Compound: Formula	Compound: Name	B. p. °C.	B. p. Mm.	d^{25}_4	$n^{25}D$	Nitrogen, % Calcd.	Nitrogen, % Found	M_D Calcd.	M_D Found
$C_{10}H_{15}N$	1-Cyclohexylpyrrole	114	19	0.953[a]	1.5140	9.39	9.29		
$C_9H_{15}N$	1-*n*-Amylpyrrole	80–82	15	.859[a]	1.4694[a]	10.20	10.12	44.33	44.52
$C_{10}H_{17}N$	1-Ethyl-2,3,4,5-tetramethylpyrrole	84–90	9	.899	1.4930	9.26	9.55	49.15	48.77
$C_9H_{15}N$	2-Ethyl-3,4,5-trimethylpyrrole	81–86	10	.895	1.4890	10.20	10.24	44.18	44.04

[a] Determined at 20°.

(1) References to earlier papers in this series are given by Adkins and Hager, THIS JOURNAL, **71**, 2962 (1949).

(2) Adkins, Richards and Davis, *ibid.*, **63**, 1320 (1941).
(3) Signaigo and Adkins, *ibid.*, **58**, 709 (1936).
(4) Coonradt and Adkins, *ibid.*, **63**, 1563 (1941).
(5) Wojcik and Adkins, *ibid.*, **56**, 2419 (1934).
(6) Adkins and Burks, *ibid.*, **70**, 4174 (1948).
(7) Paden and Adkins, *ibid.*, **58**, 2487 (1936).
(8) Bailey and McElvain, *ibid.*, **52**, 4015 (1930).
(9) Sidgwick, "The Organic Chemistry of Nitrogen," Clarendon Press, 1937, p. 498.

tion, steam distillation, crystallization and use of solid derivatives, as was appropriate to the compounds. The properties and analyses of four pyrroles apparently not reported earlier are given in Table II. Other products were identified through refractive indices, boiling points, melting points and solid derivatives.

Summary

Representative compounds, containing a pyrrolidine or piperidine nucleus, have been dehydrogenated in the liquid phase in benzene over a nickel catalyst, to compounds containing a pyrrole or pyridine nucleus.

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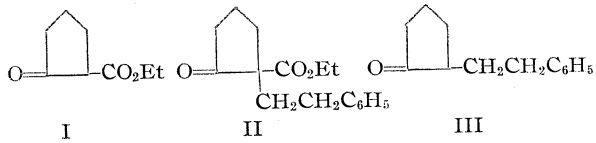
[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Synthesis of Cyclopentanohydronaphthalenes and Hydrophenanthrenes with Substituents in an Angular Position

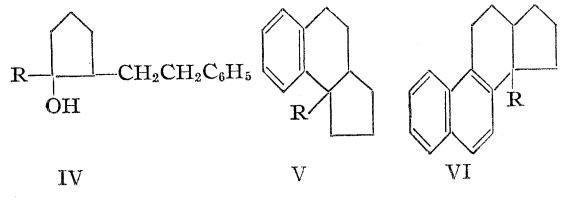
BY HOMER ADKINS AND GLENN F. HAGER[1]

In connection with another investigation,[2] a series of compounds has been made, which have a substituent in an angular position of partially or completely hydrogenated derivatives of 1,2-cyclopentenonaphthalene or 1,2-cyclopentenophenanthrene. The methods used were developments of those described earlier.[3,4,5,6,7,8,9]

The naphthalene derivatives were made through a series of reactions in which 2-carbethoxycyclopentanone (I) was alkylated with β-phenethyl bromide to give the substituted keto ester II. For one group of compounds the keto ester was decarboxylated to the ketone III, and converted to a tertiary alcohol IV, through the use of a Grignard reagent.



I II III

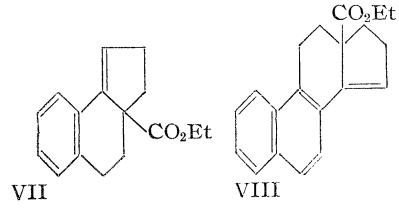


IV V VI

The latter was cyclized to a 1-alkyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene (V) where the alkyl group was methyl or *n*-butyl. The parent compound 1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene, where R equals H in formula V, was prepared by reducing the ketone III to an alcohol over copper–chromium oxide, and closing the ring as in converting IV to V.

A group of angular substituted hydrophenanthrenes was prepared, by modifying the synthesis outlined above, through the use of α-$C_{10}H_7CH_2CH_2Br$ instead of $C_6H_5CH_2CH_2Br$ in alkylating the keto ester I. Thus, three 1-alkyl-1,2-cyclopentano - 1,2,3,4 - tetrahydrophenanthrenes (VI) were obtained, where the alkyl group was methyl, ethyl or *n*-butyl.

A modification of the synthesis was made in that the keto ester II was cyclized with liquid hydrogen fluoride to give a 2-carbethoxy-1,2-cyclopenteno - 3,4 - dihydronaphthalene (VII). The corresponding 2-carbethoxy-1,2-cyclopenteno-3,4-dihydrophenanthrene (VIII) was similarly prepared. In this latter case the cyclization went so rapidly that it was complete within five minutes at 0°. This method of closure gave excellent yields of compounds with a carbethoxy group in an angular position, and seems preferable to that used by Ruzicka and his associates and more recently by Ehmann and Miescher.[10]



VII VIII

The carbethoxy groups in compounds VII and VIII were hydrogenated to methylol groups and ultimately to the 2-methyl-1,2-cyclopentanodecalin and 2-methyl-1,2-cyclopentanoperhydrophenanthrene. Three catalysts were used in sequence, *i. e.*, copper–chromium oxide, Raney nickel and finally nickel-on-alumina. Several of the dihydro- and tetrahydronaphthalene and phenanthrene derivatives were converted to the corresponding substituted decalins or perhydrophenanthrenes over Raney nickel. The hydrogenated compounds are listed in Table I and the details of hydrogenation are given under the experimental section. Chrysene and 4a-methyl-1,2,3,4,4a,11,12,12a-octahydrochrysene, prepared

(1) Monsanto Chemical Co. Fellow 1942–1943.
(2) Adkins and Hager, THIS JOURNAL, **71**, 2962 (1949).
(3) Bardhan and Sengupta, *J. Chem. Soc.*, 2520, 2798 (1932).
(4) Kon, *ibid.*, 1081 (1933).
(5) Bougault, *Compt. rend.*, **159**, 745 (1915).
(6) Von Auwers and Möller, *J. prakt. Chem.*, **109**, 124 (1925).
(7) Cook, Haslewood and Robinson, *J. Chem. Soc.*, 667 (1935).
(8) Ruzicka, Ehman, Goldberg and Hosli, *Helv. Chim. Acta*, **16**, 833 (1933).
(9) Perlman, Davidson and Bogert, *J. Org. Chem.*, **1**, 295 (1936).
(10) Ehmann and Miescher, *Helv. Chim. Acta*, **30**, 413 (1947).

TABLE I

ANALYSES AND PROPERTIES OF COMPOUNDS

Abbreviations: naph. for naphthalene; cyp. for cyclopentano; phen. for phenanthrene.

Name	Mol. form.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	$n^{25}D$	d^{25}_4	M_R Calcd.	M_R Found	B. p. °C.	Mm.
1,2-Cyclopentanodecalin	$C_{13}H_{22}$	87.55	87.52	12.45	12.40	1.5020	0 9446	55.64	55.79	128–130	17
1-Methyl-1,2-cyclopentanodecalin	$C_{14}H_{24}$	87.42	87.55	12.58	12.52	1.5020	0.9379	60.64	61.00	115–117	7
1-(*n*-Butyl)-1,2-cyp.-1,2,3,4-tetrahydronaph.	$C_{17}H_{24}$	89.41	89.39	10.59	10.42	1.5372	0.9678	73.11	73.45	127–129	3
1-Methyl-2-decalol	$C_{11}H_{20}O$	78.51	78.43	11.98	11.86	1.4995				112–119	10
1-Methyl-1,2,3,4-tetrahydro-2-naphthol	$C_{11}H_{14}O$	81.44	81.40	8.70	8.81		M. p. 113°			125–130	3
1-Methyl-2-decalone	$C_{11}H_{18}O$	79.46	79.20	10.92	10.79	1.4894				105–107	7
1-Methyl-2-allyl-2-decalol	$C_{14}H_{24}O$	80.69	80.34	11.63	11.89	1.5030				133–138	7
1-Methyl-2-(*n*-propyl)-naphthalene	$C_{14}H_{16}$	91.25	91.39	8.75	8.58	1.5928	0.9904	60.37	62.98	145–146	10
1-Methyl-2-(*n*-propyl)-naphthalene picrate	$C_{20}H_{19}N_3O_7$	58.11	58.04	4.63	4.49		M. p. 82.5°				
1-Methyl-2-(*n*-propyl)-naph. trinitrobenzene	$C_{20}H_{19}N_4O_6$	60.45	60.56	4.82	4.99		M. p. 89.5°				
1-Methyl-1,2-cyp.-perhydrophenanthrene	$C_{18}H_{30}$	87.73	87.85	12.27	12.17	1.5172	0.9751	76.50	76.48	134–136	1
1-Ethyl-1,2-cyp.-1,2,3,4-tetrahydrophen.	$C_{19}H_{22}$	91.14	91.22	8.86	8.70	1.6145	1.0625	78.74	83.4	150–152	0.2
1-(*n*-Butyl)-1,2-cyp.-1,2,3,4-tetrahydrophen.	$C_{21}H_{26}$	90.59	90.92	9.41	9.05	1.5895	1.0201	88.03	91.70	140–143	0.1
2-(β-Phenethyl)-2-carbethoxy-1-cyclopentanol	$C_{16}H_{22}O_3$	73.25	72.97	8.45	8.24	1.5128				170–185	2
1-(β-Phenethyl)-1-carbethoxycyclopentane	$C_{16}H_{22}O_2$	78.65	78.53	8.25	8.06	1.5165				123–126	0.2
2-Carbethoxy-1,2-cyp.-3,4-dihydronaph.	$C_{16}H_{18}O_2$	79.30	79.28	7.49	7.46		M. p. 63–64°			125–128	0.2
2-Carbethoxy-1,2-cyp.-1,2,3,4-tetrahydronaph.	$C_{16}H_{20}O_2$	78.65	78.08	8.25	8.16	1.5314	1.096	68.14	70.55	125–128	0.4
2-Carbethoxy-1,2-cyclopentanodecalin	$C_{16}H_{26}O_2$	76.75	76.90	10.46	10.28	1.4970	1.029	71.31	71.33	116–118	0.5
2-Methylol-1,2-cyclopentanodecalin	$C_{14}H_{24}O$	80.69	80.65	11.63	11.46	1.5203					
2-Methyl-1,2-cyclopentanodecalin	$C_{14}H_{24}$	87.43	87.32	12.57	12.56	1.4950	0.9263	60.24	60.40	107–110	10
1-(*n*-Propyl)-2-methyldecalin	$C_{14}H_{26}$	86.51	86.69	13.49	13.14	1.4790	0.883	62.34	62.35	103–109	10
2-Carbethoxy-1,2-cyp.-3,4-dihydrophen.	$C_{20}H_{20}O_2$	82.16	82.13	6.89	6.87		M. p. 98–99°				
2-Carbethoxy-1,2-cyp.-perhydrophen.	$C_{20}H_{32}O_2$	78.89	79.85	10.59	10.90	1.5110				169–173	0.7
2-Methyl-1,2-cyp.-perhydrophenanthrene	$C_{18}H_{30}$	87.73	87.71	12.27	12.14	1.5130	0.965	76.55	76.65	117	0.2
1,2-Cyp.-3,4-dihydrophen.-2-carboxylic acid	$C_{18}H_{16}O_2$	81.79	81.83	6.10	6.05		M. p. 246°				
1,2-Cyclopentanoperhydrophenanthrene	$C_{17}H_{28}$	87.86	87.82	12.14	12.15	1.5160	0.973	71.95	72.10	167–170	9
4a-Methylperhydrochrysene	$C_{19}H_{32}$	87.61	87.46	12.39	12.55	1.5233	0.987	81.14	80.70	151–153	0.7
Perhydrochrysene	$C_{18}H_{30}$	87.73	87.66	12.27	12.19	1.5215				150–152	0.4

as by Perlman, Davidson and Bogert,[9] were hydrogenated to perhydrochrysenes.

1-Methyl-2-(*n*-propyl)-naphthalene was made through a series of reactions from 2-naphthol. The latter was converted to 2-hydroxy-1-naphthaldehyde by the Reimer–Tiemann reaction. The aldehyde was hydrogenated over Raney nickel to 1-methyl-2-decalol and the latter oxidized to 1-methyl-2-decalone. The decalone was converted to a tertiary alcohol with allylmagnesium bromide. Attempts to cyclodehydrate the resulting alcohol to 1-methyl-1,2-cyclopentanodecalin gave a mixture of dienes. Dehydrogenation of either the alcohol or the diene mixture in benzene gave 1-methyl-2-(*n*-propyl)-naphthalene.

Procedures

2-Carbethoxycyclopentanone.—Diethyl adipate (606 g., b. p. 135–137° (17 mm.), $n^{25}D$ 1.4256) was slowly added to a mixture of powdered sodium (100 g.), dry benzene (2.5 l.) and dry alcohol (5 ml.) held at 0–5°. After the addition of the ester the mixture was refluxed for twelve hours. The solid sodium salt was filtered off and decomposed with ice and dilute hydrochloric acid. The oil was separated and the water solution extracted twice with benzene. The oil and ether extractions were combined, washed with water and dried over anhydrous sodium sulfate. The ester (384 g. or 81%, $n^{25}D$ 1.4526) was distilled at 113–115° (20 mm.). The procedure is that suggested but not described in detail by Linstead and Meade.[11]

2-(β-Phenethyl)-2-carbethoxycyclopentanone (II).—2-Carbethoxycyclopentanone (78 g. in 50 ml. of toluene) was added to 19.5 g. of powdered potassium suspended in 750 ml. of dry toluene. The potassium was powdered in two portions in a liter flask and transferred in an atmosphere of nitrogen to the 2-liter reaction flask. No more than 15 g. of the ester was added to the flask until reaction was definitely underway. After the potassium salt of the keto ester had formed, 94.4 g. of β-phenethyl bromide was added rapidly and the mixture refluxed for twenty-eight hours. The mixture was cooled and the solid potassium bromide was separated, dissolved in water and extracted twice with benzene. The benzene and toluene solutions were combined, washed with water and dried over anhydrous sodium sulfate. The product II (96 g., 74%, $n^{25}D$ 1.5120) was distilled at 157–163° (2 mm.).

2-(β-1′-Naphthylethyl)-2-carbethoxycyclopentanone.—This compound was prepared as described above except that 221 g. of β-(1-naphthyl)-ethyl bromide[12,13] was used instead of β-phenethyl bromide. The quantities of other reagents were 37 g. of potassium, 147 g. of 2-carbethoxycyclopentanone in 1 liter of xylene. The yield was 205 g. (70%) boiling 210–215° (1 mm.).

2-(β-Phenethyl)-cyclopentanone.—The keto ester II (47 g.) in a mixture of 200 ml. of glacial acetic acid, 150 ml. of concentrated hydrochloric acid and 50 ml. of water was refluxed for six hours in an oil-bath maintained at 160–170° as by Bachmann and Struve.[13a] The cold mixture was diluted with 250 ml. of water and extracted with three 200-ml. portions of ether. The combined extracts were washed with water and dried. There was obtained by distilling at 163–166° (12 mm.) 28.4 g. of the desired product, $n^{25}D$ 1.5240.

2-(β-1′-Naphthylethyl)-cyclopentanone.—This compound, b. p. 160–165° (0.1 mm.) was obtained in 71% yield by the hydrolysis of the corresponding keto ester, by refluxing for ten hours under the conditions described just above.

1-Alkyl-1,2-cyclopentano-1,2,3,4-tetrahydro Derivatives of Naphthalene and Phenanthrene.—Several com-

(11) Linstead and Meade, *J. Chem. Soc.*, 935 (1934).

(12) Wilds, THIS JOURNAL, **64**, 1424 (1942).

(13) Hoch, *Bull. Soc. Chim.*, [5] **4**, 268 (1938).

(13a) Bachmann and Struve, THIS JOURNAL, **63**, 2589 (1941).

pounds of this type were prepared by essentially the same procedure,[4] the difference being in the particular ketone and alkyl halide used and in the reagent for ring closure. A representative procedure was to add 37 g. of 2-(β-phenethyl)-cyclopentanone (III) to a 100-ml. ether solution of methylmagnesium iodide, which had been prepared from 6 g. of magnesium and 35.5 g. of methyl iodide. The mixture was allowed to stand overnight, refluxed for one hour and decomposed in an ice-cold saturated solution of ammonium chloride. The alcohol was extracted with ether and the crude alcohol left after the evaporation of the ether used for the next step.

The crude tertiary alcohol was heated with 80 g. of phosphoric acid for twenty-five minutes under a pressure of 6 mm. in a flask suspended in an oil-bath held at 135–140°.[3] The temperature of the bath was then raised to 170° and the crude product (29.3 g.) distilled over. The 1-methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene (28.5 g., $n^{25}D$ 1.5449) was distilled from sodium at 128–129° (12 mm.). The yield for the *n*-butyl compound was 56%. The secondary alcohol 2-(β-phenethyl)-cyclopentanol (28 g.) was also dehydrated by the procedure just described to 1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene (20.8 g., $n^{25}D$ 1.5490, b. p. 131–133° (15 mm.)).

The tertiary alcohols (50 g.) resulting from the reaction of 2-(β-1′-naphthylethyl)-cyclopentanone and a Grignard reagent were cyclized with 85% sulfuric acid (25 g.) in 50 ml. of petroleum ether at 0° as described.[9] The yields for the methyl, ethyl and *n*-butyl tetrahydrophenanthrenes were 72, 44 and 35%, respectively. The methyl compound had been previously prepared[4]; it distilled at 157–160° (0.6 mm.) and had $n^{25}D$ 1.6205.

2-Carbethoxy-1,2-cyclopenteno-3,4-dihydronaphthalene.—2-(β-Phenethyl)-2-carbethoxycyclopentanone (25 g.) was placed in a 500-ml. platinum vessel, which was cooled in an ice–salt-bath while approximately 150 ml. of liquid hydrogen fluoride was added. After standing one and one-half hours in an ice–salt-bath, the reaction mixture was poured over 400 g. of ice. The product was extracted with ether, the latter washed with a 5% sodium hydroxide solution until the washings were alkaline to litmus and the ether solution washed with water. After the solution was dried and the ether distilled there was obtained a crude product (15.5 g.) distilling at 160–170° (1 mm.). Upon fractionation through a modified Widmer column there was obtained at 125–128° (0.2 mm.) 14.5 g. of product which solidified. After crystallization from 95% alcohol the m. p. was 63–64°.

2-Carbethoxy-1,2-cyclopenteno-3,4-dihydrophenanthrene.—2-(β-1′-Naphthylethyl)-2-carbethoxycyclopentanone (50 g.) was cyclized in liquid hydrogen fluoride as described above. However, the cyclization was allowed to proceed for only five minutes instead of one and one-half hours. The product, after removal of the ether used in the extraction, was crystallized from 100 ml. of hot 95% alcohol giving 33 g., m. p. 96–98°. An additional 8 g. of product was obtained by distilling the mother liquors. After recrystallization the compound had a m. p. of 98–99°.

1-Methyl-2-decalol and 1-Methyl-5,6,7,8-tetrahydro-2-naphthol.—These compounds were obtained by the hydrogenation of 2-hydroxy-1-naphthaldehyde in ethanol over Raney nickel at 200° under 3600 p. s. i. of hydrogen during two and one-half hours. The aldehyde, m. p. 79–80°, was prepared in 40% yield as described.[14] The yield of the decalol in the hydrogenation was over 80%. Combination of the higher boiling fractions from several hydrogenations indicated the yield of the tetrahydronaphthol to be about 5%.

1-Methyl-2-decalone.—1-Methyl-2-decalol (99 g.) was slowly added to a solution of 120 g. of sodium dichromate in 100 g. of concentrated sulfuric acid and 500 ml. of water, the reaction mixture being kept below 45°. Stirring was continued for thirty minutes after all the alcohol had been added. The mixture was transferred to a separatory funnel and twice swirled, not shaken, with 200 ml. of ether. The ether was separated and the water layer again extracted by shaking with ether. The combined ether extracts were washed in a 5% sodium hydroxide solution until the ether was a light amber color. After drying and removal of the ether, the ketone (80 g.) was distilled at 105–107° (7 mm.).

1-Methyl-2-allyl-2-decalol.—The decalone (65 g. in 100 ml. of ether) was added at such a rate as to give gentle refluxing to allylmagnesium bromide in 400 ml. of ether, as obtained from allyl bromide (60.5 g.) and magnesium (72.9 g.). The addition product was decomposed by carefully mixing it with 500 ml. of a saturated solution of ammonium chloride. The desired alcohol (70 g.) was distilled 133–138° (7 mm.) and dehydrated to a mixture of dienes (30 g., $n^{25}D$ 1.4985–1.5250) distilling at 99–115° (7 mm.). The dehydration of 40 g. of the alcohol was made in a stream of nitrogen with a mixture of 40 g. of phosphoric anhydride and 200 ml. of phosphoric acid held in a bath at 180°. Dehydrogenation of the mixture of dienes in benzene over a nickel-on-alumina catalyst at 350° for twelve hours, gave 1-methyl-2-propylnaphthalene, b. p. 145–146° (10 mm.), $n^{25}D$ 1.5928. The same product was obtained in 53% yield by the dehydrogenation of the decalol.

Hydrogenations.—A number of compounds were hydrogenated in chrome–vanadium steel vessels having voids of 90 to 270 ml. at 1500 and 4500 p. s. i. of hydrogen with the standard copper–chromium oxide or W-2 Raney nickel catalyst. The hydrogenations listed immediately below were over W-2 Raney nickel. Both 1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene (16 g.) and 1,2-cyclopentenonaphthalene (6.3 g.) were hydrogenated with 5 g. of catalyst in methylcyclohexane at 250° within less than an hour to 1,2-cyclopentanodecalin. 1-Methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene (22 g.) at 200° for three hours gave 1-methyl-1,2-cyclopentanodecalin. 1-Methyl-1,2-cyclopentano-1,2,3,4-tetrahydrophenanthrene (20 g.) after a preliminary treatment at 250° in methylcyclohexane was again submitted to hydrogenation with fresh catalyst at 250° for three hours to give 1-methyl-1,2-cyclopentanoperhydrophenanthrene. 1,2-Cyclopentenophenanthrene (2 g.) in methylcyclohexane at 250° for five hours gave 1,2-cyclopentanoperhydrophenanthrene. 4a-Methyl-1,2,3,4,4a,11,12,12a-octahydrochrysene (11.5 g.) in 90 ml. of methylcyclohexane at 250° for two hours gave 4a-methylperhydrochrysene. Chrysene (3.5 g.) was similarly hydrogenated to perhydrochrysene. The yields in all of the hydrogenations described above were 80–95%, the discrepancy between the amount obtained and 100% being largely due to losses in handling small quantities with relatively large amounts (5 g.) of catalyst. 2-Carbethoxy-1,2-cyclopenteno-3,4-dihydronaphthalene and 2-carbethoxy-1,2-cyclopenteno-3,4-dihydrophenanthrene were hydrogenated to the tetrahydro compounds, at 50° over W-4 Raney nickel within an hour. Conversion of the dihydro or the tetrahydro to the perhydro compounds required in the case of decalin three hours at 175°, while two hydrogenations at 250° for several hours each were necessary in order to obtain perhydrophenanthrenes free of unsaturated compounds.

The keto groups in 2-(β-phenethyl)-cyclopentanone (27.5 g.) and 2-(β-phenethyl)-2-carbethoxycyclopentanone (100 g.) in ethanol were hydrogenated over 10% of their weight of copper–chromium oxide to the corresponding pentanols in yields of 90% at 160–175° in one to one and one-half hours.

The carbethoxy group in 2-carbethoxy-1,2-cyclopentanodecalin (10 g.) was converted in 80% yield to a methylol group after thirty-six hours at 250° over 2 g. of copper–chromium oxide. 2-Carbethoxy-1,2-cyclopenteno-3,4-dihydrophenanthrene in dioxane was hydrogenated as described just above to give a methylol derivative of a hydrophenanthrene containing two double bonds per molecule according to analysis. The hydrogenation to 2-methylol-1,2-cyclopentanoperhydrophenanthrene was completed with Raney nickel at 250° in six hours. 2-

(14) Russell and Lockhard, "Organic Syntheses," Vol. XXII, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 63.

Methylol-1,2-cyclopentano-decalin (9 g.) was hydrogenated over 4 g. of nickel-on-alumina for eight hours at 325° to give a 79% yield of 2-methyl-1,2-cyclopentano-decalin. 2-Methyl-1,2-cyclopentanoperhydrophenanthrene was prepared from the methylol compound under the conditions just stated.

Summary

A number of derivatives of 1,2-cyclopentanohydronaphthalenes and of 1,2-cyclopentanohydrophenanthrenes, with a substituent in an angular position, have been prepared by development of the methods of Bardhan, Sengupta, Kon, Bougault, Bogert and Cook. The use of liquid hydrogen fluoride at 0° has made possible the cyclization in excellent yields of certain substituted β-keto esters with the formation of 1,2-cyclopentenodihydronaphthalenes and phenanthrenes, with a carbethoxy group in an angular position. The carbethoxy group in these compounds has been reduced to methylol and methyl groups. Derivatives of chrysene have been prepared by a modified Bogert–Cook synthesis. A practical synthesis of 1-methyl-2-alkylnaphthalenes from 2-naphthol has been illustrated.

MADISON, WISCONSIN RECEIVED DECEMBER 10, 1948

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE AND THE POLYTECHNIC INSTITUTE OF BROOKLYN]

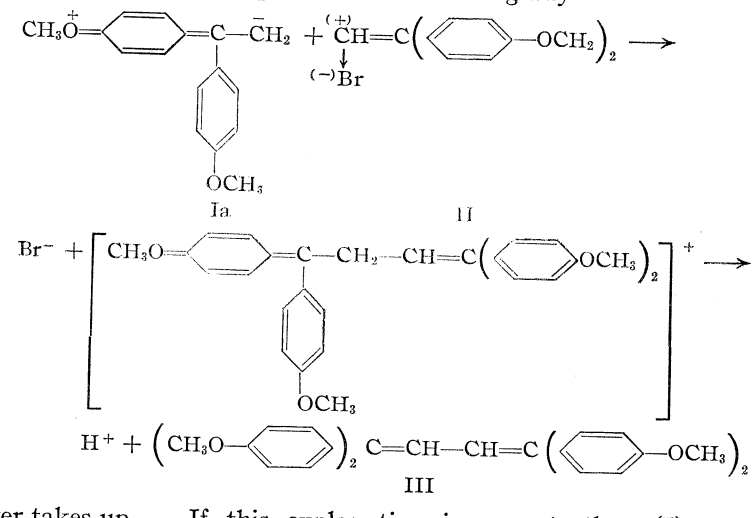
1,1,4,4-Tetraanisyl-1,3-butadiene

BY FELIX BERGMANN, JACOB SZMUSZKOWICZ AND ELCHANAN DIMANT[1]

Although 1,1-diphenylethylene can be dimerized by a variety of agents,[2] no success attended experiments to dimerize 1,1-di-(*p*-anisyl)-ethylene (I).[3] However, when we tried to convert (I) into the corresponding vinyl bromide (II) in acetic acid solution, we obtained a light-yellow substance of m. p. 207°, which we considered previously to be a "dimer."[4] Addition of sodium acetate to the bromination mixture prevented the formation of the yellow compound and stopped the reaction at the intermediate stage (II).

We have now found that the substance of m. p. 207° is not a dimer, but represents 1,1,4,4-tetraanisylbutadiene (III).[5] Proof of this structure can be given in the following way: (a) All unsaturated dimers of diarylethylenes represent butenes[2] and consequently absorb one mole of hydrogen. Compound (III) however takes up two moles of hydrogen. (b) Reaction of (II) with Grignard magnesium gives (III), in analogy to the synthesis of 1,1,4,4-tetraphenylbutadiene.[6] (c) The absorption spectrum of (III) is similar to that of 1,1,4,4-tetraphenylbutadiene (see Fig. 1).[7] Moreover, as in the latter compound, V, the spectrum remains unchanged after three hours of irradiation indicating a structure in which there is no possibility of a *cis–trans* transformation.

The direct formation of (III) during the bromination of dianisylethylene is probably to be interpreted in the following way



If this explanation is correct, then (I) and (II) should react with each other to form (III). This reaction was found to proceed smoothly at 120° and to give a quantitative yield of (III). The above reaction scheme also explains why (I) cannot be dimerized by strong acids: The intermediate carbonium ion $R_2{}^+CCH_3$, because of resonance stabilization through the *p*-methoxy group, cannot attack the β-carbon of a second ethylene molecule. In the formation of the butadiene (III) the resonance form (Ia) acts as a nucleophilic agent, directly substituting the β-bromine atom. Experiments now under hand will show whether this reaction presents a general method for the synthesis of 1,1,4,4-tetraarylbutadienes.[8]

(1) Part of a thesis, submitted to the Hebrew University, Jerusalem, 1949.

(2) Staudinger and Kon, *Ann.*, **384**, 38 (1911); E. Bergmann and Weiss, *ibid.*, **480**, 49 (1930).

(3) Schmitz-Dumont, Thömke and Diebold, *Ber.*, **70**, 175 (1937).

(4) F. Bergmann and Szmuszkowicz, THIS JOURNAL, **69**, 1777 (1947).

(5) The analytical figures for a dimer of I ($C_{32}H_{32}O_4$—calcd., C, 80.0; H, 6.7) and for III ($C_{32}H_{30}O_4$—calcd., C, 80.3; H, 6.3) are too near to permit a distinction between these two structures.

(6) Lipp, *Ber.*, **56**, 571 (1923).

(7) Hirschberg, Bergmann and Bergmann, in preparation.

(8) *E. g.*, 1,1,4,4-tetraphenylbutadiene is obtained likewise by direct interaction of 1,1-diphenylethylene with 1,1-diphenylvinyl bromide. However, due to the absence of the activating *p*-methoxy groups the conditions of this reaction are much more drastic than in the synthesis of tetraanisylbutadiene. These and other experiments will be reported in a forthcoming paper.

Experimental

1. Dianisylvinyl Bromide and Magnesium.—Because of the difficulty to induce the grignardization of this bromide we used the entrainment method:

A Grignard solution was prepared from dianisylvinyl bromide (1.6 g.), methyl iodide (0.7 g.) and magnesium (0.27 g.) in ether (40 cc.). After one hour of reflux 3 g. of (II) was added and the mixture was again refluxed for thirty-six hours. A yellow precipitate formed in the mixture. After treatment with dilute sulfuric acid the yellow material was filtered off and washed with ether; m. p. 204°, yield 0.85 g. (25%). Recrystallization from butyl acetate gave yellow needles of m. p. 206–207°, which showed no m. p. depression upon admixture of (III). No attempt was made to isolate the ether-soluble reaction products.

2. Catalytic Reduction of 1,1,4,4-Tetraanisylbutadiene.—The diene (1.2 g.), suspended in ethyl acetate (40 cc.), absorbed 155 cc. of hydrogen in the presence of Adams platinum oxide (0.5 g.) within two hours (calcd. for 31°, 755 mm., 164 cc.). The oily reduction product crystallized after treatment with *n*-hexane and was obtained from a benzene–methanol mixture as white rods of m. p. 121°; yield, 1.1 g.

Anal. Calcd. for $C_{32}H_{34}O_4$: C, 79.67; H, 7.05. Found: C, 79.64; H, 7.12.

3. Condensation of Dianisylethylene and Dianisylvinyl Bromide.—The bromide (640 mg.) and the ethylene (480 mg.) were thoroughly mixed and heated in an oil-bath with the exclusion of moisture. The mixture melts at 100–110° and gives off fumes of hydrogen bromide. After a few minutes it resolidifies. It was kept at 120° for ten hours and then treated with butyl acetate; yield 0.95 g. (quantitative), m. p. 203–204°. Recrystallization from the same solvent gave yellow rods of m. p. 206–207°, identical with the two previous preparations of (III).

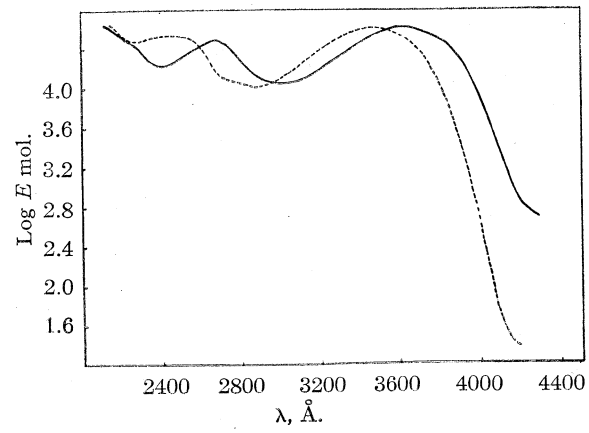


Fig. 1.—Ultraviolet absorption spectrum of — 1,1,4,4-tetraanisylbutadiene, ------ 1,1,4,4-tetraphenylbutadiene.

4. Absorption Spectra.—The spectra were measured in 95% ethanol by a Beckman quartz spectrophotometer.

Summary

The so-called "dimer," obtained in the bromination of dianisylethylene, is shown to be 1,1,4,4-tetraanisylbutadiene. The same substance can be prepared by interaction of dianisylethylene and dianisylvinyl bromide. The mechanism of this reaction is discussed.

REHOVOT, ISRAEL
BROOKLYN, N. Y.

RECEIVED DECEMBER 13, 1948

[CONTRIBUTION NO. 175 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

3-Pyridols in the Mannich Reaction[1]

BY ARTHUR STEMPEL AND ELAINE C. BUZZI

The Mannich reaction with phenols has recently been extended to 3-pyridols in attempts to prepare pyridoxine,[2] its analogs,[3] and antagonists.[4] A Mannich type of reaction employing sodium hydroxide instead of organic amines for the direct introduction of hydroxymethyl groups in 3-pyridols has also been reported.[5] Since the directive influence of the phenolic group has been studied only in cases where the ortho position is unsubstituted,[5] the following investigation of the scope and direction of the Mannich reaction with 3-pyridols was undertaken.

The substituted 3-pyridol reacted rapidly with formaldehyde and dialkylamines, alkarylamines, and heterocyclic amines such as piperidine and morpholine to give 2-(substituted amino)-methyl-3-pyridols in good yield. In all cases, the products were most readily isolated by distillation *in vacuo*. Where the products were solid, purification by distillation was still preferable to crystallization. The basic pyridols appear to be stable to heat with the exception of 2-di-*n*-butylaminomethyl-3-pyridol which showed signs of decomposition during distillation. Although attempts to prepare an analytically pure crystalline dihydrochloride of this compound were unsuccessful, it has been included since, in work to be reported at a later date, an ester of the correct analysis has been isolated. In general, these compounds have been characterized as the dihydrochlorides. The side chain basic group reacts readily with one mole of methyl bromide in the cold to give nicely crystalline quaternary salts. Quaternization of the pyridine nitrogen requires higher temperatures. Compounds of this type are listed in Table I.

By the catalytic debenzylation of 2-(N-methylbenzylaminomethyl)-3-pyridol, 2-methylaminomethyl-3-pyridol was readily prepared. In this manner, by the selection of the proper N-sub-

(1) Presented at the Meeting-in-Miniature of North Jersey Section, American Chemical Society, January 10, 1949.

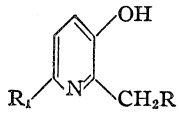
(2) Perez-Medina, Mariella and McElvain, THIS JOURNAL, **69**, 2574 (1947).

(3) Brown and Miller, *J. Org. Chem.*, **11**, 388 (1946).

(4) (a) Martin, Avakian and Moss, *J. Biol. Chem.*, **174**, 495–500 (1948); (b) Martin and Avakian, U. S. Patent 2,455,259, November 30, 1948.

(5) Urbanski, (a) *J. Chem. Soc.*, 1104–1105 (1946); (b) 132–134 (1947).

TABLE I



R	R_1	B. p. °C.	Mm.	Yield, %	M. p., °C.[c]	Hydrochloride analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$N(CH_3)_2$	H	95–96	8[a]	70	178–186	42.68	6.27	12.44	42.80	6.54	12.23
$N(C_2H_5)_2$	H	85–92	1	61	195–197	47.43	7.16	11.07	47.54	7.15	11.06
$N(C_3H_7)_2$	H	103–105	1	44	164–168	51.25	7.89	9.96	51.44	7.62	10.06
$N(C_4H_9)_2$	H	112–114	1.4	51							
NC_5H_{11}	H	153–158	11	74	201–203	49.82	6.84		50.09	6.64	
NC_4H_8O	H	163–167	12[b]	77	206–211	44.95	6.04	10.48	45.07	6.32	10.51
$N(CH_3)CH_2C_6H_5$	H	135–137	0.7	63	210–212	55.82	6.02	9.30	56.13	5.99	9.35
$NH(CH_3)$	H				231–233	39.82	5.73		40.14	5.63	
$N(CH_3)_2$	CH_3	121–125	13		202–206	45.20	6.74	11.71	44.76	6.44	11.75
$N(CH_3)CH_2C_6H_5$	CH_3	157–160	2.7		196–198	56.81[d]	6.85	8.28	56.31	6.65	8.38
$NH(CH_3)$	CH_3				226–230	42.69	6.27	12.44	42.47	6.18	12.28

[a] M. p. 56–59°. [b] M. p. 91–94°. [c] Dihydrochloride, m. p. with dec. [d] Contains 0.5 C_2H_5OH: Cl, calcd., 20.96; found, 20.69.

stituted benzylamine, a series of the secondary amines may be prepared.

The extension of this reaction to the preparation of 2-(N-methylanilinomethyl)-3-pyridol by the reaction of 3-pyridol with formaldehyde and methylaniline was unsuccessful. This compound was, however, prepared with little difficulty by the reaction of 2-bromomethyl-3-pyridol hydrobromide[5a] with methylaniline. The extreme reactivity of the bromine in the side chain made it impossible to isolate free 2-bromomethyl-3-pyridol but the base was prepared in organic solvent by the use of an excess of amine to neutralize the hydrobromic acid. This approach allows the preparation of compounds similar to those obtained by the Mannich reaction in cases where the latter reaction does not occur.

In the preparation of 2-hydroxymethyl-3-pyridol, Urbanski[5a] proved that the hydroxymethyl group is in the 2-position. As proof that the Mannich reaction took the same course, 2-diethylaminomethyl-3-pyridol was synthesized by the reaction of 2-bromomethyl-3-pyridol hydrobromide with diethylamine and on reaction with methyl bromide, (3-hydroxy-2-pyridylmethyl)-diethylmethylammonium bromide was obtained, identical with the substance made by treating the product of a Mannich reaction between 3-pyridol, formaldehyde and diethylamine with methyl bromide.

Brown and Miller[3] have carried out the Mannich reaction with 6-methyl-3-pyridol,[6] formaldehyde and diethylamine, di-*n*-butylamine and piperidine, respectively. In this work we have also used dimethylamine[4a] and methylbenzylamine and prepared the secondary amine by the catalytic debenzylation of the tertiary amine. These compounds are listed in Table I.

It is evident from the work of Urbanski[5b] and Martin and Avakian[4] that the basic group enters the 2-position in 6-methyl-3-pyridol.[7]

A further proof that the basic groups entered the 2-position and not the 4-position was established as follows. In carrying out Urbanski's preparation of 2-hydroxymethyl-3-pyridol, a fraction, isolated as the hydrochloride, was found which analyzed for $C_7H_9O_3N\cdot HCl$ indicating that two hydroxymethyl groups had entered the pyridine ring. The yield was about 20%. Heating with 48% hydrobromic acid gave the corresponding bis-bromomethyl-3-pyridol and this was then reduced to the dimethylpyridol. The product is 2,6-dimethyl-3-pyridol[8] since the same compound was obtained by reduction of 6-methyl-2-bromomethyl-3-pyridol hydrobromide prepared from 6-methyl-3-pyridol.[5b]

The bis-hydroxymethyl compound is probably formed by a secondary reaction between 2-hydroxymethyl-3-pyridol and formaldehyde. This would indicate that the Mannich reaction would probably occur in the 6-position if the 2-position were blocked.

In order to obtain 2-methyl-3-pyridol for further study of the effect of a blocking group in the 2-position, a series of reactions were carried out with the indicated yields

$$\text{3-Pyridol} + CH_2O + (CH_3)_2NH \xrightarrow{70\%} \text{2-Dimethylaminomethyl-3-pyridol} \xrightarrow[87\%]{Ac_2O}$$

(6) McElvain and Goese, THIS JOURNAL, **65**, 2233 (1943), and Parker and Shive, *ibid.*, **69**, 63 (1947), have shown that the product isolated by sulfonation of α-picoline and subsequent alkali fusion is 6-methyl-3-pyridol and not the 2-methyl-3-pyridol claimed by Brown and Miller[3] and Wolff, U. S. Patent 1,880,645-6 (1932).

(7) The structure of 2-methyl-4-dimethylaminomethyl-3-pyridol proposed by Brown and Miller[3] for the Mannich product was accepted by Martin and Avakian[4] and their end-product was, therefore, erroneously assumed to be 2-methyl-4-hydroxymethyl-3-pyridol.

(8) Plazek, *Ber.*, **72**, 577 (1939), prepared 2,6-dimethyl-3-pyridol by nitration of 2,6-lutidine, reduction of the nitro compound to the amine, and diazotization. The product melted at 209°, and the material obtained above melted at 203–204° (uncor.).

$$\text{2-Acetoxymethyl-3-acetoxypyridine} \xrightarrow[82\%]{48\%\ HBr} \text{2-Bromomethyl-3-pyridol hydrobromide} \xrightarrow[90\%]{H_2 + Pd} \text{2-Methyl-3-pyridol hydrobromide}$$

The over-all yield in a typical run was 45%.

The process has the advantage that the product of the Mannich reaction is readily purified by distillation while the Urbanski method yields an impurity in the preparation of 2-hydroxymethyl-3-pyridol, as shown above, which must be removed by fractional crystallization.

The final proof that the basic group would enter in the 6-position if the 2-position were blocked was hoped to be obtained by the conversion of 2-methyl-3-pyridol to 2,6-dimethylpyridol by the series of reactions shown above for the preparation of 2-methyl-3-pyridol from 3-pyridol. The reactions of 2-methyl-3-pyridol have proved to be unlike those of the isomeric 6-methyl-3-pyridol. We have as yet been unable to isolate any pure product from the reaction of 2-methyl-3-pyridol with formaldehyde and dimethylamine or sodium hydroxide. When the first reaction of the series was carried out using diethylamine, the crude product was acetylated directly without further purification but instead of the expected replacement of the basic group by an acetoxy group, a readily distillable acetate was obtained which on hydrolysis by heating with 48% hydrobromic acid gave the hydrobromide of 2-methyl-6(?)-diethylaminomethyl-3-pyridol. The unusual resistance of the basic group to attack by acetic anhydride is in marked contrast with the behavior of the isomeric 6-methyl-2-diethylaminomethyl-3-pyridol.[4]

Investigation of the position of the basic group in the Mannich reaction with 2-methyl-3-pyridol is still in progress, since the possibility of reaction in the 4-position has not been ruled out. However, Perez-Medina, Mariella and McElvain[2] could not isolate any product after an attempted Mannich reaction with 2-methyl-5-hydroxymethyl-3-pyridol.

There is also the possibility of reaction on the methyl group in the α-position although α-picoline itself gives only small yields of a Mannich base. In the case of 6-methyl-3-pyridol there has been no evidence of reaction on the methyl groups.

Experimental

The preparation of 2-dimethylaminomethyl-3-pyridol is representative of the compounds listed in Table I.

2-Dimethylaminomethyl-3-pyridol.—To a solution of 41 g. of 3-pyridol in 65 cc. of water and 67 cc. of a dimethylamine solution (19.5 g. of dimethylamine), 36 cc. of a 35% formalin solution was added. After heating on a steam-bath for two hours, the solvent was removed by distillation *in vacuo* and the residue distilled. The fraction distilling at 86–96° (3.7 mm.) was collected as a light yellow oil that crystallized rapidly; yield, 46 g. (70%). It could be further purified by sublimation *in vacuo* at 60° and 0.3 mm.; m. p. 56–59°.

Anal. Calcd. for $C_8H_{12}ON_2$: N, 18 41. Found: N, 17.86.

Diacetate of 2-Hydroxymethyl-3-pyridol.—A solution of 10 g. of 2-dimethylaminomethyl-3-pyridol in 35 cc. of acetic anhydride was refluxed for one and one-half hours. The solution turned dark brown soon after heating began. Excess acetic anhydride and acetic acid were removed *in vacuo* and the residue distilled. The product was a light yellow oil distilling at 109–110° (0.8 mm.); literature,[5a] 118–122° (4 mm.); yield, 12 g. (87%).

2-Bromomethyl-3-pyridol Hydrobromide.—A solution of 11 g. of the diacetate of 2-hydroxymethyl-3-pyridol in 60 cc. of 48% hydrobromic acid was refluxed for one-half hour. After distillation of 45 cc. of hydrobromic acid, large crystals of 2-bromomethyl-3-pyridol hydrobromide formed on cooling. The crystals were filtered and washed with a small amount of cold water and acetone: yield, 11.6 g. (82%); m. p. 187–188° (dec.); literature,[5a] 182–184°. A portion of the product was recrystallized from a mixture of methanol and ether; m. p. 186–188° (dec.).

Anal. Calcd. for $C_6H_7ONBr_2$: C, 26.79; H, 2.62; N, 5.21. Found: C, 27.08; H, 2.59; N, 5.35, 5.23.

2-Methyl-3-pyridol.—A solution of 125 g. of 2-bromomethyl-3-pyridol hydrobromide in 1 liter of methanol containing 4–5 g. of 3% palladium on charcoal was shaken at room temperature with hydrogen. The theoretical quantity was taken up rapidly. After removal of the catalyst by filtration, most of the solvent was distilled off and anhydrous ether added to turbidity. Crystals of 2-methyl-3-pyridol hydrobromide formed: yield, 79 g. (90%); m. p. 195–197°. Recrystallization from a mixture of methanol and ether did not change the melting point.

Anal. Calcd. for C_6H_8ONBr: C, 37.92; H, 4.24; N, 7.37. Found: C, 37.72; H, 4.23; N, 7.47, 7.33.

The free base melted at 163–165°; literature, 160–161°,[5b] 167–168°.[9]

2-(N-Methylanilinomethyl)-3-pyridol.—A solution of 23 g. of methylaniline in 10 cc. of chloroform was added slowly to a stirred suspension of 27 g. of 2-bromomethyl-3-pyridol hydrobromide in 250 cc. of chloroform. The temperature rose from 26 to 42° and all the material went into solution. The solution was then heated slowly to reflux. When the temperature reached 50°, a crystalline solid began to separate. The mixture was refluxed for one hour, cooled and the crystalline product filtered off: yield, 26 g. (88%); m. p. 176–180° (dec.). Neutralization with sodium carbonate gave a white crystalline precipitate of 2-(N-methylanilinomethyl)-3-pyridol. After recrystallization from 80% ethanol, the product melted at 136–138°; yield, 16 g.

Anal. Calcd. for $C_{13}H_{14}ON_2$: C, 72.87; H, 6.55; N, 13.06. Found: C, 72.91; H, 6.59; N, 12.67.

(3-Hydroxy-2-pyridylmethyl)-diethylmethylammonium Bromide.—To a suspension of 5 g. of 2-bromomethyl-3-pyridol hydrobromide in 50 cc. of chloroform, 6 cc. of diethylamine was added slowly. The mixture became very warm and all the solid went into solution. After refluxing for one-half hour, the solvent was boiled off and the residue dissolved in water. After neutralization with sodium bicarbonate and evaporation to dryness, an acetone extract of the residue was treated with a 25% solution of methyl bromide in acetone. On standing in the refrigerator, crystals of (3-hydroxy-2-pyridylmethyl)-diethylmethylammonium bromide formed. After recrystallization from a mixture of methanol and ether, the product melted at 132–133° (dec.).

Anal. Calcd. for $C_{11}H_{19}ON_2Br$: C, 48.01; H, 6.96; N, 10.18. Found: C, 48.08; H, 7.13; N, 10.04.

2-Methylaminomethyl-6-methyl-3-pyridol Dihydrochloride.—To a prehydrogenated suspension of 1 g. of 3% palladium on charcoal in 50 cc. of methanol, 2.0 g. of (3-hydroxy-6-methyl-2-pyridylmethyl)-methylbenzylamine dihydrochloride was added. The theoretical amount of hydrogen was taken up after shaking for one-half hour at atmospheric pressure. The catalyst was removed by filtration and the solvent distilled off. The product was recrystallized from ethanol; m. p. 226–230° (dec.).

(9) Dornow, *Ber.*, **73B**, 78 (1940).

2,6-bis-Hydroxymethyl-3-pyridol Hydrochloride.—Nineteen grams of 3-pyridol was dissolved in 100 cc. of an aqueous solution containing 8 g. of sodium hydroxide. After addition of 42 cc. of a 35% formaldehyde solution, the reaction mixture was kept at room temperature for one hour and then heated on the steam-bath for two hours. The color was a light amber. It was then cooled, acidified with 15 cc. of glacial acetic acid, concentrated to dryness *in vacuo*, and the solid residue extracted with 2 liters of boiling acetone. After removal of the acetone by distillation, the residue was dissolved in about 200 cc. of 9 *N* alcoholic hydrochloric acid. Crystals formed within five minutes. They were kept in the refrigerator overnight, filtered, washed with acetone, and dried; yield, 28 g. About 16 g. of this material was dissolved in 50 cc. of water and acetone added to turbidity. Overnight in the refrigerator, 1.4 g. of 2-hydroxymethyl-3-pyridol hydrochloride crystallized. The melting point was not sharp but the compound darkened slowly above 170° and then decomposed above 200°. On addition of acetone to the filtrate, an additional 2.6 g. of the same material was isolated. At this point, 1175 cc. of acetone had been added. Addition of 900 cc. of acetone to the filtrate gave 10.5 g. of crystalline material, m. p. 135–139°. This fraction was recrystallized from 30 cc. of water and 300 cc. of acetone. This gave 5 g. of 2,6-bis-hydroxymethyl-3-pyridol hydrochloride, m. p. 143–146°. An additional 3.6 g. melting at 136–144° was isolated from the mother liquors. Recrystallization of the product melting at 143–146° from a mixture of methanol and ether raised the m. p. to 145–147°.

Anal. Calcd. for $C_7H_{10}O_3NCl$: C, 43.87; H, 5.26; N, 7.31; Cl, 18.50. Found: C, 44.37; H, 5.37; N, 7.61; Cl, 18.21, 18.52.

2,6-bis-Bromomethyl-3-pyridol Hydrobromide.—A solution of 4.5 g. of 2,6-bis-hydroxymethyl-3-pyridol hydrochloride in 100 cc. of 48% hydrobromic acid was refluxed for one hour. On concentration to a small volume *in vacuo*, crystals of 2,6-bis-bromomethyl-3-pyridol hydrobromide separated. They were filtered, washed with cold water, acetone, and ether, and dried, m. p. 186–188°. Two recrystallizations from a mixture of methanol and ether raised the m. p. to 188–190°.

Anal. Calcd. for $C_7H_8ONBr_3$: C, 23.23; H, 2.23; N, 3.87. Found: C, 23.16; H, 2.04; N, 3.88.

2,6-Dimethyl-3-pyridol.—To a prehydrogenated suspension of 1 g. of 3% palladium on charcoal in 50 cc. of methanol, 2.4 g. of 2,6-bis-bromomethyl-3-pyridol hydrobromide was added. The theoretical amount of hydrogen was taken up rapidly at room temperature and atmospheric pressure. After removal of the catalyst by filtration, most of the solvent was distilled off. Anhydrous ether was then added to turbidity and crystallization of 2,6-dimethyl-3-pyridol hydrobromide occurred rapidly on scratching; m. p. 183–185°. Recrystallization from a mixture of methanol and ether did not change the m. p.

Anal. Calcd. for $C_7H_{10}ONBr$: C, 41.20; H, 4.94; N, 6.86. Found: C, 40.83; H, 5.03; N, 6.90, 6.98.

The free base, m. p. 200–203°, was purified for analysis by sublimation at 0.4 mm. and a bath temperature of 100–110°. The sublimate melted at 202.5–204°.

Anal. Calcd. for C_7H_9ON: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.12; H, 7.40; N, 11.38, 11.47.

Acetate of 2-Methyl-6(?)-diethylaminomethyl-3-pyridol.—To a solution of 10.9 g. of 2-methyl-3-pyridol and 7.3 g. of diethylamine in 25 cc. of water, 9 cc. of a 35% formaldehyde solution was added. The mixture was kept at room temperature for five days, and then warmed for one hour on a steam-bath. An oily layer, that seemed to be soluble in the cold and insoluble when hot, began to separate soon after heating began. On removal of the solvent by distillation *in vacuo*, the residue set to a solid. It was dissolved in 75 cc. of acetic anhydride and refluxed for one hour. The excess of acetic anhydride was distilled off *in vacuo* and the residue then distilled. A rough cut boiling at 78° (5 mm.)–120° (0.5 mm.) was taken and then redistilled. The acetate was collected in the fraction boiling at 111–115° (1.4 mm.); yield, 10.5 g.

2-Methyl-6(?)-diethylaminomethyl-3-pyridol.—A solution of 10.5 g. of acetate of 2-methyl-6(?)-diethylaminomethyl-3-pyridol in 50 cc. of 48% hydrobromic acid was refluxed for one-half hour. After removal of 35 cc. of hydrobromic acid by distillation, addition of acetone to the cooled residue gave crystals of 2-methyl-6(?)-diethylaminomethyl-3-pyridol hydrobromide. The product was filtered and washed with acetone. It melted at 219–220° (dec.); yield, 12 g. Recrystallization from a mixture of methanol and ether did not change the melting point.

Anal. Calcd. for $C_{11}H_{20}ON_2Br_2$: C, 37.10; H, 5.66; N, 7.87. Found: C, 37.29; H, 5.59; N, 7.91.

The free base was liberated with sodium carbonate, the solution evaporated to dryness *in vacuo*, and the base extracted with acetone. After removal of acetone, the free base was recrystallized from benzene; m. p. 139–141°.

Anal. Calcd. for $C_{11}H_{18}ON_2$: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.20; H, 9.03; N, 14.26.

Acknowledgment.—The authors wish to express their appreciation to Dr. J. A. Aeschlimann for many helpful discussions during this investigation. We are also indebted to Mr. L. A. Dolan for the preparation of 3-pyridol and to Dr. A. Steyermark and his staff for the microanalyses reported in this paper.

Summary

Methods of preparation of 2-(substituted amino)-methyl-3-pyridols have been described.

The Mannich reaction with 6-methyl-3-pyridol has been extended.

An improved synthesis of 2-methyl-3-pyridol is described.

2,6-bis-Hydroxymethyl-3-pyridol has been isolated as a by-product in the preparation of 2-hydroxymethyl-3-pyridol.

The behavior of 2-methyl-3-pyridol in the Mannich reaction is discussed.

NUTLEY, NEW JERSEY RECEIVED FEBRUARY 23, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Equilibria of Nickel Hydroxide, $Ni(OH)_2$, in Solutions of Hydrochloric Acid and Sodium Hydroxide at 25°

BY KARL H. GAYER AND A. B. GARRETT

The purpose of this investigation was to obtain data on the equilibria of nickel hydroxide in dilute solutions of sodium hydroxide and hydrochloric acid. Such data make possible (1) the determination of the character of the ions in dilute solutions, (2) the evaluation of the free energy of formation of these ions, (3) the evaluation of the solubility and the solubility product of nickel hydroxide, and (4) the amphoteric nature of the hydroxide.

Previous work on nickel hydroxide is at variance as to the magnitude of the water solubility and the solubility product. Almkvist[1] reported the solubility of nickel hydroxide to be 1×10^{-4} mole at 20°. Britton[2] calculated the solubility product to be 2.07×10^{-17} at 25°; while Wijs[3] reported a value of 1.6×10^{-14}.

No work is reported which can be used to show the complete record of the behavior of nickel hydroxide in acid and basic solutions; data for that record are presented in this paper.

Procedure

The general procedure is similar to that in a previous paper by Garrett and Heiks.[4]

Water.—Triply distilled water was used. It was boiled to free it from carbon dioxide and oxygen then it was stored under nitrogen.

Sodium Hydroxide Solutions.—Baker and Adamson Reagent sodium hydroxide pellets were dissolved in freshly boiled distilled water; barium hydroxide was added in slight excess to precipitate all the carbonate. The solutions were standardized against potassium acid phthalate using phenolphthalein indicator.

Nickel Nitrate Solutions.—Mallinckrodt C. P. reagent was used to prepare the hydroxide and to prepare the standards for the colorimetric determination of nickel.

Hydrochloric Acid Solutions.—Standard solutions for analysis and for the solubility measurements were prepared from C. P. reagent and standardized gravimetrically.

Other Reagents.—Nickel ammonium sulfate was used to prepare a second set of colorimetric and polarographic standards. A 1% alcoholic solution of dimethylglyoxime was prepared as specified by Sandell.[5]

Nickel Hydroxide.—The nickel hydroxide was prepared is an atmosphere of nitrogen. A hot solution containing 1 g. of nickel nitrate hexahydrate per liter of water was precipitated with an equal volume of 0.02 molar solution of sodium hydroxide. Ten two-liter washings of distilled water sufficed to give pure nickel hydroxide as evidenced by the total absence of sodium from a flame test.

Equilibration.—Two 180-ml. samples contained in 200-ml. round-bottom flasks were always prepared at each concentration of alkali or acid. One sample was agitated in a thermostat at 35° for a period of five to seven days, then transferred to the thermostat at 25 ± 0.02° for an additional period of seven days. The mates were placed directly in the 25° thermostat for five to seven days. By this means, equilibrium was approached from supersaturation and undersaturation. Both values were found to check within experimental limits.

Sedimentation.—After the completion of the agitation period, the flasks were clamped in an upright position in the 25° thermostat, and allowed to sediment for seven days.

Filtration.—The flasks were opened and the contents removed under an atmosphere of nitrogen to a covered sintered glass funnel and from this into a glass-stoppered bottle.

Measurement of Hydrogen Ion Concentration.—The *p*H values of the equilibrated samples were obtained by using a Beckman portable a. c., glass electrode. The meter was calibrated with potassium acid phthalate–sodium hydroxide buffer at *p*H 4, with disodium phosphate–monopotassium phosphate buffer at *p*H 7 and with boric acid–sodium hydroxide buffer at *p*H 10.

Analysis of Nickel.—The nickel analysis of the equilibrated samples was made with a Lumetron spectrophotometer using dimethylglyoxime to produce the colored complex; the method is described by Sandell.[5] The analyses were reproducible to ±2%.

The data are collected in Tables I and II and are shown graphically in Figs. 1, 2, and 3. Figure 1 shows the change of solubility of nickel hy-

TABLE I

SOLUBILITY OF $Ni(OH)_2$ IN SOLUTIONS OF NaOH AT 25°

Moles of NaOH/1000 grams H_2O	Moles of $Ni(OH)_2$/1000 grams H_2O	$K_2 = \frac{m_{HNiO_2^-} \times \gamma_{HNiO_2^-}}{m_{OH^-} \times \gamma_{OH^-}}$
[a] 1.60×10^{-3}	1×10^{-7}	
1.00×10^{-2}	4×10^{-7}	
1.00×10^{-1}	2×10^{-6}	3×10^{-5}
1.00	6×10^{-6}	9×10^{-6}
8.00	7×10^{-6}	Ionic strength too high to calculate K_2 accurately
10.00	4×10^{-6}	
15.00	5×10^{-6}	
	Av.	6×10^{-5}

[a] By radioactive tracer.

TABLE II

SOLUBILITY OF $Ni(OH)_2$ IN SOLUTIONS OF HCL AT 25°

Moles of HCl/1000 grams H_2O (initial concn.)	a_{H^+} in 1000 g. H_2O from *p*H values at equilibrium	Moles of $Ni(OH)_2$/1000 g. H_2O	$K_6 = \frac{m_{Ni^{++}} \times \gamma_{Ni^{++}}}{m^2_{H^+} \times \gamma^2_{H^+}}$
0.0000	.....	0.00010[a]	.....
.0025	1.35×10^{-7}	.0013	$6.4 \times 10^{+10}$
.0056	1.68×10^{-7}	.0029	8.6
.0100	2.24×10^{-7}	.0053	8.1
.0160	3.09×10^{-7}	.0083	6.5
.0236	3.72×10^{-7}	.0120	6.3
.0308	4.27×10^{-7}	.0160	6.1
.0447	5.13×10^{-7}	.0230	5.8
.0523	5.37×10^{-7}	.0271	5.9
.0811	6.61×10^{-7}	.0413	5.6
.1001	7.08×10^{-7}	.0511	5.8
		Av.	$6.5 \times 10^{+10}$

[a] Extrapolated value.

(1) Almkvist, *Z. anorg. Chem.*, **103**, 240 (1918).
(2) Britton, *J. Chem. Soc.*, **127**, 2110 (1925).
(3) Wijs, *Rev. trav. chim.*, **44**, 663 (1925).
(4) Garrett and Heiks, THIS JOURNAL, **63**, 562 (1941).
(5) Sandell, "Colorimetric Determination of Traces of Metals," Interscience Publishers, New York, N. Y., 1945, p. 339.

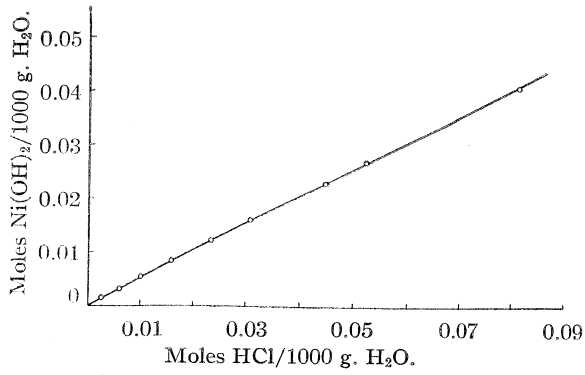


Fig. 1.—Solubility of nickel hydroxide in hydrochloric acid solutions.

droxide in hydrochloric acid solutions and Fig. 2 shows the change of solubility of nickel hydroxide in dilute hydrochloric acid solutions with the

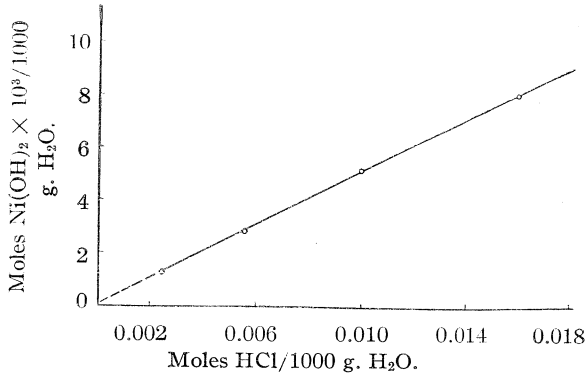


Fig. 2.—Solubility of nickel hydroxide in hydrochloric acid solution.

extrapolation to *p*H 7. Figure 3 shows the change of nickel hydroxide solubility near *p*H 7. Due to the extremely low solubility of nickel hydroxide in water and basic solutions, the inflection of the curve in Fig. 3 is drawn by interpolation and shows the most probable change.

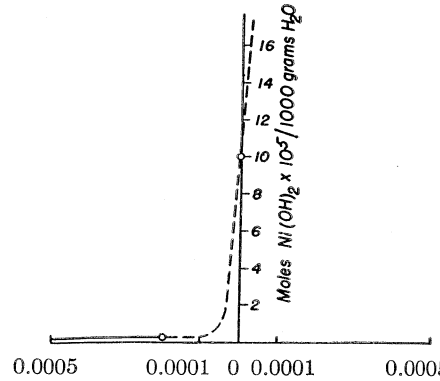


Fig. 3.—Change of nickel concentration near *p*H 7.

The high solubility of nickel hydroxide in acid solutions along with the *p*H values of these solutions (in the order of *p*H 7) and the low solubility of nickel hydroxide in basic solutions give qualitative evidence that nickel hydroxide is a strong base. Quantitative evidence for the basic character of nickel hydroxide is given by the values of the acidic and basic ionization constants.

The solubility of nickel hydroxide in sodium hydroxide solution was checked by means of several radioactive tracer experiments using the $^{58}_{27}Ni$ isotope (half life of 36 hours). The nickel was prepared by alpha bombardment of iron in The Ohio State University Cyclotron.

The values for the activity coefficients for hydroxyl ions and divalent nickel ions were taken from Harned and Owen.[6]

General Equilibria.—In general the possible equilibria of nickel hydroxide in neutral, acidic and alkaline solutions may be represented by equations (1) to (8).

(1) $Ni(OH)_2(s) \rightleftarrows Ni^{++} + 2OH^-$

(2) $Ni(OH)_2(s) \rightleftarrows NiOH^+ + OH^-$

(3) $Ni(OH)_2(s) + OH^- \rightleftarrows HNiO_2^- + H_2O$

(4) $Ni(OH)_2(s) + 2OH^- \rightleftarrows NiO_2^= + 2H_2O$

(5) $Ni(OH)_2(s) + H^+ \rightleftarrows NiOH^+ + H_2O$

(6) $Ni(OH)_2(s) + 2H^+ \rightleftarrows Ni^{++} + 2H_2O$

(7) $Ni(OH)_2(s) \rightleftarrows HNiO_2^- + H^+$

(8) $Ni(OH)_2(s) \rightleftarrows Ni(OH)_2$

The value of K_8 is in the order of 10^{-7} and is too small to affect the values of K_3 and K_6 within the limits of their determinations from these data.

Equilibria in Basic Solutions.—Unfortunately the solubility of nickel hydroxide in alkaline solutions up to 15 molar sodium hydroxide was found to be so slight that only estimates of its solubility could be made by the analytical means available. We can make the very probable assumption that the solubility of nickel hydroxide in alkali is due to the reaction indicated by equation (3).

$$Ni(OH)_2(s) + OH^- \rightleftarrows HNiO_2^- + HOH \quad (3)$$

Values of K_3 calculated over the range of 0.0016 to 0.1 molar sodium hydroxide give an average value of $K_3 = 6 \times 10^{-5} \pm 5 \times 10^{-5}$ with a corresponding ΔF° of 6000 cal.

Using the value for K_3 and K_w, the ionization constant for water at 25°, the ionization constant K_7

$$Ni(OH)_2(s) \rightleftarrows HNiO_2^- + H^+ \quad (7)$$

for nickel hydroxide was computed

$$K_7 = K_3K_w/a_{H_2O} = 6 \times 10^{-19}$$
$$\Delta F^\circ = 25{,}000 \text{ cal.}$$

Equilibria in Acid Solutions.—The data of columns 1 and 3 of Table II indicate that equation 6 can account for the chemical change involved; if any $NiOH^+$ ions are present, they must

(6) Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943, pp. 384, 423.

be so in small amounts. The value of K_6 was obtained by the use of the a_{H^+} measured by the glass electrode

$$Ni(OH)_2(s) + 2H^+ \rightleftarrows Ni^{++} + 2H_2O \qquad (6)$$

$$K_6 = \frac{m_{Ni^{++}}\gamma_{Ni^{++}}}{m^2_{H^+}\gamma^2_{H^+}} = 6.5 \times 10^{10}$$

$$\Delta F^\circ = -15{,}000 \text{ cal.}$$

the values of $m_{Ni^{++}}$ are given in column 3 of Table II, and the values of $\gamma_{Ni^{++}}$ were obtained from a table of activity coefficients for divalent ions compiled by Harned and Owen.[6] Further evidence that the reaction indicated by equation 5 has little or no effect on the value of K_6 is the constancy of K_6 over the concentration range of $m_{HCl} = 0$ to 0.1. The error in K_6 is in the order of $\pm 0.5 \times 10^{10}$.

The high solubility of nickel hydroxide in acid solution and its low solubility in alkaline solution indicate qualitatively that nickel hydroxide is a relatively strong base. Finally, the calculated values of the acid and base constants of nickel hydroxide fully verify the strong basic character.

The Value of the Water Solubility at 25°.—The value of the water solubility of nickel hydroxide, 1.0×10^{-4}, was determined by extrapolating the solubility of nickel hydroxide in dilute acid solution of $m_{HCl} = 0$ (see Figs. 2 and 3). The extrapolation was made graphically (large scale) by the aid of the value of the slope of the line obtained in 0.006 to 0.05 molal acid solutions. This procedure was necessary because the solubility of nickel hydroxide in water is below that which can be determined accurately by any classical chemical method. Furthermore, this is probably a more accurate value than could be obtained by direct measurement, were a satisfactory method of analysis available, because of the error involved in a direct measurement due to (1) any adsorbed hydroxyl ions on the nickel hydroxide and (2) the colloidal nature of highly purified samples of nickel hydroxide. The value of the water solubility is probably good to $\pm 0.5 \times 10^{-4}$.

The Solubility Product Constant.—From the value of the ion product K_w of water and $K_6 = 6.5 \times 10^{+10}$ obtained from the solubility of nickel hydroxide in acid, the solubility product constant K_1 was calculated for the equation

$$Ni(OH)_2(s) \rightleftarrows Ni^{++} + 2OH^- \qquad (1)$$

$$K_1 = \frac{K_6 K^2_w}{a^2_{H_2O}} = m_{Ni^{++}}\gamma_{Ni^{++}} m^2_{OH^-}\gamma^2_{OH^-}$$

$$K_1 = 6.5 \times 10^{-18}$$

$$\Delta F^0 = 23{,}000 \text{ cal.}$$

Summary

The solubility of nickel hydroxide has been determined in dilute acid and base at 25 ± 0.02°. The data show nickel hydroxide to be a relatively strong base. The reactions occurring in basic and acid solution are shown by equations

$$Ni(OH)_2(s) + OH^- \rightleftarrows HNiO_2^- + H_2O \qquad (3)$$

$$Ni(OH)_2 + 2H^+ \rightleftarrows Ni^{++} + 2H_2O \qquad (6)$$

The value for the solubility product of nickel hydroxide, is 6.5×10^{-18}. The value for the water solubility of nickel hydroxide is 1.0×10^{-4}. The acid dissociation constant of nickel hydroxide is 6×10^{-19}.

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[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

Measurement of the Capacity of the Electrical Double Layer at a Mercury Electrode

BY DAVID C. GRAHAME

It has long been known that the slope of the electrocapillary curve of a liquid metal in a salt solution gives the surface charge density of electricity at the interface.[1-5] In a like manner the second derivative of the electrocapillary curve gives the differential capacity,[3,4] a quantity which can also be measured directly with fair precision. It is less well known that from the interfacial tension or from the differential capacity one can obtain a considerable amount of further information about the electrical double layer. For example, it is possible to calculate the charge contributed by each ion separately,[4] the entropy and enthalpy changes associated with the electrochemical process which accompanies an infinitesimal transfer of charge through the cell,[6] and other less easily described properties.[6] In addition there are certain non-thermodynamic properties which are obtained by combining the thermodynamic properties with quantities calculated from the kinetic theory of the electrical double layer.[4] All this has been discussed elsewhere.

It is a matter of great difficulty to make interfacial tension measurements with sufficient precision to serve for these calculations, and we have accordingly attempted to develop apparatus for the precise measurement of the differential capacity of the double layer at a mercury surface. Two models of this apparatus have already been described.[3,7] Considerable changes have now

(1) Lippmann, *Ann. Physik Chem.* (*Wied. Ann.*), **11**, 316 (1880).
(2) Koenig, *J. Phys. Chem.*, **38**, 111, 339 (1934).
(3) Grahame, THIS JOURNAL, **63**, 1207 (1941).
(4) Grahame, *Chem. Revs.*, **41**, 441 (1947).
(5) Grahame and Whitney, THIS JOURNAL, **64**, 1548 (1942).
(6) Grahame, *J. Chem. Phys.*, **16**, 1117 (1948).
(7) Grahame, THIS JOURNAL, **68**, 301 (1946).

been made, and it is the principal function of the present paper to describe these changes, which are of importance to anyone planning a duplication or extension of the work. Some results obtained with the new form of the apparatus are also described.

Experimental Method

In principle the method remains unchanged. A droplet of mercury forms at the tip of a fine capillary (o. d. *ca.* 0.10 mm., i. d. *ca.* 0.04 mm.), Fig. 1, under the deaerated solution to be investigated. A second electrode, for which we use a platinized platinum gauze sphere Pt, with openings at the poles, surrounds the mercury droplet symmetrically. The system mercury–solution–platinum now forms a cell somewhat like a conductivity cell except that we are primarily interested in its capacity rather than its resistance. This cell is made the fourth arm of a bridge which differs from conventional conductance bridges primarily in that it measures the *series capacitance* of the cell. Stray capacitance and inductance must be severely limited, the effects being minimized by the use of a low frequency; 1000 cycles is convenient and sufficiently low, with good technique, for tenth-normal and possibly hundredth-normal salt solutions, but below this concentration the unavoidable bridge errors become large and a lower frequency must be used. The results obtained are believed to be independent of frequency within the experimental error.[7]

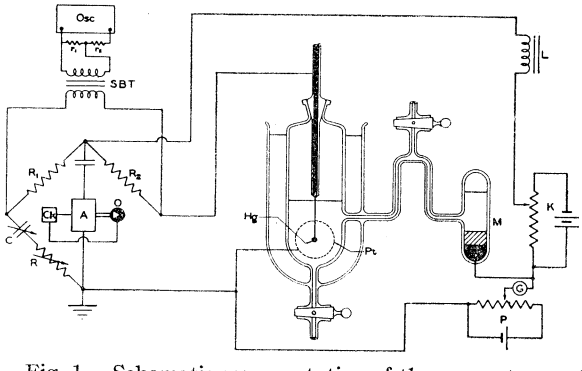

Fig. 1.—Schematic representation of the apparatus used for the determination of the capacity of the electrical double layer at a mercury–solution interface. The cell shown schematically here is depicted in more detail in Fig. 3 of the following paper.

The capacity of the double layer in contact with the platinum is enormous because of its relatively large surface area. Thus the observed capacity is sensibly the capacity of the double layer in contact with the mercury, the two capacitances being in series.

Because the capacity of the electrical double layer depends upon the d. c. potential, an additional electrode is required. Usually a calomel electrode is employed, especially when chlorides are to be investigated. A type K potentiometer, K, is used to impose a potential upon the double layer, as shown in Fig. 1. In order to keep the d. c. resistance from the mercury to the potential-fixing electrode as low as possible, the platinum gauze electrode in the solution is employed as the potential-fixing electrode. Since its potential wanders in an unpredictable manner relative to that of the calomel electrode M, the potential difference between the two is measured with a conventional potentiometer–galvanometer system P–G, and the difference applied as a correction to the potential imposed by the other potentiometer. In the circuit shown, the potentiometer P not only measures the correction but also applies it simultaneously, so that no actual reading of the magnitude of the correction is required.

An important new feature of the circuits was the inclusion of wholly different timing methods from those previously described. Since the mercury droplet is constantly growing in size until it falls, it is necessary to measure the time interval from the moment of its "birth" to the moment at which the bridge is balanced. Knowing the rate of flow of the mercury, which is also measured, it is then a simple calculation to find the area of the droplet at the moment of bridge balance. It may be mentioned in passing that the measured capacity is proportional to this area, other things being equal, as accurately as can be measured from 0.2 sec. after the "birth" of the droplet until just before the moment of fall, perhaps five seconds later.

The new method of timing is as follows: When a droplet falls, it produces a very abrupt change in the amplitude of the signal representing the degree of unbalance of the bridge. This signal is rectified or "detected" and applied to the grid of a thyratron which actuates a relay which starts a high-speed (2 r. p. s.) interval timer, Ck, Fig. 1. The interval timer is arranged so that with every revolution of the hand it produces a pulse which starts the sweep of the oscilloscope on which the bridge unbalance is presented. The sweep presents an expanded view of the manner in which the state of the bridge balance varies with time. A long-persistence screen is necessary, since successive sweeps do not present the same pattern. When R and C are adjusted to values such that a moment of perfect balance occurs during the lifetime of a droplet, one sees on the oscilloscope screen a pattern like that depicted in Fig. 2. The moment at which this state of perfect balance occurs is ascertained by means of auxiliary markers obtained from the clock and presented on the screen.

The instrumental accuracy is estimated at 0.1% or better in tenth-normal solutions under not-too-unfavorable conditions. Systematic errors not associated with the electrical circuits as such probably produce somewhat greater errors, perhaps up to 1% in unfavorable cases.

The rate of flow of the mercury is ascertained

by weighing the mercury delivered from the capillary over an interval of about 500–1000 seconds. The rate of flow was usually of the order of 0.8 mg./sec., although capillaries with rates ranging from 0.5 to 1.5 mg./sec. have been used satisfactorily.

The solutions were deaerated with nitrogen. It was not found necessary to remove the last traces of oxygen.

Experimental Results

In the development of the above technique, a tenth-normal solution of twice recrystallized potassium chloride in conductivity water was most often used for test purposes. Most of the measurements at this concentration were taken at 1000 cycles and at 25°. The results obtained are given in Table I, together with values of the first and second integrals with respect to potential. The integration was done by numerical summation, using segments 10 mv. wide in the potential interval 0.14–1.90 volt, and one mv. wide in the potential interval 0–0.14 volt. The adequacy of this procedure was checked by checking certain "critical" regions over still smaller intervals.

TABLE I

SOME ELECTROCAPILLARY PROPERTIES OF 0.1 N KCl AT 25°

E, volts	C, μf/cm.^{2}	$\int C\mathrm{d}E$ μcoul./cm.^{2}	$\int\int C\mathrm{d}^2E$ ergs/cm.^{2}
0	123	22.19	49.03
0.005	109	21.61	47.93
.01	97.4	21.09	46.86
.02	81.4	20.20	44.80
.03	71.2	19.44	42.82
.04	63.9	18.77	40.91
.05	58.5	18.16	39.06
.07	51.9	17.05	35.54
.10	45.80	15.60	30.65
.15	40.48	13.46	23.40
.20	38.30	11.50	17.16
.23	38.00	10.36	13.89
.25	38.16	9.59	11.89
.30	38.94	7.669	7.574
.35	39.86	5.695	4.231
.40	39.01	3.715	1.880
.45	35.62	1.838	0.4992
.50	30.50	0.1825	.00555
.506	29.91	0.0000	.0000
.55	25.91	−1.223	.2758
.60	23.00	−2.440	1.198
.65	21.23	−3.542	2.698
.70	20.04	−4.572	4.729
.80	18.40	−6.491	10.27
.90	17.15	−8.264	17.66
1.00	16.40	−9.94	26.77
1.10	16.06	−11.56	37.52
1.15	16.04	−12.36	43.50
1.20	16.08	−13.16	49.88
1.30	16.38	−14.79	63.85
1.40	17.00	−16.45	79.46
1.50	17.80	−18.19	96.8
1.60	18.83	−20.03	115.9
1.70	20.05	−21.97	136.9
1.80	21.77	−24.05	159.9
1.90	24.46	−26.36	185.0

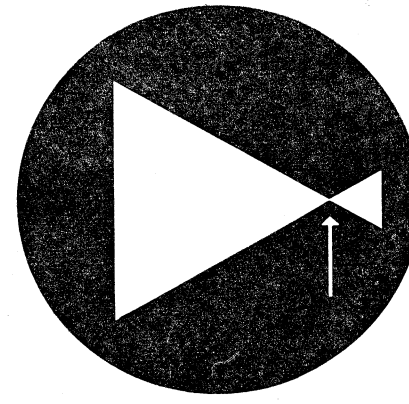

Fig. 2.—Appearance (except for the arrow) of the oscilloscope screen during a measurement. The pattern is a sine wave of variable amplitude, but because of the relatively slow sweep speed (~10 in./sec.) the sine waves are not resolved. At the point marked by the arrow the bridge is in a state of balance. A mark is made on the screen indicating the position of the sweep at a known time after the birth of the mercury droplet, and the bridge is adjusted to make its moment of balance coincident with this mark.

The results are mostly given to one more place (in small figures) than the absolute accuracy of the data warrants because the differences are known more accurately than the absolute values. The first column in Table I gives the potential relative to a normal calomel electrode. The liquid junction between normal and tenth-normal potassium chloride is not, of course, a source of any uncertainty. The second column gives the differential capacity C in microfarads per sq. cm. A plot of these data is not noticeably different from a plot already published[4] for tenth-normal sodium chloride. Minima occur at $E = 0.23$ and 1.15 volts. The intervening maximum occurs at $E = 0.35$ volt. The third column gives the value of $\int C\mathrm{d}E$ starting from the potential of the electrocapillary maximum which we take at $E = 0.506$ volt as found in the following paper. The values of $\int C\mathrm{d}E$ given in column 3 represent the surface charge density of electricity, as one can readily deduce from our two opening remarks.

Column 4 gives values of $\int\int C\mathrm{d}^2E$ where the second constant of integration has been arbitrarily set at zero at the potential of the e. c. max. At 18° its true value would be 426.7 ergs/cm.^{2} according to Gouy,[8] and it is usually considered that this changes very little with temperature, although there seem to be no published data on the matter. Fortunately, it is of minor consequence. Except for this slight uncertainty as to the magnitude of the additive constant, this

(8) Gouy, *Compt. rend.*, **146**, 1374 (1908); *Ann. phys.*, [9] **6**, 25 (1916).

column then gives the electrocapillary curve of tenth-normal potassium chloride. There are no published data of high precision with which to compare these results.

Discussion of Results

A rather full treatment of the significance of electrocapillary data has been published in another place.[4] The data here presented differ from those already published for *sodium* chloride[4] by only a small amount, the differential capacities of the two chlorides being within 2% of one another at comparable potentials over the range of potentials E = 0.01 to 1.2 volts. This great similarity indicates that sodium and potassium ions are hydrated in the double layer, since otherwise their different radii would necessarily be reflected in their capacities. Investigations with other cations now under way also point to this conclusion.

A further interpretation of the data (beyond that given in reference 4) has been attempted, but since it is not the purpose of this paper to present an extensive theoretical treatment of the electrical double layer, this interpretation will be postponed. For the present we shall be content to show, in the following paper, how the differential capacity may be used in conjunction with other data to give a fairly precise value of the potential of the e. c. max.

Acknowledgment.—The author is grateful to the Research Corporation for a Frederick Gardner Cottrell grant of funds in support of this work.

Summary

1. Recent modifications in the author's apparatus for measurement of the capacity of the electrical double layer at a mercury surface in contact with aqueous salt solutions are described.

2. The differential capacity of the electrical double layer, the surface charge density, and the electrocapillary curve of mercury in tenth-normal potassium chloride are presented in tabular form.

AMHERST, MASS. RECEIVED FEBRUARY 23, 1949

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

The Potential of the Electrocapillary Maximum of Mercury

BY DAVID C. GRAHAME, ROBERT P. LARSEN[1] AND MARILYN A. POTH

The potential of the electrocapillary maximum (e. c. max.) of mercury in contact with aqueous solutions is of the first importance in any theoretical or experimental study of the electrical double layer at such an interface. In addition to its direct thermodynamic significance, it has interest in connection with the kinetic theory of the electrical double layer, and a knowledge of its value is indispensable if one wishes to make full use of the very extensive information provided by studies of the differential capacity of the electrical double layer. In particular, integration of the last-named quantity with respect to potential gives the magnitude of the surface electronic charge except for a constant of integration, which is *zero* if the integration is begun at the potential of the electrocapillary maximum.

To the authors' knowledge there are only four papers on this subject, plus a few incidental measurements of the potential of the e. c. max. to be mentioned later. The first paper of importance in this connection, by Paschen,[2] uses a technique which has not been successful in the hands of later workers (who have found it necessary to remove dissolved oxygen), and it therefore comes as a surprise to find, as a result of the present work, that Paschen's values are very nearly correct. The second paper is by Gouy,[3] whose values of the e. c. max. potential are often quoted, but which the authors now believe to be somewhat in error for reasons explained below. A third paper by Winkel and Siebert,[4] gives value which sometimes agree and sometimes disagree with those of Gouy. The fourth paper, by Erdey-Gruz and Szarvas,[5] is difficult to compare with the others because these authors employed a saturated potassium chloride salt bridge, unlike the rest, and so measured a somewhat different quantity. We have attempted to make the conversion in a few simple cases and find satisfactory agreement with our own results when this is done.

The present authors have measured the potential of the electrocapillary maximum of mercury in tenth-normal potassium chloride and sodium chloride by five more or less independent methods. It is the principal function of this paper to describe these methods and their results.

Principle of Experimental Methods I, II and III

It is desirable to describe first the main principle upon which the first three methods depends. These three methods are really only variants of a single method, but since the least certain measurement is carried out differently in the three variants, we regard them as essentially independent.

Suppose that one knows the differential capacity of the electrical double layer in the solution in

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(2) Paschen, *Ann. Physik*, **43**, 568 (1891).

(3) Gouy, *Ann. chim. phys.*, [7] **29**, 145 (1903).

(4) Winkel and Siebert, *Z. Elektrochem.*, **44**, 127 (1938).

(5) Erdey-Gruz and Szarvas, *Z. physik. Chem.*, **A177**, 277 (1936).

question as a function of the potential relative to any convenient reference electrode. Suppose that one now assumes a value of the e. c. max. potential relative to the same electrode. By integrating the differential capacity from the assumed potential of the e. c. max. one obtains the corresponding values of the surface charge density of electrons, as has been done in the preceding paper.[6] A further integration starting from the same point gives the *shape* of the electrocapillary curve, but not the absolute magnitude of the interfacial tension at any point. This latter need not be known for the method we are describing. Results of this second integration are also given in the preceding paper.

A horizontal line drawn through the electrocapillary curve intersects it at two points of equal interfacial tension. The two potentials thus defined will be called isotension potentials. The average (or the sum) of these pairs of potentials will be a constant in the ideal case of an electrocapillary curve symmetrical about a vertical axis. In a typical real case (0.1 *N* potassium chloride) the sum or average changes by about 20% over the experimentally studied portion of the electrocapillary curve.

One can plot the sum of the isotension potentials against any convenient parameter, and as far as the methods we are discussing now are concerned, it would suffice to plot the sum against either one of the two components of the sum. In connection with another method (IV) to be described below, it is desirable to plot the sum against *both* components of the sum, and this has been done in Fig. 1. In Fig. 2 the same calculated points are shown, but in this case only the right-hand branch of the curve has been represented. In Figs. 1 and 2 the solid circles are taken from the electrocapillary curve calculated in the preceding paper.[6] It should be recalled that these points depend upon an assumed value of the potential of the e. c. max.

If one had assumed a value 1 mv. greater, the solid circles would have lain almost exactly 2 mv. above the ones shown and so on. Thus one can compute a *family* of curves, of which only one member is shown, corresponding to various assumed values of the e. c. max. These computations have been made. If the differential capacity measurements were in error by 1% over the range of potentials where such an error would have its greatest effect, an error of about 0.7 mv. would be introduced into the final result. A more likely estimate of the uncertainty arising on this account is ±0.3 mv.

It will be apparent that if one can observe a pair of isotension potentials on a capillary electrometer or otherwise, one can select from the family of curves that member corresponding to the correct value of the e. c. max. Three methods of observing isotension potentials will be described which, taken together with the above curves, constitute what we shall call methods I, II and III.

A fourth and fifth method of obtaining the e. c. max. potential are described below.

(6) Grahame, THIS JOURNAL, 71, 2975 (1949).

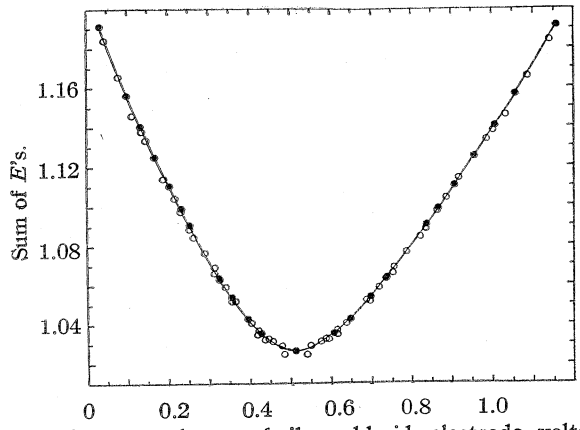

Fig. 1.—Sum of isotension potentials in tenth-normal potassium chloride *vs.* each one singly. Method I. Without the calculated points this figure is also used in method IV. The two lowermost points (really one point plotted twice) are of low accuracy and show how the experimental accuracy deteriorates near the potential of the e. c. max: calculated values, ●; observed by Method I, O.

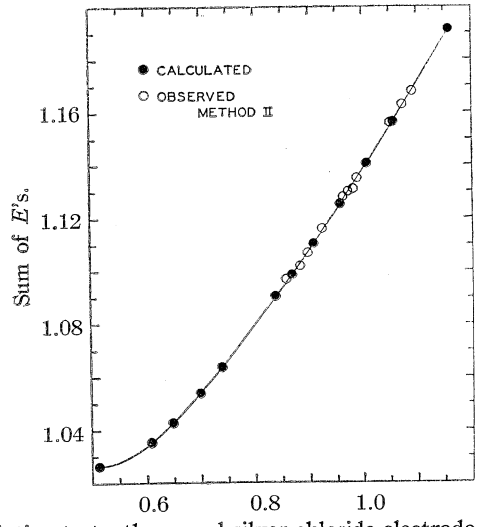

Fig. 2.—Sum of isotension potentials in tenth-normal potassium chloride *vs.* larger value of the pair, method II.

Experimental Methods

Method I.—We shall describe first the method developed last and considered by us to provide the most reliable results. In this method we determine isotension potentials with a capillary electrometer modeled after that used by Gouy[3] but improved and modified to take advantage of the increased accuracy made possible by the fact

that we do not need to measure the height of the mercury column but only to hold it constant. Our instrument is shown in Fig. 3. The solution to be investigated is deaerated either in the reservoir A or in the main body of the cell B. Two electrodes are used, a working electrode C and a primary standard D. In the work to be described in this paper, the latter was silver chloride in tenth-normal potassium chloride, prepared in the manner of Noyes and Ellis.[7] The working electrode was also of this type, except that the electrolyte was whatever chloride happened to be under investigation. By refilling the cell B with tenth-normal potassium chloride, the potential of the working electrode could be compared with that of the primary standard and checked for its proper operation.

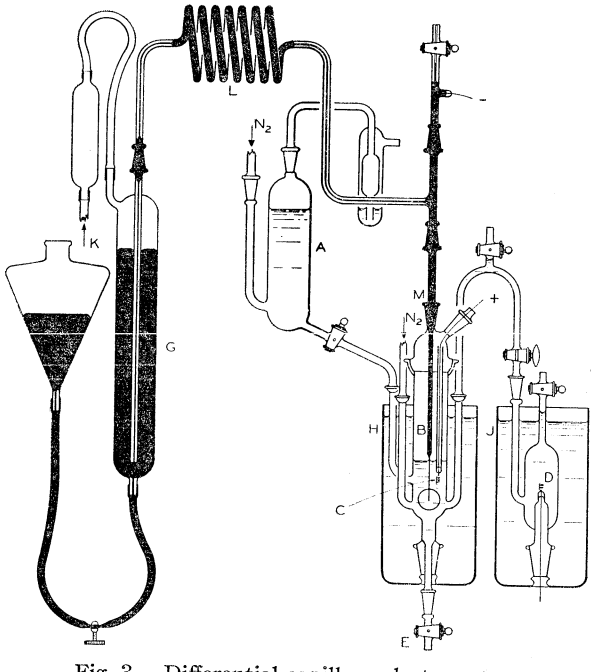

Fig. 3.—Differential capillary electrometer.

The capillary was drawn from Pyrex glass tubing and was approximately 1 mm. o. d. and 0.06 mm. i. d. The stopcock at the bottom of the cell was not greased for most of the measurements reported in this paper, but it was later found that Apiezon L grease could be used without deleterious effect, presumably because it was soon covered by mercury and was not in any case in intimate contact with the solution near the capillary. The ground-glass joints were not greased but were provided with mercury cups (not shown) except in the case of joint M, which was of the feed-through type, and therefore not susceptible to leakage. This construction made it easy to remove the capillary for cleaning whenever that became necessary.

The flexible tubing which connects the leveling bulb to the vertical reservoir was of Tygon tubing (a flexible semi-transparent plastic).[8] The rubber tubing K connects to a mouthpiece which can be used to oscillate the mercury in the capillary in the manner recommended by Gouy.[3] This is an indispensable feature of the apparatus. Two water jackets, H and J, were used to control the temperature of the cells, although temperature control is hardly necessary, since the temperature coefficient of the effect being measured is very small.

The main body of the cell and also the water jacket were provided with windows of optically flat glass. The former was fused into the cell, the latter was held on with picein wax. A cathetometer with a short travel, but with high magnification, made it possible to observe differences in level of the mercury in the capillary of the order of 0.002 mm.

The treatment of the capillary has been given much attention by those who have worked in this and similar fields. We have found it possible and desirable to clean the capillaries in very hot cleaning solution (sulfuric acid + sodium chromate). The subsequent rinsing is done in such a manner as to prevent dust-laden air from being drawn through the capillary. When this was not done, bits of lint lodged in the capillary could be seen under the microscope. It was not necessary to dry the capillary. Sometimes this treatment did not suffice to produce a clean capillary. In these cases a very brief (five seconds) treatment with 50% hydrofluoric acid always sufficed to overcome the difficulty. The enlargement of the capillary was not noticeable, nor was it rendered translucent. This cleaning of the capillary with hydrofluoric acid was sometimes done without removing it from the cell. For this purpose equal parts of 0.2 *N* potassium chloride and 50% hydrofluoric acid were mixed and introduced into the cell in order to avoid "shocking" the silver chloride working electrode. No damage to the cell, the optical flats, the stopcocks or the electrode was noted. Sometimes tenth-normal hydrochloric acid alone would suffice to clean the capillary *in situ* in case it had become contaminated with the hydroxides of the heavy metals when solutions of their chlorides were introduced.

Theoretical considerations indicate that the capillary should be very slightly tapered in order to achieve stability. The sensitivity depends upon the magnitude of the taper. Apparently some taper is always achieved when the capillary is drawn, but the behavior of seemingly identical capillaries might be found to be very different depending upon the amount of taper present.

The glass spiral L is intended to give flexibility to the top piece so that it can be removed and replaced.

(7) Noyes and Ellis, THIS JOURNAL, **39**, 2532 (1917).

(8) In a later model (not used in the measurements here reported and therefore not represented in the figure) we have eliminated the clamp, which causes incipient cracking of the tubing, by connecting the top of the leveling bulb to the top of the vertical reservoir by another piece of Tygon tubing.

It was found by experiment that the same results were obtained whether the solutions were deaerated or not.[9] Deaeration is desirable as a means of reducing the current flow (and thus protecting the working electrode) when mercury droplets are expelled from the tip. It would also seem to be desirable to prevent the products of the reduction of oxygen from accumulating at the mercury surface where measurements are being taken, but, very surprisingly, no effect traceable to this cause has been observed.

Two calibrated Leeds and Northrup student potentiometers were employed to fix the potential. These were wired in the usual manner and provided with a switch which made it possible to change over rapidly from one to the other. Thus the interfacial tension at two potentials could be the more readily compared. The technique employed in making measurements was as follows: The potential of the mercury in the capillary would be brought to such a value on the descending (cathodic) branch of the electrocapillary curve that the equilibrium position of the mercury would lie approximately one mm. from the tip of the capillary. In order to be sure that the mercury surface was clean, a droplet of mercury would be expelled by blowing gently upon the mouthpiece attached to the rubber tube K. There was usually no difficulty in obtaining reproducible values on this branch of the curve. Another droplet of mercury would then be expelled, and with the mercury flowing, the potential would be switched to a value on the ascending branch thought to have the same interfacial tension. The mercury flow would be arrested by sucking momentarily on the mouthpiece, whereupon the mercury came to its new equilibrium position. If this position was the same as that found at the other potential, the values so found corresponded to the same interfacial tension (isotension potentials). If not, it was found necessary to repeat the measurement at the higher (cathodic) potential before repeating the measurement (with a new potential) on the low side. The reason for this is not clear except that the mercury is apparently not completely freed from capillary-active impurities on the low potential side even after one or more droplets have been expelled. On the high potential side, this is not so. The equilibrium position on the low side usually does not persist for more than five or ten seconds, at best, after which a steady fall of the meniscus attests to the adsorption of impurities from the solution. It is remarkable that the most carefully purified solutions did not differ in this or in any other observable respect from solutions made up from ordinary C.P. salts. The measurements reported in this paper were all carried out with purified solutions, however.

(9) This is not to be confused with the statement made earlier that the method used by Paschen is generally considered to require deaeration for its successful execution. The method here described differs entirely from that used by Paschen.

The results obtained by this method for tenth-normal potassium chloride at 25° are shown by the open circles in Fig. 1. They are seen to agree with the calculated curve with an accuracy of ±1 mv., which represents an uncertainty in the e. c. max. potential of not over half a millivolt for any one reading, except near the e. c. max., where the rate of change of interfacial tension with potential is approaching zero, and the accuracy of the measurements is accordingly much diminished. Such points were not taken into account in selecting a "best" fit from the family of curves.

The "best" curve, which is the only one shown, corresponds to an e. c. max. potential of 0.506_0 volt relative to a normal calomel electrode or 0.559_0 volt relative to a tenth-normal calomel electrode or 0.513_5 volt relative to a tenth-normal silver chloride electrode. These values are considered correct within ±0.5 mv.

The method we are here discussing does not give satisfactory results in hundredth-normal solutions of chlorides (the only salts we have tried at this dilution). Not only are the results in disagreement with all curves in the family of curves calculated from the differential capacity, but they are in disagreement with other methods, and also with all reasonable expectation. The difficulty is undoubtedly associated with the fact that the equilibrium position in the capillary is achieved only slowly, by which time the mercury surface could have and generally would have become contaminated. Method V, to be discussed below, is believed to be the best of the five in more dilute solutions.

The only values of the e. c. max. potential to be found in the literature for tenth-normal potassium chloride are two very old values, one by Paschen,[2] who arrives at a result 6 mv. lower than ours, and another by Smith,[10] whose final result is 9 millivolts higher than ours.

Method II.—It was found that when the head of mercury which caused mercury to flow from the capillary tip in the apparatus shown in Fig. 3 was barely sufficient to maintain the flow, a gradual change of the potential toward that of the e. c. max. caused a fairly abrupt cessation of flow. More accurately stated, as the potential was changed, there would appear a point when there was a monentary pause, amounting to perhaps five-tenths of a second at first, between the fall of one droplet and the beginning of the formation of the next. This phenomenon could be observed directly or by watching a galvanometer in series with the capillary.[11] It was suspected that the arrest potential corresponded to a definite interfacial tension, depending upon the

(10) Smith, *Phil. Trans. A*, **193**, 47 (1899); quoted by Smith and Moss, *Phil. Mag.*, [6] **15**, 478 (1908).

(11) The galvanometer swings as the mercury droplet begins to flow, even in the absence of air, because of the charging current familiar in polarographic measurements. It swings abruptly back to zero when the mercury droplet falls unless a new droplet immediately begins to form.

head of mercury and the diameter of the capillary, and that two such arrest points on opposite sides of the e. c. max. potential would constitute a pair of isotension potentials. This expectation was tested and found to be valid in tenth-normal solutions. Figure 2 illustrates the kind of agreement obtained. The "best" value is not perceptibly different from that found by method I, although the uncertainty is about twice as great. In more dilute solutions there is some evidence that method II may constitute a more accurate method of estimating isotension potentials than method I.

Method III.—Measurements of drop weight have long been popular as a means of measuring surface tension or interfacial tension. In a modification of this method we have sought pairs of potentials having the same drop *time*. The apparatus is the same. An interval timer accurate to 0.01 sec. is used to measure the drop time. Usually five droplets are counted at each potential setting and a great many sets of values are taken alternately until a pair of potentials with the same drop time is found. One such pair is sufficient to fix the potential of the e. c. max. By this method, taking only one pair, we arrive at a value one millivolt higher than our "best" value quoted above. This method has not been explored to the fullest extent in our laboratory. It is very laborious, but may be advantageous under some circumstances.

Method IV.—All of the above methods demand a knowledge of the differential capacity, which may not be available in some cases. However, one knows that if the data were available, the family of curves would be qualitatively similar to those found for, say, potassium chloride. In particular, it is a necessary consequence of the method of calculation that the curves should have a minimum ordinate at the abscissa of the assumed value of the e. c. max. potential and that this minimum ordinate should be twice the e. c. max. potential. This fact can be understood by remembering that we are plotting twice the abscissa of the diameter of the electrocapillary curve against the abscissas of each of the two points of intersection of a horizontal transversal. Obviously all three abscissas coincide at the e. c. max.

Accordingly it is possible to obtain a fairly good estimate of the potential of the electrocapillary maximum by plotting the isotension potentials as before and interpolating the flat minimum portion without the aid of any theoretical curves, except insofar as one knows that the curve cannot bend sharply at any point. Half the ordinate of the minimum is then taken as the desired value of the e. c. max. potential.

Experience with this method indicates that an accuracy of ± 1 mv. is attainable by a very skillful operator in tenth-normal solutions of chlorides. This method may lead to very large errors, however, if it is not corroborated with independent evidence for at least some of the electrolytes under test. The values here given for tenth-normal potassium chloride can serve for such corroboration in future work. The method cannot be recommended, however, in view of the extreme skill required of the operator and the consequent danger of error in particular cases.

Method V.—This method is not new to this paper. It consists of allowing a stream of mercury to flow into a carefully purified and deaerated solution of the electrolyte under test and measuring its potential relative to some electrode. It has been used by Paschen, Palmaer, Smith and Moss, Erdey-Gruz and Szarvas, and perhaps by others. We have investigated the method thoroughly in this Laboratory and consider it to be the most reliable of the methods available for more dilute solutions than those mentioned in this paper. It can be carried out in the apparatus already described with the following changes: A short jagged fine-tipped capillary is used and arrangements are made for increasing the pressure on the mercury column. This may be done with a compressed gas and a commercial pressure regulator since only very rough control of the pressure is needed. Pressures of from 5 to 20 lb. per sq. in. are generally needed to reach a "plateau" in the readings, and only readings obtained on a good "plateau" may be regarded as valid. Because of the difficulty of removing reducible substances, and perhaps for other reasons of which we are not fully aware, it is not as highly reproducible as the sensitivity of the meter readings suggests. Moreover, in tenth-normal potassium chloride it gives values about 3 mv. lower than the other methods, which we consider the more reliable at this concentration. This amount of error would not be objectionable for many purposes, but it would be desirable to find its source before depending too heavily upon values obtained in this manner.

By the use of method V we find a temperature coefficient of -0.0705 mv./deg. for the potential of the e. c. max. of tenth-normal potassium chloride in the neighborhood of room temperature. This is for the case where the reference electrode (calomel or silver chloride) is in the same solution at the same (variable) temperature.

The results obtained by these five methods are summarized in Table I, along with other results discussed below.

Measurements with Tenth-Normal Sodium Chloride.—For a further check on our methods we have measured the potential of the e.c. max. in tenth-normal *sodium* chloride relative to an electrode in sodium chloride and again relative to an electrode in potassium chloride. This was done because more work has been reported on sodium chloride than on any other electrolyte and because the results have sometimes been reported relative to an electrode in potassium

TABLE I

POTENTIAL OF THE ELECTROCAPILLARY MAXIMUM IN TENTH-NORMAL SODIUM OR POTASSIUM CHLORIDE RELATIVE TO A TENTH-NORMAL CALOMEL ELECTRODE IN THE SAME ELECTROLYTE

Method	Source	Potential, volts NaCl	KCl
I	This work	0.5585	0.5590
II	This work	.562	.559
III	This work	.560	.560
IV	This work	.5585	.5595
V	This work	.558	.556
V	Paschen	.557	.553
V	Erdey-Gruz and Szarvas	.551	
	Gouy	.58	
I	Gouy + this work	.56	
	Smith		.57
V	Palmaer		.573

chloride. No two authors have done exactly the same thing, and in order to make a comparison, we have made the best conversions we could to a single standard. Values given in Table I for tenth-normal sodium chloride are expressed relative to a calomel electrode in the *same* solution.

Except for the value by Gouy, these measurements are in reasonably good accord. Gouy obtained his result by extrapolation of the diameters of the electrocapillary curve, and close examination of his data reveals that the extrapolation was a long one, especially in this case. If one combines his interfacial tension measurements with our differential capacity data as in method I, thus eliminating the extrapolation, the disagreement with our "best" value disappears to within less than the accuracy to which Gouy's values are reported. This corrected value is entered along with the others in Table I.

Acknowledgment.—We are grateful to the Research Corporation for two grants from the Frederick Gardner Cottrell fund in support of this work.

Summary

1. Three techniques are described for the determination of "isotension potentials," pairs of potentials at which the interfacial tension is the same on the two branches of the electrocapillary curve.

2. A method is described for the determination of the potential of the electrocapillary maximum by combining isotension potential data with measurements of the capacity of the electrical double layer.

3. Values of the potential of the e. c. max. in tenth-normal potassium and sodium chlorides are obtained by these three methods and also by two other methods of which one is new. Good agreement is obtained.

4. A value of 0.559_0 volt is obtained for the e. c. max. potential of tenth-normal potassium chloride relative to a tenth-normal calomel electrode, both at 25°.

5. Essentially the same value is obtained for tenth-normal sodium chloride relative to a tenth-normal calomel electrode in sodium chloride. This value is compared with previously published values.

6. A temperature coefficient of −0.0705 mv./deg. is found for the e. c. max. potential in tenth-normal potassium chloride.

AMHERST, MASS. RECEIVED NOVEMBER 29, 1948

[CONTRIBUTION FROM METCALF RESEARCH LABORATORY, BROWN UNIVERSITY]

Properties of Electrolytic Solutions. XLIII. Effect of Ammonia and Water on the Conductance of Lithium, Sodium and Silver Ions in Pyridine at 25°[1]

BY CHARLES J. CARIGNAN[2] AND CHARLES A. KRAUS

I. Introduction

Burgess has shown that the conductance of tetrabutylammonium picrate in pyridine is changed but little on addition of ammonia. The observed effect may be accounted for by the viscosity change of the solvent; the dissociation constant of the salt remains unchanged. However, when ammonia is added to a solution of sodium picrate, the conductance of the salt is greatly increased. In view of the fact that the conductance of the quaternary ammonium picrate remains constant (except for viscosity effect), it may be concluded that the increased conductance of sodium picrate is due to an increase in the conductance of the sodium ion.

It seemed worth while to investigate this phenomenon in somewhat greater detail. Accordingly, we have measured the conductance of lithium picrate at five different concentrations of ammonia, sodium picrate at two concentrations, and sodium iodide and silver nitrate, each at one concentration of ammonia. In addition, we have measured the conductance of sodium picrate at three different concentrations of water.

II. Experimental

1. Materials.—Pyridine was purified according to the procedure of Luder[3] and Burgess[4]

(1) This paper is based on a portion of a thesis presented by Charles J. Carignan in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in the Graduate School of Brown University, June, 1947.

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(3) Luder and Kraus, THIS JOURNAL, **69**, 2481 (1947).

(4) Burgess and Kraus, *ibid.*, **70**, 706 (1948).

except that the treatment with zinc chloride was omitted. The fact that our conductance values for lithium picrate check those of Burgess and that the density and viscosity of our solvent agree with those in the literature indicates that the zinc chloride step is unnecessary.

Ammonia was dried over sodium amide in a special stock cylinder. In making up known solutions of ammonia in pyridine, the ammonia was condensed in a weighed cylindrical tube of 100-cc. capacity containing ammonium nitrate. The vapor pressure of the saturated solution is one atmosphere at 23.6°. The pyridine, about 800 cc., was weighed in a round-bottom flask; it was then attached to the system, cooled to −78° and exhausted to remove all air. The desired amount of ammonia was then condensed on the pyridine, the amount of ammonia being found by weight difference of the ammonium nitrate container. The pyridine was warmed up to 25° in a water-bath, being stirred by means of a magnetic stirrer. After noting the pressure of ammonia above the solvent, dry air was admitted to bring the pressure to one atmosphere. The solvent was transferred from the stock flask to the cell as needed, the stock flask being connected to a supply of an air–ammonia mixture having the same composition as the atmosphere in the flask.

The conductance of pure pyridine was of the order of 5×10^{-10}. On addition of ammonia or water, the conductance was increased approximately tenfold. The conductance of these solvent mixtures usually ranged from 1 to 1.5×10^{-8}; it was necessary to apply a solvent correction in the case of the more dilute solutions.

1. Salts.—Lithium picrate was recrystallized from nitromethane; sodium picrate was recrystallized from ethanol. Both salts were dried *in vacuo* at 80°. Care should be exercised not to overheat the picrates. Sodium iodide and silver nitrate were recrystallized from water; the former was dried at 100°, the latter *in vacuo* at room temperature in the dark.

2. Physical Constants.—Densities were determined with a pycnometer of 30-cc. capacity with a capillary 5 cm. long and 1.0 mm. diameter. This pycnometer was provided with a ground-glass cap. Values are given in the tables.

Viscosities were determined with a modified Ostwald viscometer. An atmosphere of ammonia and air was maintained above the liquid with which it was in equilibrium. Values are given in the tables.

Dielectric constants were determined with a special cell and the parallel arm bridge that was also used for measuring the conductance of the pure solvents. The cell was calibrated with pyridine, using the value 12.01 for the dielectric constant of pure pyridine. With a 0.4798 *N* solution of ammonia, the dielectric constant was found to be 12.06. The difference with respect to pure pyridine is negligible for present purposes. With water, a marked increase of the dielectric constant was found. Values are given in Table II.

3. Experimental Techniques and Procedure.—Conductance measurements were carried out at 25 ± 0.01° as described in earlier papers.[4] The conductance cell was provided with gray platinum electrodes and had a capacity of 60 cc. It was well filled so as to reduce the vapor space to a minimum. Dilution was made as already

TABLE I

CONDUCTANCE OF SALTS IN PYRIDINE–AMMONIA MIXTURES AT 25°

A. Lithium Picrate

c, NH_3 = 0.0; d = 0.97801; η_0 = 0.008827		c, NH_3 = 0.1009; d = 0.97655; η/η_0 = 0.987	
$C \times 10^4$	Λ	$C \times 10^4$	Λ
1.4724	31.98	3.8084	27.92
0.78358	37.74	1.8247	34.90
.41304	43.32	1.0039	41.06
.21674	48.22	0.42081	48.83
.12145	51.61	.23643	53.09
		.14800	55.79
c, NH_3 = 0.2169; d = 0.97534; η/η_0 = 0.971		c, NH_3 = 0.2922; d = 0.97442; η/η_0 = 0.963	
2.0186	39.68	2.0142	40.51
0.92759	47.39	1.0244	47.75
.46282	53.55	0.53857	54.02
.22722	58.48	.26277	59.55
.12277	61.60	.12886	63.14
c, NH_3 = 0.3408; d = 0.97455; η/η_0 = 0.958		c, NH_3 = 0.3716; d = 0.97362; η/η_0 = 0.955	
2.0905	40.69	5.5596	30.81
0.86685	50.39	1.9409	41.55
.63120	53.63	0.96736	48.80
.25967	60.65	.41633	57.86
.10281	65.87	.21028	62.63
		.09994	65.91

B. Sodium Picrate

c, NH_3 = 0.0954; d = 0.97671; η/η_0 = 0.986		c, NH_3 = 0.2230; d = 0.97543; η/η_0 = 0.970	
$C \times 10^4$	Λ	$C \times 10^4$	Λ
33.328	8.97	5.321	21.17
5.0785	18.66	1.620	31.95
2.5396	24.13	1.149	34.26
1.1306	31.62	0.7750	38.27
0.46056	41.13	.2326	52.58
.27380	46.21		
.13622	52.51		

C. Sodium Iodide

c, NH_3 = 0.2299; d = 0.97501; η/η_0 = 0.969	
3.3813	55.73
1.1672	68.15
0.59343	74.42
.33533	78.74
.16969	83.06

D. Silver Nitrate

c, NH_3 = 0.3415; d = 0.97379; η/η_0 = 0.958	
6.8843	59.35
3.7403	66.77
1.8421	74.74
0.97121	80.84
.48290	86.03
.20259	90.69

described except that an atmosphere of air and ammonia was maintained above the liquid which was in equilibrium with it. When water was used, an atmosphere of dry carbon dioxide-free air was maintained over the solution.

III. Results

The results for the lithium and sodium picrates, for sodium iodide and silver nitrate in the presence of ammonia are presented in Table I. The concentration of ammonia and values of the density and relative viscosity, η/η_0, are given at the head of the several tables.

Results for sodium picrate in the presence of water are given in Table II. At the head of the several tables are given the concentration of water, the density, the relative viscosity and the dielectric constant.

TABLE II

CONDUCTANCE OF SODIUM PICRATE IN PYRIDINE–WATER MIXTURES

c, H_2O = 0.1018; d = 0.97783; η/η_0 = 1.004; D = 12.32

$C \times 10^4$	Λ
7.5151	21.12
3.4469	27.52
0.90357	39.96
.45399	46.07
.19335	52.23
.12088	54.65

c, H_2O = 0.2048; d = 0.97795; η/η_0 = 1.011; D = 12.44

$C \times 10^4$	Λ
9.4212	23.51
3.5930	31.70
1.5512	39.42
0.72532	46.00
.32705	51.64
.17025	55.03

c, H_2O = 0.3148; d = 0.97815; η/η_0 = 1.019; D = 12.52

$C \times 10^4$	Λ
11.626	25.51
4.9599	32.79
2.2814	39.82
0.95102	47.42
.38970	53.44
.15429	57.59

IV. Discussion

The data presented in Tables I and II have been analyzed by the method of Fuoss and values of the limiting conductance, Λ_0, and the dissociation constant, K, have been determined. Fuoss plots are shown for lithium picrate in Fig. 1 and for sodium picrate, sodium iodide and silver nitrate in Fig. 2 (all in the presence of ammonia).

Plots for sodium picrate in the presence of water are shown in Fig. 4.

It will be noted that all the plots are linear, conforming to the Bjerrum–Fuoss relation. It is of particular interest to point out that our values for lithium picrate in pure pyridine are in good agreement with those of Burgess, although we used a simpler method in the purification of the solvent. Evidently, the treatment with zinc chloride is unnecessary.

1. Salts in Presence of Ammonia.—Values of Λ_0 and K as derived from the plots for ammonia–pyridine mixtures are listed in Table III (columns

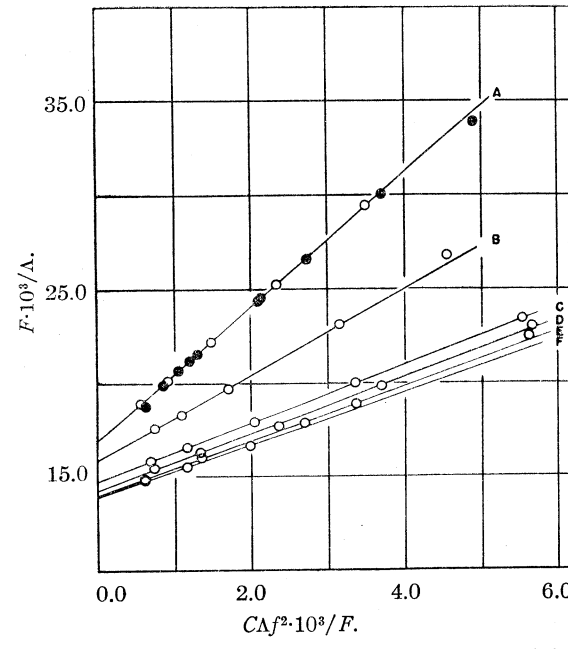

Fig. 1.—Fuoss plots for lithium picrate in pyridine–ammonia mixtures: concentration of ammonia: (A), 0.00; (B), 0.1009 m; (C), 0.2169 m; (D), 0,2922 m; (E), 0.3408 m; (F), 0.3716 m.

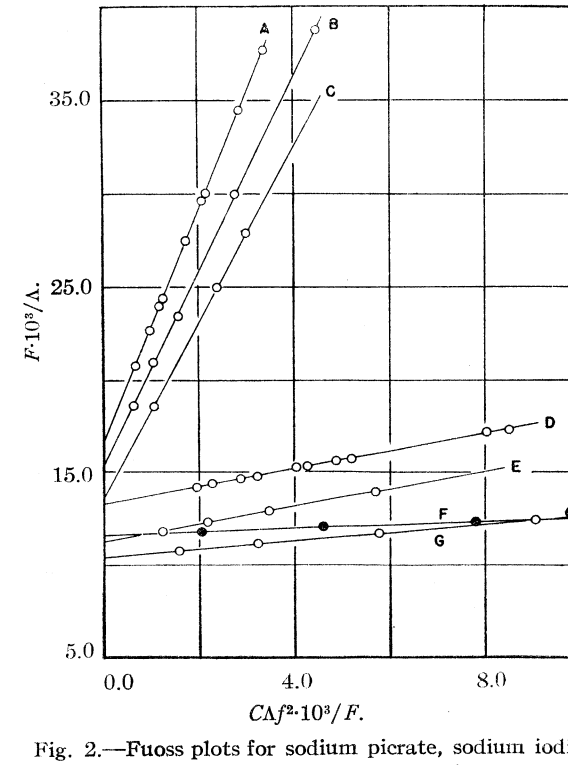

Fig. 2.—Fuoss plots for sodium picrate, sodium iodide and silver nitrate in pyridine–ammonia mixtures: concentration of ammonia: NaPi (A) 0.00 (B) 0.0954 m; (C) 0.2230 m; NaI (D) 0.00, (E) 0.2299 m; $AgNO_3$ (F) 0.00, (G) 0.3415 m.

TABLE III

LIMITING EQUIVALENT CONDUCTANCES, ION CONDUCTANCES AND DISSOCIATION CONSTANTS OF ELECTROLYTES IN PYRIDINE–AMMONIA MIXTURES

NH_3 concn. moles/liter	Λ_0	Λ_0^- [a]	Λ_0^+	% Increase in Λ_0^+	Dissoc. const. $K \times 10^4$
		A. Lithium Picrate			
0.0	58.45	33.68	24.77	..	0.81
0.1009	63.17	34.12	29.05	17.3	1.09
.2169	67.70	34.69	33.01	33.2	1.40
.2922	70.18	34.97	35.21	42.1	1.35
.3408	71.22	35.15	36.07	45.6	1.38
.3716	72.20	35.26	36.94	49.1	1.25
		B. Sodium Picrate			
0.0	60.5	33.7	26.8	..	0.43
0.0954	65.3	34.2	31.1	16.0	.45
.2230	73.8	34.7	39.1	45.9	.39
		C. Sodium Iodide			
0.0	75.20	48.4	26.8	..	3.7
0.2299	88.50	49.9	38.6	44.1	2.70
		D. Silver Nitrate			
0.0	86.9	52.6	34.3	..	9.3
0.3415	95.6	54.9	40.7	18.7	4.96

[a] Corrected for change in solvent viscosity on addition of ammonia.

2 and 6). In the third column is given the anion conductance corrected for viscosity change, in the fourth column, the cation conductance, and in the fifth column, the percentage increase of cation conductance over that in the pure solvent.

As may be seen from Table III as well as from Fig. 3, the conductance of the lithium ion is greatly increased on addition of ammonia. The conductance evidently approaches a limiting value with increasing ammonia concentration; for an ammonia concentration of 0.37 molar, the conductance increase is 49%. In the limit, the increase must be considerably greater than this.

With sodium picrate, the cation conductance increases more rapidly than with the corresponding lithium salt. For an ammonia concentration of 0.22 molar, the (ion) conductance increase is 46%. It is of interest to note that the conductance increase of the sodium ion is the same for the iodide as for the picrate. It is also of interest to note that the conductance increase of the silver ion is much smaller than that of the lithium or the sodium ion.

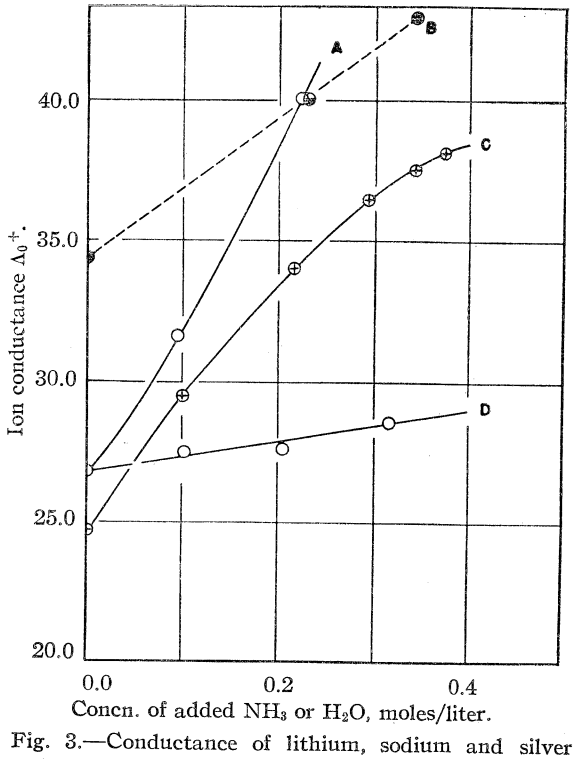

Fig. 3.—Conductance of lithium, sodium and silver ions in pyridine–ammonia mixtures and sodium ion in pyridine–water mixtures: (A) NaPi O, NaI ◒; (B) $AgNO_3$ ●; (C) LiPi ⊕; (D) NaPi with H_2O O.

TABLE IV

LIMITING EQUIVALENT CONDUCTANCE, ION CONDUCTANCES AND DISSOCIATION CONSTANT OF SODIUM PICRATE IN PYRIDINE–WATER MIXTURES

H_2O concn. moles/liter	Λ_0	Λ_0^- (cor.)	Λ_0^+	% Increase in Λ_0^+	Dissoc. const. $K \times 10^4$
0.0	60.5	33.7	26.8	...	0.43
0.1018	61.2	33.5	27.7	3.3	1.01
.2048	61.3	33.3	28.0	4.5	1.61
.3148	62.3	33.1	29.2	9.0	2.29

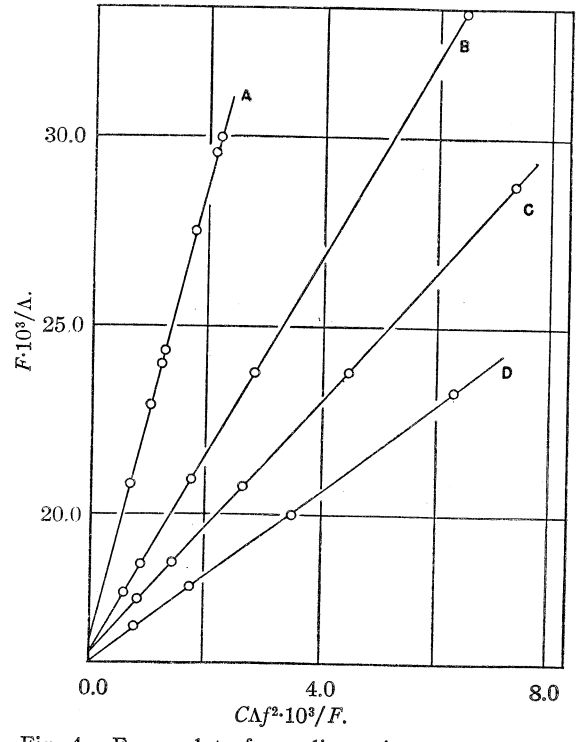

Fig. 4.—Fuoss plots for sodium picrate in pyridine–water mixtures: water concentration: (A) 0.00; (B) 0.1018 *m;* (C) 0.2048 *m;* (D) 0.3148 *m.*

The dissociation constant, on addition of ammonia, may increase, decrease or remain unchanged. Thus, for lithium picrate, there is an increase, for sodium iodide and silver nitrate, a decrease, while for sodium picrate there is no change. It appears that although free ions of lithium, sodium and silver become effectively smaller due to the presence of ammonia, in their ion pairs they may become either larger or smaller or undergo no change. Ion conductances are shown as a function of ammonia concentration in Fig. 3.

2. Sodium Picrate in Presence of Water.—In Table IV are given values for the constants of sodium picrate in the presence of water. Graphs are shown in Fig. 4.

As may be seen from Table IV, the conductance of the sodium ion in pyridine is increased on addition of water, but much less than on addition of ammonia. The increase is only 9% with 0.32 molar water. On the other hand, there is a marked increase of the dissociation constant, approximately six times for 0.32 molar water. This increase may be due, in part, to the higher dielectric constant of the water mixtures. At the concentration mentioned above, the dielectric constant is 7% greater than that of pyridine.

V. Summary

1. The conductance of lithium and sodium picrates and of sodium iodide and silver nitrate have been measured in pyridine solutions to which ammonia had been added.

2. The conductance of sodium picrate has been similarly measured in pyridine to which water had been added.

3. Values of the limiting conductance and the dissociation constant have been derived for the salts in these solutions by the Fuoss method and ion conductances have been determined.

4. The conductance of the three cations increases markedly on addition of ammonia. At an ammonia concentration of 0.2 molar, the conductance increase for the lithium, sodium and silver ions is, respectively, 33, 42 and 15%.

5. The conductance increase for the sodium ion on addition of 0.2 molar water is 4.5%.

6. On addition of ammonia, the dissociation constant of lithium picrate increases somewhat. Those of sodium iodide and silver nitrate decrease and that of sodium picrate remains unchanged. The dissociation constant of sodium picrate is increased markedly on addition of water.

PROVIDENCE, R. I. RECEIVED MARCH 18, 1949

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Effect of Centrifugal Force on Galvanic Potentials: (a) The Transference Numbers of Potassium Iodide, (b) The Iodide–Iodine Ion

BY D. A. MACINNES AND B. ROGER RAY[1a]

The effect of gradients of centrifugal force on the potentials of simple galvanic cells has been studied by Des Coudres[1] and more extensively by Tolman,[2] and some preliminary measurements have been reported by MacInnes.[3] Tolman and MacInnes used galvanic cells of the type

$$\underset{r_2}{(\mathrm{Pt})};\ \mathrm{I_2},\ \mathrm{KI},\ \mathrm{I_2};\ \underset{r_1}{(\mathrm{Pt})} \qquad \text{(A)}$$

in which two, otherwise identical, iodide–iodine electrodes with a uniform solution between them are placed at radii r_1 and r_2 in a centrifugal field. These researches have been interpreted by the equation

$$EF = 2\pi^2 n^2 (r_2^2 - r_1^2)[t_K(M_{KI} - \bar{V}_{KI}\rho) - (M_I - \bar{V}_I\rho)] \qquad (1)$$

in which F is the faraday, n is the number of revolutions per second, t_K is the transference number of the cation constituent, ρ is the density of the solution, M_{KI} and $\bar{V}_{KI}$ are the molecular weights and partial molal volumes of potassium iodide, and M_I and $\bar{V}_I$ are the atomic weight and partial atomic volume of iodine. It will be shown below that this is a limiting form of an equation which is based on more complete knowledge of the mechanism of cell A.

Studies of the closely related effect of differences of height on the potentials of galvanic cells have been made by Des Coudres[4] and more recently by Grinnell and Koenig.[5]

The results to be described below are the outcome of a long research undertaken to develop the centrifugal e. m. f. procedure into a precision method for obtaining transference numbers. It is of particular importance in that it can be used, as has been demonstrated by experiments already made, in the determination of transference numbers in non-aqueous solvents, where, due to Joule heat, the Hittorf and moving boundary methods encounter difficulties.

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(1) Des Coudres, *Ann. Physik*, **49**, 234 (1893).

(2) Tolman, *Proc. Am. Acad. Arts Sci.*, **46**, 109 (1910); THIS JOURNAL, **33**, 121 (1911).

(3) MacInnes, *Ann. New York Acad. Sci.*, **43**, 243 (1942).

(4) Des Coudres, *Ann. Physik*, **57**, 232 (1896).

(5) Grinnell and Koenig, THIS JOURNAL, **64**, 682 (1942).

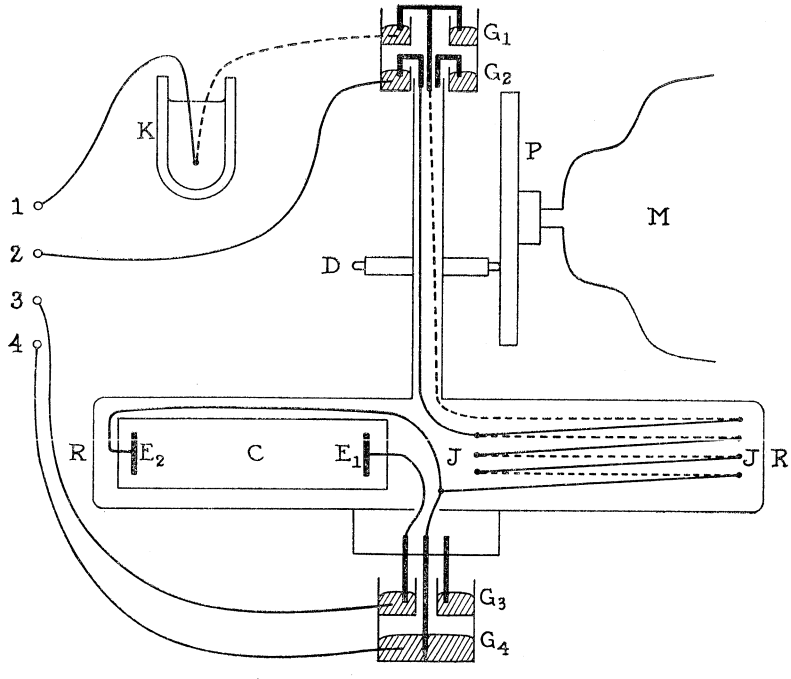

Fig. 1.—Diagram of apparatus.

The Apparatus

The apparatus,[6] and the electrical connections, are shown diagrammatically in Fig. 1. The rotor R-R, which is a disk of magnesium 23 cm. in diameter and 5 cm. thick, is turned in a horizontal plane by means of the pressure of the disk D on the plate P, which is rotated by the synchronous motor M. The rotor speed can be varied by changing the position of the disk D with the relation to the plate P. The potential between the electrodes E_1 and E_2 of the galvanic cell C can be measured, during the rotation, by electrical contacts through the mercury commutators G_3 and G_4. The difference of temperature at radii corresponding to the positions of E_1 and E_2 is obtained by means of the thermojunctions J-J. Twenty-two junctions are used, and are actually arranged around cell C. The resulting thermopotential is measured between the commutators G_2 and G_4. Finally, the temperature of the rotor is found using a single junction in the rotor, the commutators G_1 and G_2 and the reference junction in the external ice-bath K. Thus by shifting the leads of the potentiometer to the appropriate pairs of the contacts 1, 2, 3 and 4 the e. m. f. of the cell, the differential temperature, and the temperature of the rotor may be measured. The temperature measurements are essential since the measured potentials have been found to be considerably affected by radial temperature gradients. Such gradients are minimized by surrounding the rotor with a chamber in which a vacuum of 1 μ or better can be maintained. This prevents the production of appreciable heat through gas friction. The heat generated at the vacuum bearing is controlled by the circulation of cooling water. Radial temperature differences are reduced to less than 0.01° by empirically choosing the temperature of the water. This arrangement also greatly reduces the rise, during a determination, of the temperature of the rotor.

The cell used in obtaining the data to be described below is shown in Fig. 2. The electrodes E_1 and E_2, which are platinum disks 1 cm. in diameter and 6.4 cm. apart, are sealed into the Jena 16 III glass ends of the cell. The platinum leads, L_1 and L_2, are enclosed in flexible plastic tubing. Filling and removal of the solution are carried out through the tube T which is closed with a ground-glass cap G. The cell is enclosed in the brass shell S, the space between the shell and the cell being filled with vaseline. This semi-fluid material helps to equalize the pressure on the two sides and bottom of the cell when in a centrifugal field. The Bakelite spacers, V_1 and V_2, hold the glass cell in a fixed position in the shell S.

To determine the radii r_1 and r_2 of eq. 1 the procedure was as follows. The glass portion of the cell shown in Fig. 2 was filled with, and immersed in, a microscope immersion oil with the same coefficient as glass, and the distances of the electrodes E_1 and E_2 from the top edge of the cell, P, which was ground flat, were read with an accurate comparator, equipped with a travelling microscope. The cell was then assembled, as shown in the figure, inserted in the centrifuge, and run at top speed to ensure definite settling into place. The cell assembly was then placed on a surface plate and the distance between the top edge P and the bottom of the brass shell S was measured with a depth gage. When placed in the rotor R-R of Fig. 1, the cell and its counterpoise rest against disks closing the ends of the channel. The effective diameter of the rotor, *i. e.*, the distance between these disks, was measured with the aid of a precision vernier caliper. With these data

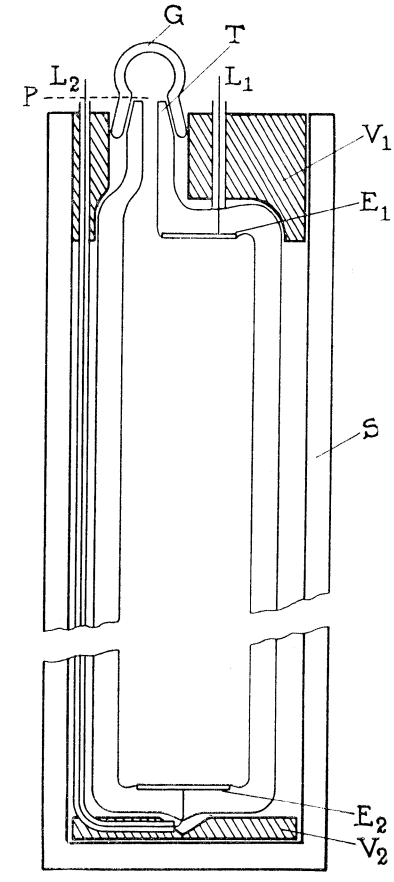

Fig. 2.—The galvanic cell.

(6) The apparatus is more fully described in an article by Ray and MacInnes in the *Rev. Sci. Inst.*, **20**, 52 (1949).

the radii r_1 and r_2 may be computed. Since the electrodes E_1 and E_2 are not exactly parallel the factor $(r_2^2 - r_1^2)$, which for the cell used in these experiments was 86.04 cm.,[2] may be in error by about ±0.2%. Another design of cell which allows for greater precision in this factor has also been used in our work.[6]

It is quite important that the counterpoise have the same moment of inertia as the cell, *i. e.*, imitate it closely in distribution of weight, since otherwise the rotor may precess, and may not rotate about its geometrical center.

The mercury commutators G_1, G_2, G_3 and G_4 are described in detail elsewhere.[6] With them it was possible to make measurements to one microvolt, or better, of potentials developed in the rotor, this precision being necessary because the highest potentials determined are of the order of one millivolt.

The measurements of the speeds of rotation, which ranged between 400 and 7200 r. p. m., were made with the aid of stroboscopic patterns, as described in a paper from this Laboratory.[7] The rotating top surface of the commutator G_1 of Fig. 1 is painted black, with a white radial streak. This surface is illuminated by a stroboscopic lamp, which is operated from the local a. c. current, and yields flashes at the rate of 60 per second. At definite speeds stationary stroboscopic patterns are observed which are related by the formula r. p. m. $= (3600 \times m)/n$ in which n is the number of bands in the pattern, and m is the "multiplicity." Patterns are observed for integral values of m and n except when they have a common factor. As the same pattern occurs at a series of related speeds it is necessary to have a rough preliminary estimate of its value. This is furnished by a scale attached to the adjustment mechanism of the disk D of Fig. 1. Since stationary patterns could be obtained for indefinite periods, with occasional slight manual adjustments, the accuracy of the speed measurement was nearly that of the a. c. source, and was more than necessary for our purpose.

The Preparation of the Solutions

The measurements described in this paper were made with 0.1941 *N* potassium iodide, to which varying amounts of iodine were added. In preparing this solution the best commercial salt was recrystallized several times, dried in an electric oven, followed by heating to 500° in a platinum boat in a current of purified nitrogen. The material was then weighed with the aid of the Richards bottling apparatus[8] procedure, after which the salt was dissolved in a weighed amount of conductivity water. A solution 0.1941 *N* in potassium iodide and 0.1585 *N* in iodine was made by adding a weighed amount of iodine (several times resublimed) to the stock potassium iodide solution. The solutions with smaller proportions of iodine were made by diluting, by volume, with carefully calibrated pipets, with the stock potassium iodide solution.

After many experiments designed to discover the source of persistent irregularities in the measurements, a source of difficulty was located in the minute suspended particles in the solutions. These were present although every effort had been made to ensure cleanliness in preparing the solutions. Such particles are far more important in this centrifugal work than in other e. m. f. measurements, since particles that are denser than the solution in which they are suspended will drift toward the outer, and less dense ones to the inner electrode, in both cases producing contamination of the platinum surface, and thus affecting the measured potential. To overcome this difficulty many of the solutions were ultrafiltered, with suction, through collodion membranes supported on sintered glass. This procedure yielded solutions which appeared optically clear in a Tyndall beam. Another procedure gave somewhat less complete, but apparently sufficient, removal of suspended material. This was the repeated filtration between each crystallization of the hot saturated solutions of potassium iodide, using the most dense hardened filter paper obtainable. The paper was pre-washed and supported on a steam-heated funnel. Solutions made up from this salt were very nearly optically clear and were used for part of the work. In earlier work the results appeared to be influenced by the presence of oxygen in the solutions, and elaborate precautions were made to exclude it from the solutions and the surroundings of the cell. With the use of ultrafiltration, the need of these precautions apparently disappeared. It seems possible that a really clean surface of platinum can overcome the disturbing effect of a small concentration of oxygen, whereas a contaminated surface is unable to do so. However, we do not consider the matter to be fully settled.

(7) MacInnes, *Rev. Sci. Inst.*, **14**, 14 (1943).

(8) Richards and Parker, *Proc. Am. Acad. Arts Sci.*, **32**, 59 (1896).

The Experimental Results

The Effects of Temperature Control.—As mentioned above, correct, constant values of the e. m. f. of the galvanic cell were obtained only when there was no difference of temperature between the radii of the rotor corresponding to the positions of the electrodes E_1 and E_2. This is clearly indicated by some typical measurements illustrated in Fig. 3. In this figure the top curve shows the potentials of the galvanic cell, the next lower one the temperature of the rotor, and the bottom curve the difference of temperature at the points occupied by the electrodes, all plotted as functions of the time, the zero being the moment at which the rotor attained a speed of 5400 r. p. m. It will be seen that there is a quick rise of the e. m. f. of the cell, followed by a slower decrease. During the same period there is a slow increase of the temperature of the rotor, and a corresponding rise to a low maximum of the differential temperature. At a time indicated by the vertical dotted line running water was used to fix, at an appropriate point, the temperature of the rotor bearing. It will be observed in the figure that the differential temperature dropped rapidly to nearly zero, and shortly after the e. m. f. of the

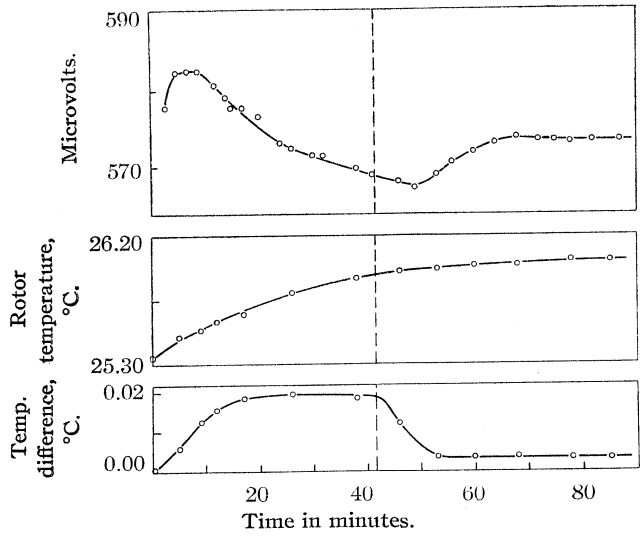

Fig. 3.—Effect of temperature difference on e. m. f. of cell and on rotor temperature.

cell, and the temperature of the rotor, assumed constant values.

With experience, it was possible to adjust the temperature of the bearing at the start so as to avoid appreciable temperature gradients in the cell during the measurements. The measured potentials of the cell at each speed were, in general, established immediately, and remained constant, within one or two microvolts, for the period of the measurement, generally about ten minutes.

A Typical Experiment.—The results of a typical experiment are shown in line A of Fig. 4, in which the values of the potentials E, in microvolts, are plotted as functions of the square, n^2 of the speed of rotation in seconds. According

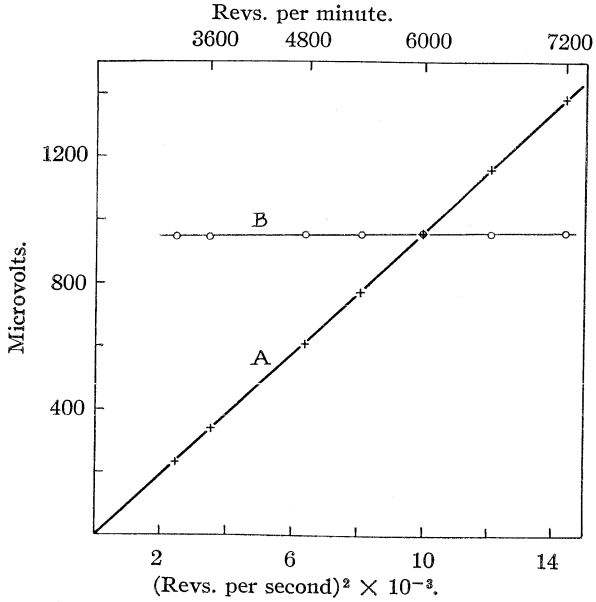

Fig. 4.—Results of a typical experiment.

to eq. 1 and the following eq. 8 this relation should be linear and pass through the origin. That A is a straight line is shown by plotting the slopes, E/n^2, against n^2 as shown in line B. The slope is thus seen to be constant within a very small limit of error. These data were obtained using solution 8, of Table I, in the galvanic cell.

TABLE I

RESULTS OF MEASUREMENTS OF POTASSIUM IODIDE–IODINE SOLUTIONS

	Iodine normality	Density 25°	Molar cond. Λm 25°	E/n^2 × 10^8 obs.	No. runs	Av. dev., %	E/n^2 × 10^8 comp.
1	0	1.02037	126.70	(6.71)			6.684
2	0.00165	1.02053	126.57	6.738	2	0.1	6.71_2
3	.00990	1.02135	125.91	6.874	4	.1	6.853
4	.01981	1.02230	125.09	6.967	2	.05	7.005
5	.03961	1.02418	123.49	7.38_0	5	.4	7.34_1
6	.07922	1.02798	120.31	8.049	1		8.047
7	.1188	1.03178	117.15	8.85_1	4	.6	8.790
8	.1585	1.03558	114.05	9.586	1		9.604

If, at the higher speeds, the experiment is prolonged the measured potentials drop slowly. This is to be expected, since, under the influence of the centrifugal force, there is a tendency of the salt and of the iodine to drift in the direction of the outer electrode. In an ultracentrifuge at much higher speeds than those used in our experiments Pedersen[9] attained sedimentation equilibrium for a number of salts, such as cesium chloride and lithium iodate.

The e. m. f. data plotted in Fig. 4 and recorded in Table I were obtained using a series of increasing speeds. The same accuracy has not yet been obtained with decreasing speeds, a phenomenon for which we can give no explanation.

A Summary of the Measurements.—Table I contains the results of a series of measurements on solutions of potassium iodide containing 0.1941 mole per liter at 25° and in addition varying amounts of iodine. The normalities of the iodine, *i. e.*, gram atomic weights per liter, are shown in column 2 of the table. The densities of the solutions, given in column 3, were determined by a magnetic float method which will be described in a future publication from this Laboratory. In the fourth column are given the observed molar conductances, $\Lambda_m = 1000\kappa/0.1941$, in which κ is the measured specific conductance. We are indebted to Dr. Theodore Shedlovsky for aid in making these measurements, which were made with the conductance bridge developed in this Laboratory, and in an oil thermostat regulating to 0.003°. The E/n^2 values given in column 5 were obtained by the method of least squares from the original data. Each "run" consisted of an experiment such as is shown in the results plotted in Fig. 4, with the potentials, E, measured at seven different speeds. For the cases in which more than one run was made, as indicated in column 6, the average deviation in per cent. is given in the following column.

Discussion of the Results

It will be seen from the data in Table I that the value of the quantity E/n^2 increases quite rapidly as the proportion of iodine in solution ascends. In the following discussion it is shown, quantitatively, that the effect is due to the effect of an iodide–iodine complex on the mechanism of the cell.

During the passage of current through the cell

$$(Pt);\ I_2,\ KI,\ I_2;\ (Pt) \qquad (A)$$

the electrochemical reaction

$$I^- = I^0 + \epsilon^- \qquad (2)$$

occurs at the anode and at the cathode. Here

$$\epsilon^- + I^0 = I^-$$

I^0 represents iodine in an uncharged condition. It may be in the form of I_2 or as a complex I^-_{j+1} with the iodine ion, in which j is the number of equivalents of uncharged iodine in the complex. During the passage of one faraday F through the cell, t_K equivalent of potassium ion constituent

(9) K. O. Pedersen, *Z. physik. Chem.*, **A170**, 41 (1934).

will migrate from the region of the anode and appear at the cathode, t representing a Hittorf transference number. The remainder of the current is transported in the reverse direction by t_I equivalent of I^- and t_C equivalent of the complex ion. The net loss around the anode is t_K equivalent of potassium ion and $(1 - t_I - t_C) = t_K$ equivalent of negatively charged ion. Thus there is a net loss of t_K equivalent of potassium iodide from the region of the anode. Since reverse phenomena occur at the cathode, a transport of t_K equivalent of the salt from one electrode to the other takes place. This is accompanied by the appearance of one equivalent of I^0 at the anode by the electrochemical reaction, eq. 2, and jt_C equivalent of that material by transference.

The transport process per faraday for the galvanic cell A is therefore t_K equivalent of potassium iodide from the anode to cathode and $(1 + jt_C)$ equivalents of I^0 in the reverse direction. If gradients of chemical potential $\Delta\mu$ exist in the cell the Gibbs free energy ΔZ of its reversible operation will be

$$-\Delta Z = EF = t_K \Delta\mu_K - (1 + jt_C)\Delta\mu_{I^0} \qquad (3)$$

Since the operation of the cell takes place in a centrifugal field the chemical potentials μ will be functions of the radius r in addition to the usual variables which are temperature, pressure, P, and the mole fractions of the components of the solution.

Assuming constant temperature and uniform concentration of the solution in the cell we have

$$\frac{d\mu_i}{dr} = \left(\frac{\partial\mu_i}{\partial r}\right)_P + \left(\frac{\partial\mu_i}{\partial P}\right)_r \frac{dP}{dr} \qquad (4)$$

Now the change of μ_i with r is given by

$$(\partial\mu_i/\partial r) = -M_i\phi \qquad (5)$$

in which ϕ is the centrifugal force per unit mass and M_i is the molecular or atomic weight. The negative sign is due to the fact that the energy of a component is increased by movement toward the center of rotation. The differential Gibbs free energy dZ of a solution is given by

$$dZ = -sdT + VdP + \mu_1\, dN_1 + \mu_2\, dN_2 \ldots \mu_i\, dN_i \qquad (6)$$

in which N_1, N_2, . . . , N_i represent the numbers of moles. Since dZ is an exact differential the partial molal volume $\bar{V}_i$ can be obtained by the cross differentiation[10]

$$\partial\mu_i/\partial P = \partial V/\partial N_i = \bar{V}_i \qquad (7)$$

Substituting $dP/dr = \rho\phi$ and eqs. 5 and 7 into eq. 4 we obtain

$$-d\mu_i/dr = \phi(M_i - \bar{V}_i\rho) = 4\pi^2 n^2 r(M_i - \bar{V}_i\rho) \qquad (8)$$

since $\phi = 4\pi^2n^2r$, in which n is the number of rotations per second. Using this expression in eq. 3 after integrating between radii r_2 and r_1 yields[11]

$$-EF = 2\pi^2n^2(r_2^2 - r_1^2) \times [t_K(M_{KI} - \bar{V}_{KI}\rho) - (1 + jt_C)(M_I - \bar{V}_I\rho)] \qquad (9)$$

It will be observed that this equation reduces to eq. 1, as the proportion of iodine, and thus the transference number t_C, decreases. Thus using eq. 1 and a limiting value of E/n^2 obtained by a short linear extrapolation from the data in Table I the transference number of the potassium ion in 0.1941 normal potassium iodide is found to be $t_K = 0.487_3$. This agrees closely with the value 0.4887 obtained by Longsworth[12] by the quite independent method of moving boundaries. In our computation values of the partial molecular and atomic volumes $\bar{V}_{KI}$, and $\bar{V}_I$ are necessary. Longsworth gives a formula, based on existing density data, from which $\bar{V}_{KI} = 46.34$ is obtained, and the value $\bar{V}_I = 30.31$ was computed from the density data in Table I. These quantities will be the subject of another contribution from this Laboratory.

With the aid of the conductance measurements, given in Table I, for potassium iodide solutions, with varying proportions of added iodine, a test of the validity of eq. 9 may be made. Assuming Kohlrausch's law of independent ion mobilities[13] the measured equivalent conductance Λ_m is given by

$$\Lambda_m = \lambda_K + (1 - R/j)\lambda_I + (R/j)\lambda_C \qquad (10)$$

in which the λ values are equivalent conductances of ion constituents; R is the ratio C_{I^0}/C_{KI}, and j is, once more, the number of equivalents of uncharged iodine carried by the complex. From this equation

$$\lambda_C = \lambda_I - (j/R)(\Lambda_{KI} - \Lambda_m) \qquad (11)$$

and also

$$t_K = \lambda_K/\Lambda_m \text{ and } t_C = R\lambda_C/j\Lambda_m \qquad (12)$$

since transference numbers are the proportion of the total current carried by a given ion constituent. Substituting these values in eq. 9 we have

$$-FE = 4\pi^2n^2(r_2^2 - r_1^2) \times \left[\frac{\lambda_K}{\Lambda_m}(M_{KI} - \bar{V}_{KI}\rho) - \left(1 + \frac{R\lambda_I - j(\Lambda_{KI} - \Lambda_m)}{\Lambda_m}\right)(M_I - V_I\rho)\right] \qquad (13)$$

To test the validity of this equation in terms of our experimental results we must have, in addition to the data given in Table I, values of the ion conductances λ_K and λ_I. With the aid of Longsworth's[12] value 0.4887 of t_K for 0.2 N potassium iodide and the value of Λ_m for solution 1 of Table I, $\lambda_K = 61.92$ and $\lambda_I = 64.78$ are obtained.

On the assumption that for the complex I^-_{j+1},

(10) The thermodynamic function, Z, applicable to processes at constant temperature and pressure, is of service here since, although there is a gradient of pressure along the galvanic cell, the cell mechanism does not involve any alteration of this pressure distribution. Equations 6 and 7 are eqs. Nos. 92 and 272 of Gibbs' "Equilibrium of Heterogeneous Substances."

(11) This equation is equivalent to equation 83, for the effect of height, in the paper by Koenig and Grinnell, *J. Phys. Chem.*, **44**, 463 (1940).

(12) Longsworth, THIS JOURNAL, **57**, 1185 (1935).

(13) This law is only approximate at 0.2 N, but it is a sufficiently good assumption for computing the relatively small term jt_C of eq. 9.

j should be an integer, values of E/n^2 were computed for $j = 1$, 2 and 3, corresponding to ratios R from the data in Table I. Those for $j = 2$ are given in that table in the eighth column, and are seen to agree closely with the quantities E/n^2 obtained experimentally. That the experimental results indicate the presence of the complex I_3^-, and are not in accord with I_2^- or I_4^- is shown graphically in Fig. 5 in which values E/n^2 for $j = 1$, 2 and 3 computed from eq. 13 are given as functions of the ratio $R(= C_{I^0}/C_{KI})$ as abscissas and the corresponding experimental values of E/n^2 from Table I are plotted as small circles. Here again the indication is clearly in close quantitative agreement with $j = 2$, or the complex ion I_3^-.

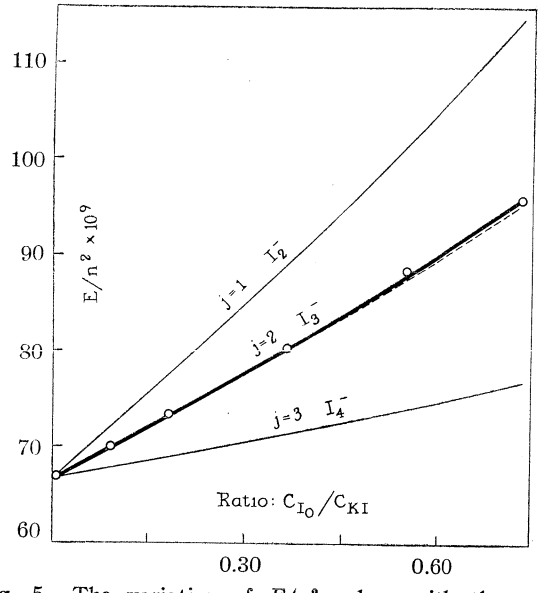

Fig. 5.—The variation of E/n^2 values with the ratio C_{I^0}/C_{KI}.

The existence of a complex of that composition has, from transference and distribution measurements, been known for a long time.[14] The results of this paper may, therefore, be regarded as a confirmation, by a quite new method, of the earlier conclusions.

A number of workers have determined the mass law constant for the equilibrium

$$I^- + I_2 = I_3^-$$

the most recent value being 1.40×10^{-3} at 25° for a total iodide concentration of 0.2 N as found by Jones and Kaplan.[14] A small proportion of the iodine in solution, therefore, exists in the form I_2 and the ratio R should, strictly, be corrected for this effect. The effect of the correction is shown in Fig. 5 by the dotted line diverging from the curve for $j = 2$, and is within the experimental error of the present series of measurements.

Summary

The potential, E, of a galvanic cell consisting of two iodide–iodine electrodes at two different radii in a rotor has been measured at different speeds of rotation, n. Reproducible potentials were obtained only when radial temperature gradients were eliminated and the solutions in the cell were free from suspended particles. A series of measurements were made on solutions which had a constant concentration of potassium iodide, but varying concentrations of iodine. For each solution values of E/n^2 were found to be accurately constant, through a range of values of of n from 1800 to 7200 r. p. m. The ratio E/n^2 increases with the proportion of free iodine, a fact that is quantitatively accounted for by the presence in solution of the ionic complex I_3^-. The measurements also yielded a value of the transference numbers of potassium iodide in agreement with those obtained by the moving boundary method.

New York 21, N. Y. Received March 24, 1949

(14) Bibliographies on the early work in this field are given by Bray and MacKay, This Journal, **32**, 914 (1910), and by Jones and Kaplan, *ibid.*, **50**, 1845 (1928).

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Effect of Ethanol in the Electro-reduction of *p*-Nitroaniline at the Dropping Mercury Electrode

BY O. D. SHREVE[1] AND E. C. MARKHAM

For solubility reasons, many of the organic polarographic reductions reported in the literature have been studied in mixtures of water with ethanol or other water miscible organic solvent. As pointed out by Kolthoff and Lingane,[2] the effect of such solvents on the measured half-wave potentials and diffusion currents is often overlooked, with resulting confusion in the interpretation of organic polarographic data. When reductions at the dropping mercury electrode are carried out in the approved manner, *i. e.*, in well buffered solutions, the over-all effect of added organic solvent on the potential will include: (a) the change resulting from any alteration in the hydrogen ion activity of the aqueous buffers; (b) any change in potential of the quiet mercury anode (or change due to the introduction of a liquid junction if an outside reference anode is used); and (c) any effect on the inherent reduction potential of the reducible compound. The effect on the diffusion currents will reflect the influence of the solvent on one or more of the terms in the Ilkovic equation (diffusion coefficient or capillary characteristics).

Investigations of the effect of organic solvents on metal ion reductions[3] indicate that diffusion currents are depressed but potentials only slightly affected. In the organic field a few experiments on the effect of varying solvent composition[4] have been reported, but these are limited in scope and incidental to the investigator's chief purpose.

The present report describes a complete quantitative study of the effect of ethanol, the most commonly used polarographic solvent, on (a) the *p*H values as calculated from hydrogen electrode potentials, for a series of commonly used buffers covering a wide *p*H range and (b) the usual polarographic values measured in the reduction of *p*-nitroaniline in these buffers. The appreciable solubility of this compound in water makes possible a direct comparison of its polarographic behavior in the presence of varying amounts of ethanol with that in water.

(1) Present address: E. I. du Pont de Nemours and Co., Philadelphia Laboratory, Philadelphia, Pennsylvania.

(2) Kolthoff and Lingane, "Polarography," N. Y. Interscience Publishers, New York, N. Y., 1941, p. 344.

(3) Bachman and Astle, THIS JOURNAL, **64**, 1303 (1942); Sartori, *Gazz. chim. ital.*, **71**, 233 (1941); Parracchio and Meloche, THIS JOURNAL, **60**, 1770 (1938); Sartori and Giacometto, *Gazz. chim. ital.*, **70**, 178 (1940); Zanko and Manusova, *J. Gen. Chem. (U. S. S. R.)*, **10**, 1171-76 (1940); Zlotowski and Kolthoff, *Ind. Eng. Chem., Anal. Ed.*, **14**, 473 (1942); THIS JOURNAL, **64**, 1297 (1942); **66**, 1431 (1944), *J. Phys. Chem.*, **49**, 386 (1945); Gentry, *Nature*, **157**, 479 (1946); Jessop, *ibid.*, 158 (1946); Brasher and Jones, *Trans. Faraday Soc.*, **42**, 775 (1946).

(4) Shikata and Tachi, *Mem. Coll. Agr., Kyoto Imp. Univ.*, **8**, 31 (1930); Tachi, *ibid.*, **40**, 17 (1937); Kolthoff and Lehmicke, THIS JOURNAL, **70**, 1879 (1948); Pasternak and Halban, *Helv. Chim. Acta*, **29**, 190 (1946).

Experimental

Using the polarographic cell-aqueous calomel electrode combination described below, polarographic and glass electrode potential measurements were made on 5.4×10^{-4} *M* *p*-nitroaniline solutions in nine buffer series, each series comprising a commonly used buffer system made up in water and in six ethanol–water mixtures. All solutions contained 0.02% gelatin as maximum suppressor and the total concentrations of buffer constituents in each series were held constant at those calculated to yield an ionic strength of 0.1 in water.[5]

Using the same cell combination, hydrogen and glass electrode potential measurements were made on 5 of the above series (compositions being identical except for the absence of the small amount of *p*-nitroaniline). The glass electrode potentials in these solutions were identical with those in the corresponding solutions containing *p*-nitroaniline and a plot of glass electrode *versus* hydrogen electrode potentials (Fig. 1) yielded a 45° straight line. Hydrogen electrode potentials for the remaining four series were not measured directly, but were derived from glass electrode measurements with the aid of this calibration curve. "Apparent" *p*H values for all solutions polarographed were then calculated from the measured or derived hydrogen electrode potentials.

Cell Assembly.—All measurements were made in a polarographic cell–aqueous saturated calomel electrode combination similar to that described by Lingane and Kolthoff[6] except that the cell was all Pyrex glass and was designed to accommodate both hydrogen and glass electrodes as well as a dropping electrode and salt bridge[7] through ground joints. The whole assembly was thermostated at 25°.

Polarographic Measurements.—A manually operated polarographic apparatus capable of accurate potential and current measurements was used. The circuit was similar to one which has been described by Lingane and Kolthoff.[6] Potentials were simultaneously applied and measured with a Leeds and Northrup potentiometer. Currents were measured in microamperes with a sensitive, long period Leeds and Northrup D'Arsonval galvanometer in conjunction with a lamp and curved scale. The galvanometer was calibrated in a manner similar to that recommended by Kolthoff and Lingane[8] and was adjusted to a "round number" sensitivity before each run (0.05 μa./mm. for most of the work) to facilitate conversion of scale readings to microamperes.

The observed diffusion current in each solution was corrected for residual current by the direct method[6] to obtain the true diffusion current, (i_d), and the potential corresponding to $i_d/2$ was taken as the half-wave applied potential. The half-wave applied potential was then corrected for *i*R drop after measurement of the cell circuit resistance[9] to give the true half-wave potential ($E_{1/2}$).

The same dropping capillary sealed directly to a Pyrex glass mercury reservoir was used throughout the study; the pressure on the dropping mercury was maintained constant

(5) The small contribution of the weakly ionized buffer acids to the ionic strength was ignored in these calculations.

(6) Lingane and Kolthoff, THIS JOURNAL, **61**, 828 (1939).

(7) Irving and Smith, *Ind. Eng. Chem., Anal. Ed.*, **6**, 480 (1934).

(8) Ref. 2, p. 228.

(9) Heyrovsky, *J. Coll. Czechoslov. Chem. Commun.*, **4**, 480 (1932).

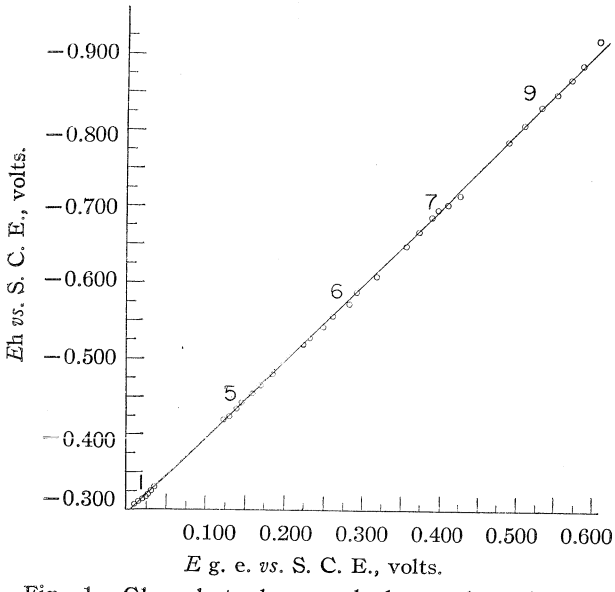

Fig. 1.—Glass electrode *versus* hydrogen electrode potential. Numbers refer to buffers identified in Table II. Points from left to right in each group correspond to increasing ethanol concentrations given in Table II.

at 30.8 cm. of mercury by a pressure regulating device.[6] All solutions were deaerated with purified nitrogen which passed through a portion of the solution under study in a side arm of the cell before entering the cell proper.

Hydrogen and Glass Electrode Measurements.—The hydrogen electrode measurements were made with a Leeds and Northrup Type K potentiometer, in the usual way, with a sensitive D'Arsonval galvanometer as null point indicator. The purified hydrogen bubbled through a portion of the solution in the cell side arm before entering the cell proper and measurements were taken until constant within ±1 mv. for buffers containing 0–35% ethanol and ±2 mv. for those richer in ethanol.

The glass electrode potentials were measured with a Coleman Model 3D *p*H electrometer, using a Coleman 3001 F electrode.

The cell set-up used in these measurements was exactly the same as that used for the polarographic measurements except, of course, for the replacement of the dropping electrode by a glass or hydrogen electrode.

Materials.—The *p*-nitroaniline used was an Eastman product purified by recrystallization from water and alcohol, m. p. 146–147°.

Absolute ethanol (U. S. Industrial Chemicals, Inc.) was distilled from alkaline silver oxide and the middle fraction of the distillate redistilled from aluminum amalgam to give the pure dry product used in the experiments.

"Hydrion Buffer Salts" (Micro Essential Laboratory, Brooklyn, N. Y.) were used for preparing buffers without further purification. The salts used included potassium chloride, glycine, sodium acetate, monopotassium phosphate and boric acid. The hydrochloric acid, acetic acid and potassium hydroxide stock solutions used in preparing buffers were made from J. T. Baker Analyzed C. P. grade chemicals and were standardized by the usual methods.

The tank nitrogen, used for deaerating, was purified by passing through a train consisting of (a) a Drierite tube; (b) copper gauze, maintained at 500° by an electric furnace; (c) solid potassium hydroxide; (d) phosphorus pentoxide; and (e) a second Drierite tube, before entering the polarographic cell.

The electrolytic hydrogen used for the hydrogen electrode measurements was purified by passing through a train consisting of (a) a soda-lime tube; (b) a bubble counter containing concentrated sulfuric acid; (c) a Pyrex furnace containing platinized asbestos at 500°; and (d) a Drierite tube before entering the cell.

Baker U. S. P. gelatin was used for suppressing maxima. Fresh solutions were frequently prepared and a trace of thymol added as preservative.

Results

Reduction in Aqueous Medium.—Shikata and Taguchi[10] studied the reduction of the nitroanilines in aqueous buffers at 25°. Since their work was done before the introduction of the half-wave potential concept, however, they reported "tangent" potentials and these were derived from polarograms showing maxima in varying degree. In agreement with the results reported by these investigators, we have observed only one wave in the reduction of *p*-nitroaniline throughout the *p*H range studied in buffer solutions but two waves in an unbuffered solution consisting of 10^{-4} *N* hydrochloric acid in 0.1 *N* potassium chloride.

The effect of varying concentration of the reducible compound on half-wave potential and diffusion current in aqueous acetate buffer (no. 6) is given in Table I. These data indicate that the Ilkovic equation holds reasonably well for the reduction. The half-wave potentials are fairly constant over the range 10^{-4} to 10^{-3} *M* but decrease below and increase above this concentration range.

TABLE I

EFFECT OF CONCENTRATION OF *p*-NITROANILINE ON HALF-WAVE POTENTIAL AND DIFFUSION CURRENT IN AQUEOUS ACETATE BUFFER OF *p*H 4.62

Concn., mmol./l.	$E_{1/2}$, v. *vs.* S. C. E.	i_d, μa	i_d/C
0.054	−0.509	1.13	20.9
.100	− .522	2.14	21.4
.140	− .525	2.88	20.6
.279	− .520	5.70	20.4
.400	− .518	8.40	21.0
.541	− .523	11.35	21.0
.729	− .526	15.32	21.0
.940	− .529	19.30	20.5
1.082	− .537	22.45	20.8

Effect of Ethanol on *p*H of Buffers and Half-Wave Potentials.—The *p*H values for the alcoholic as well as the aqueous buffers were calculated from the hydrogen electrode potentials using the usual equation for the *aqueous* saturated calomel–hydrogen electrode combination, $pH = (E_h - 0.2438)/0.0591$ as recommended for such cases.[11] It should be emphasized that the observed effect of ethanol on the *p*H values thus calculated includes the unknown effect on the E_0 value of the hydrogen electrode and the liquid junction potential as well as the effect on the actual hydrogen ion activity of the solutions.

(10) Shikata and Taguchi, *Mem. Coll. Agr. Kyoto Imp. Univ.*, **29**, 1 (1934).

(11) Dole, "Glass Electrode," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 300.

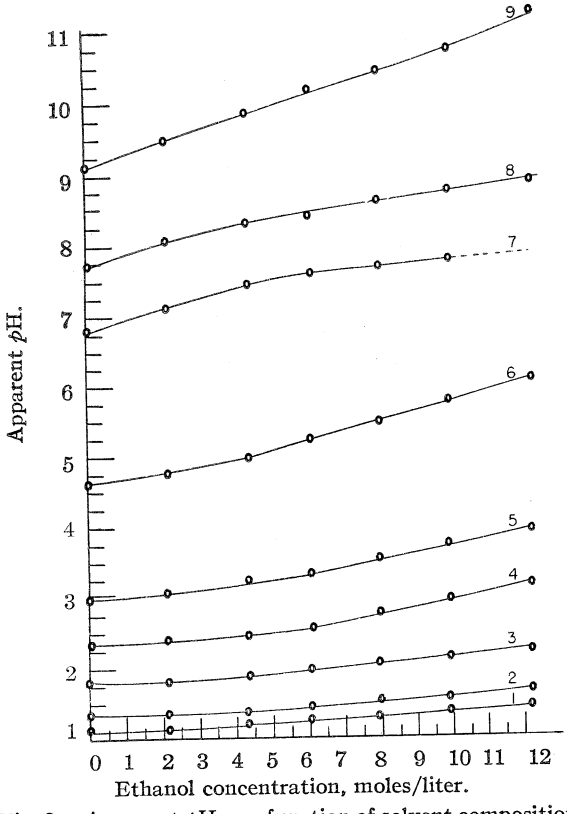

Fig. 2.—Apparent *p*H as a function of solvent composition. Curve numbers refer to buffer numbers in Table II.

The *p*H values are therefore designated as "apparent" *p*H numbers.

The curves of Fig. 2 show the effect of ethanol on the *p*H values of the nine buffers studied. It is seen that each of the curves for the acidic buffers undergoes an increase in slope after the addition of a certain amount of ethanol while those for the buffers near the neutral region tend to decrease in slope after the initial additions. The curve for the basic buffer is approximately linear over the entire range. The slopes of the curves beyond their inflection regions increase with increasing original *p*H of the buffers through the acid region, decrease in the neutral region and increase again in the case of the basic buffer. It will be noted that the more acidic buffers will tolerate considerable ethanol without serious effect on *p*H while the buffers of higher original *p*H are affected by relatively low concentrations.

The effect of ethanol on the half-wave potentials in the reduction of *p*-nitroaniline in these buffers is given in Fig. 3. It is seen that the potentials are shifted strongly to more negative values. In the acidic buffers the presence of about 2 to 3 *M* ethanol has little effect but beyond this concentration the curves increase sharply in slope and proceed linearly, the slopes increasing with increasing original *p*H of the buffers. In the neutral and basic buffers 2 *M* ethanol has a considerable effect but the slopes of the main portions of the curves tend to decrease with increasing original buffer *p*H.

Effect of Ethanol on Diffusion Currents.—The diffusion currents obtained in each buffer in the various solvent media are given in Table II. In all cases the values decrease with increasing ethanol, pass through a flat minimum at 8 to 10 *M* ethanol, and then tend to increase. This behavior is graphically illustrated in Fig. 4 where the diffusion currents in 0.1 *N* hydrochloric acid and in the acetate buffer (no. 6), are plotted as a function of solvent composition. In the case of these two media, it was possible to extend the experiments to higher ethanol content (14.66 *M*) and thus better illustrate the increase in i_d beyond the minimum.

Effect of Varying *p*H on Half-Wave Potentials, Diffusion Currents and Capillary Characteristics in Each Solvent Medium.—Plots of half-wave potential *versus* apparent *p*H (Table II) in each of the seven solvent media are linear over the entire *p*H range studied in water and in 2.17, 4.34 and 6.08 *M* ethanol. In the solvents richer in ethanol the relation is linear up to an apparent *p*H of about 8 beyond which point the curves undergo a decrease in slope. Empirical equations for the variation of half-wave potential with *p*H in the various solvent media are given in Table III.

In water and 2.17 *M* ethanol the diffusion currents show a slight initial increase with increasing *p*H (Table II). In each solvent medium richer in ethanol the diffusion currents are nearly constant over the entire *p*H range, no appreciable initial rise occurring.

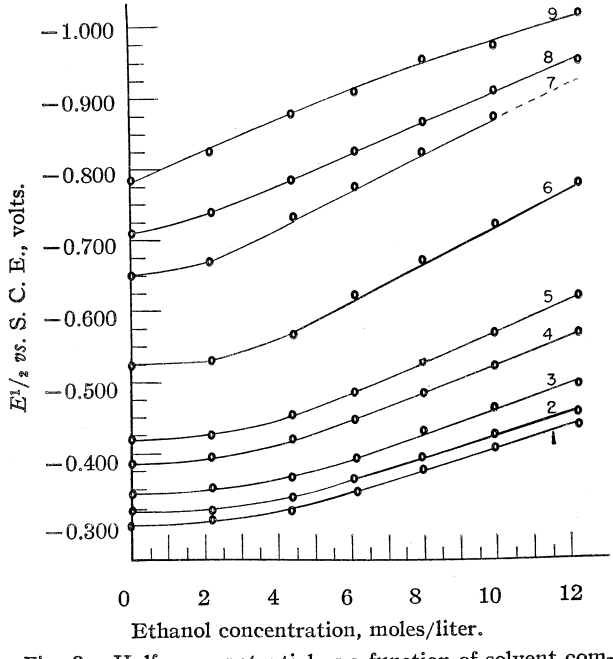

Fig. 3.—Half wave potential as a function of solvent composition: 5.4×10^{-4} *m* *p*-nitroaniline in nine buffers. Curve numbers refer to buffer numbers in Table II.

TABLE II

DIFFUSION CURRENTS —(5.4 × 10^{-4} *M* *p*-NITROANILINE)

Buffer no.[a]	*p*H in H_2O	Ethanol concentration, moles/liter 0	2.17	4.34	6.08	7.95	9.92	12.21	14.66
1	1.09	10.7	9.55	8.40	7.65	7.20	7.20	7.35	8.05
2	1.34	11.17	9.60	8.32	7.60	7.35	7.20	7.55	
3	1.79	11.30	10.00	8.50	7.65	7.35	7.40	7.85	
4	2.32	11.50	10.10	8.50	7.60	7.40	7.40	7.60	
5	2.98	11.50	10.10	8.50	7.65	7.25	7.20	7.65	
6	4.62	11.35	9.95	8.45	7.65	7.25	7.30	7.88	8.55
7	6.80	11.30	10.30	8.65	7.73	7.30	7.43	..	
8	7.72	11.40	10.20	8.55	7.70	7.35	7.30	7.85	
9	9.12	11.65	10.25	8.60	7.80	7.40	7.30	8.05	

[a] 1, 0.1 *m* HCl; 2, 0.05 *m* HCl, 0.05 *m* KCl; 3, 0.017 *m* HCl, 0.083 *m* KCl; 4, 0.04 *m* HCl, 0.06 *m* KCl, 0.06 *m* glycine; 5, 0.02 *m* HCl, 0.08 *m* KCl, 0.08 *m* glycine; 6, 0.1 *m* HAc, 0.1 *m* NaAc; 7, 0.025 *m* KOH, 0.05 *m* KH_2PO_4; 8, 0.032 *m* KOH, 0.036 *m* KH_2PO_4; 9, 0.03 *m* KOH, 0.07 *m* KCl, 0.06 *m* H_3BO_3.

TABLE III

EQUATIONS FOR THE POLAROGRAPHIC WAVE AND α VALUES (5.4 × 10^{-4} *M* *p*-NITROANILINE IN VARIOUS SOLVENT MEDIA)

Medium	Equation	Valid *p*H range	α[a]
Water	$E_{1/2} = -0.244 - 0.061\ p\mathrm{H}$	1 to 9	0.83
2.17 *M* Ethanol	$E_{1/2} = -0.244 - 0.062\ p\mathrm{H}$	1 to 9.5	.81
4.34 *M* Ethanol	$E_{1/2} = -0.250 - 0.064\ p\mathrm{H}$	1 to 9.8	.78
6.08 *M* Ethanol	$E_{1/2} = -0.270 - 0.066\ p\mathrm{H}$	1 to 9	.75
7.95 *M* Ethanol	$E_{1/2} = -0.293 - 0.068\ p\mathrm{H}$	1 to 9	.70
9.92 *M* Ethanol	$E_{1/2} = -0.308 - 0.072\ p\mathrm{H}$	1 to 8	.68
12.21 *M* Ethanol	$E_{1/2} = -0.332 - 0.074\ p\mathrm{H}$	1 to 8	.63

[a] Average for nine buffers.

The $m^{2/3}t^{1/6}$ value of the capillary is practically independent of solvent composition and *p*H. In all solutions, except those comprising the most basic buffer (no. 9), this value is 1.95 ± 0.01 mg.$^{2/3}$sec.$^{-1/2}$. In buffer 9 a somewhat lower average value of 1.90 ± 0.01 is observed.

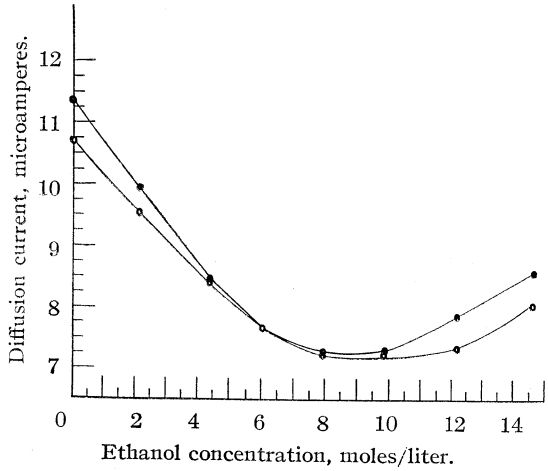

Fig. 4.—Diffusion current as a function of solvent composition: 5.4 × 10^{-4} *m* *p*-nitroaniline: ●, buffer no. 6 (HAc–NaAc); ○, buffer no. 1 (0.1 *N* HCl).

Effect of Ethanol on the Potential–Current Relationship at Points on the Polarographic Wave.—Plots of log $i/(i_d - i)$ *versus* cathode potential at points on the waves yield straight lines for all polarograms in all solvent media and the potential at which log $i/(i_d - i) = 0$ coincides with the measured half-wave potential. The values of *n* in the usual expression

$$E = E_{1/2} \frac{-0.059}{n} \log \frac{i}{i_d - i}$$

however, as determined from the slopes of the log plots[12] are not integral but are always less than 1. The equation for the waves therefore, takes the form

$$E = E_{1/2} \frac{-0.059}{\alpha} \log \frac{i}{i_d - i}$$

where α is *fractional*. The α values as determined from the slopes of the log plots are practically independent of buffer composition in a given solvent medium but decrease with increasing ethanol concentration as indicated in Table III.

Discussion

The general equation for the polarographic waves experimentally established in this reduction is of the form which has been found to hold in several irreversible organic reductions.[13] Although numerous theories have been advanced, the mechanism of the electrode reaction in such reductions has not been established. For this reason, and because of the many variables involved, no theoretical interpretation of the effect of ethanol on the half-wave potentials and the slopes of the waves will be attempted.

The variation in the magnitude of the *p*H increment produced by the addition of a given quantity of ethanol to each of the nine buffers is attributed mainly to the variable effect of this solvent on the dissociation of the various buffer acids. A similar variation was observed by Smith,[14] who determined *p*H values for several buffers in water and in 50% ethanol solutions. Investigations of the effect of ethanol on the dissociation of various acids are reviewed (through 1937) by Kolthoff and Rosenbloom in their monograph "Acid-Base Indicators."[15] There are also

(12) Ref. 2, p. 145.
(13) Ref. 2, p. 195.
(14) R. B. Smith, *J. Am. Pharm. Assoc.*, **17**, 241 (1928).
(15) Kolthoff and Rosenbloom, "Acid-Base Indicators," The Macmillan Co., New York, N. Y.

more recent investigations too numerous to list here. As might be expected the effect is slight in the case of strong acids but the dissociation constants of weak acids may be 10^4 to 10^6 times smaller in absolute ethanol than in water.[16]

Diffusion Current Data and Calculation of Diffusion Coefficient.—The diffusion current behavior illustrated in Fig. 4 may be attributed mainly to the effect of the viscosity of the medium on the diffusion coefficient. No viscosity data for the electrolyte solutions studied are available but if the viscosities of water–ethanol mixtures[17] are plotted against ethanol content, the curve shows a flat maximum over a region coinciding roughly with that of the minimum in the curves of Fig. 4. A similar effect was observed by Pasternack and Halban in the reduction of two ketones[4] and by Zlotowski and Kolthoff in the reduction of barium and strontium.[3]

The electroreduction of *p*-nitroaniline at a mercury electrode has been found to involve 6 electrons.[18] Assuming $n = 6$ in the Ilkovic equation, it is possible to calculate the diffusion coefficient (D) for the *p*-nitroaniline molecule from the polarographic data. In the aqueous phosphate buffer of *p*H 6.8 (no. 7, Table II), such a calculation yields a value of $D = 8.79 \times 10^{-6}$cm.^{2}sec.$^{-1}$. No data permitting a direct calculation of a diffusion coefficient value for this molecule could be found in the literature; an approximate value can be obtained, however, by assuming, as suggested by Kolthoff and Lingane,[19] that the required diffusion coefficient is equal to that of an organic ion of similar size and shape for which conductivity data are available and applying the equation

$$D^\circ = 2.67 \times 10^{-7} (\lambda^\circ/\text{valence})$$

Thus, the diffusion coefficient for the *p*-aminobenzoate ion, for which $\lambda^\circ = 32$ mhos.,[20] is 8.54×10^{-6} cm.^{2}sec.$^{-1}$, a value in good agreement with that calculated from the polarographic data above and tending to confirm the assumption that six electrons are indeed involved in the reduction. Using the value $n = 6$, together with the $m^{2/3}t^{1/6}$ values given above, and applying the Ilkovic equation, values for the diffusion coefficient, D, in all buffer solutions studied can be obtained from the data of Table II.[21]

(16) Kolthoff and Rosenbloom, ref. 15, p. 97.

(17) "Handbook of Chemistry and Physics," 24th ed., Chem. Rubber Co., Cleveland, O., 1940.

(18) Glasstone and Hickling, "Electrolytic Oxidation and Reduction," D. Van Nostrand Co., New York, N. Y., 1936, p. 204.

(19) Ref. 2, p. 51.

Summary

1. "Apparent" *p*H values have been determined for a series of commonly used buffer systems in water and 6 ethanol–water mixtures and the polarographic reduction of *p*-nitroaniline in these buffers has been investigated.

2. The Ilkovic equation has been shown to hold for the reduction and evidence that 6 electrons are involved has been given.

3. Equations relating half-wave potentials to apparent *p*H in each solvent medium have been given.

4. Data showing the effect of ethanol on (a) the equation for the polarographic waves, (b) the magnitude of the half wave potential and (c) the various terms in the Ilkovic equation have been presented and discussed.

5. The polarographic data given affords a means of obtaining diffusion coefficient values for *p*-nitroaniline in the solutions studied.

(20) "International Critical Tables," Vol. VI, p. 278.

(21) Such calculations will of course involve the assumption that ethanol does not affect the validity of the Ilkovic equation or the value of n.

CHAPEL HILL, N. C. RECEIVED OCTOBER 27, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE CHEMICAL RESEARCH LABORATORY OF POLAROID CORPORATION]

The Ultraviolet Absorption Spectra of Alkoxy- and Hydroxybenzils

BY NELSON J. LEONARD, RICHARD T. RAPALA,[1] HERSHEL L. HERZOG[2] AND ELKAN R. BLOUT

The yellow color of glyoxal and benzil was contrasted by Robinson[3] with the absence of color in ethyl oxalate and crystalline 4,4′-diethoxybenzil. The difference was explained on the basis that ethyl oxalate possesses a neutralized system (an electron-donating group attached to an electron-accepting group) and that the ethoxyl groups in 4,4′-diethoxybenzil have an influence on the diketone system of benzil through the benzene nuclei similar to that which obtains by direct union in ethyl oxalate. A quantitative comparison of the color of these compounds can be found in the determination of their absorption spectra.

The ultraviolet absorption maximum for ethyl oxalate[4] has been shown to lie at much shorter wave length than the maxima of glyoxal,[5] methyl-

(1) Present address: Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

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(3) Robinson, "Outline of an Electrochemical Theory of the Course of Organic Reactions," Institute of Chemistry of Great Britain and Ireland, London, 1932, p. 30.

(4) Scheibe, *Z. Elektrochem.*, **34**, 497 (1928), reported $\lambda_{max.} = 250$ mμ and $\log \epsilon = 1.35$ in methanol.

(5) Lüthy, *Z. physik. Chem.*, **107**, 285 (1923), reported $\lambda_{max.} = 450$ mμ and $\log \epsilon = 0.50$ in ethanol.

TABLE I

SUBSTITUTED BENZILS

Benzil	Color of solid[e]	M. p., °C.	Yield	λmax. mμ	log ε	λmax. mμ	log ε[g]	mμ	log ε	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Unsubstituted[8]	y	94–95	93[a]	259	4.31			370	1.89	$C_{14}H_{10}O_2$				
2-Methoxy[12]	y	71–72	60[a]	257	4.28	323	3.64			$C_{15}H_{12}O_3$				
3-Methoxy	y	87–88	30[b]	255	3.90	319	4.12	365	3.26	$C_{15}H_{12}O_3$	74.98	74.91	5.04	5.36
4-Methoxy[13]	y	64–65	68[a]	255	4.18	291	4.26	~380	2.08	$C_{15}H_{12}O_3$				
2-Ethoxy	p	101–102	60[a]	253	4.19	326	3.63			$C_{16}H_{14}O_3$	75.57	75.72	5.55	5.66
4-Ethoxy	p	70–71	60[a]	260	4.30	292 277	4.34 4.31	~390	2.0	$C_{16}H_{14}O_3$	75.57	75.31	5.55	5.67
2,2′-Dihydroxy[14]	p	154–155	50[d]	257	4.22	332	3.86			$C_{14}H_{10}O_4$				
4,4′-Dihydroxy[11]	y	244–246	87[d]			299	4.52	~400(?)	2.0	$C_{14}H_{10}O_4$				
2,2′-Dimethoxy[15]	0	128–129	40[a]	254	4.29	318	3.92			$C_{16}H_{14}O_4$				
3,3′-Dimethoxy[16]	y	82–83	60[a]	262	4.06	322	4.18	~380	2.67	$C_{16}H_{14}O_4$				
4,4′-Dimethoxy[17]	y	132–133	52[a]			298	4.35	~380(?)	2.16	$C_{16}H_{14}O_4$				
2,2′-Diethoxy[16]	0	157–158	50[a]	255	4.29	317	3.98			$C_{18}H_{18}O_4$				
3,3′-Diethoxy	p	55–56	50[a]	262	3.97	321	3.97	~375	2.97	$C_{18}H_{18}O_4$	72.47	72.05	6.08	6.19
4,4′-Diethoxy[18]	0[f]	148–149	62[c]			300	4.51			$C_{18}H_{18}O_4$	72.47	72.46	6.08	6.27
3,3′,4,4′-bis-Methylenedioxy[11]	y	171–172	54[a]	235	4.28	281	3.98	324	4.12	$C_{16}H_{10}O_6$				
3,3′,4,4′-Tetraethoxy	0	162–163	40[a]	232	4.40	285	4.29	323	4.30	$C_{22}H_{26}O_6$	68.38	68.34	6.78	6.70
2,2′,3,3′-Tetramethoxy	0	143–144	37[a]	261	4.29	320	3.70			$C_{18}H_{18}O_6$	65.45	65.69	5.49	5.98
5,5′-Dibromo-2,2′-dimethoxy[14]	0	231–232	53[a]	250	4.29	331	3.86			$C_{16}H_{12}Br_2O_4$				

[a] Benzoin condensation (symmetrical or unsymmetrical) followed by oxidation of the benzoin with copper sulfate–pyridine. Over-all yield is based on the original aldehyde. [b] Formation of the benzyl phenyl ketone by reaction between a substituted benzamide and benzylmagnesium chloride, followed by oxidation of the substituted benzyl phenyl ketone with selenium dioxide. Over-all yield is based on the substituted benzamide. [c] Friedel–Crafts reaction between oxalyl chloride and phenetole with aluminum chloride. Over-all yield is based on the oxalyl chloride. [d] Hydrolysis of the corresponding dialkoxybenzyl. [e] y = yellow; p = pale yellow; 0 = colorless. [f] Yellow in 95% ethanol or in chloroform solution. [g] ~ Indicates an inflection point.

glyoxal,[6] and biacetyl,[7] which is consistent with Robinson's theory. However, our investigation shows that the absorption spectra of 4,4′-diethoxybenzil and of a series of alkoxy- and hydroxybenzils do not have an analogous relationship when compared with that of benzil. We have found that the introduction of alkoxyl and hydroxyl groups into the benzil molecule produces a bathochromic shift in ultraviolet absorption, and we have observed that, whereas crystalline 4,4′-diethoxybenzil is colorless, solutions of the compound are yellow.

Experimental

Preparation of Substituted Benzils: Method A

Preparation of Symmetrical Benzoins.—One-tenth mole of the aldehyde was dissolved in 30 ml. of ethanol and 15 ml. of water. Two grams of potassium cyanide was added and the solution was heated under reflux for one and one-half hours. After the material had been allowed to cool and to stand for three hours, it was poured into two volumes of water. The oil which separated was extracted with ether. The ether was removed and the residual oil was used directly in the oxidation.

Preparation of Unsymmetrical Benzoins.—Five hundredths mole of the substituted benzaldehyde and 0.05 mole of benzaldehyde were dissolved in 30 ml. of ethanol and 15 ml. of water. The condensation and isolation methods were identical with those employed for the symmetrical benzoins.

Oxidation of Benzoins to Benzils.[8]—To 0.05 mole of impure benzoin was added a solution of 20 g. of copper sulfate in 30 ml. of pyridine and 10 ml. of water. The mixture was heated under reflux for two hours, after which it was poured into three volumes of water. The product was extracted with ether and the ether was removed. The residue was recrystallized at least five times from aqueous ethanol.

Method B

Preparation of *m*-Alkoxyphenyl Benzyl Ketones.—The reaction between the *m*-alkoxybenzamide and benzyl magnesium chloride was conducted according to the method of Jenkins[9] to obtain the corresponding *m*-alkoxyphenyl benzyl ketone.

Oxidation of *m*-Alkoxyphenyl Benzyl Ketones to Benzils.—The oxidation was carried out according to the method of Hatt, Pilgrim and Hurran.[10] The benzil was recrystallized five times from aqueous ethanol.

Method C

Friedel–Crafts Reaction. Preparation of 4,4′-Diethoxybenzil.—To a well-stirred, ice-cooled solution of 0.2 mole of phenetole and 0.1 mole of oxalyl chloride in 100 ml. of carbon disulfide, 30 g. of aluminum chloride was added in small portions over a period of two hours. The reaction mixture was then warmed gently on the steam-bath for thirty minutes. The complex was decomposed by means of hydrochloric acid and ice. The carbon disulfide was removed by distillation and the residue was filtered. The 4,4′-diethoxybenzil thus collected was recrystallized first from glacial acetic acid and then several times from aqueous ethanol.

Method D

Hydrolysis, Preparation of 4,4′-Dihydroxybenzil.[11]—A solution of 20.2 g. (0.074 mole) of 4,4′-dimethoxybenzil in

(6) Woo and Chang, *Trans. Faraday Soc.*, **41**, 157 (1945), reported $\lambda_{max.}$ = 440 mμ and log ε = 1.14 in ether.

(7) Lüthy, *Compt. rend.*, **176**, 1547 (1923), Lardy, *ibid.*, **176**, 1548 (1923), and Herold, *Z. physik. Chem.*, **B18**, 265 (1932), reported $\lambda_{max.1}$ = 430 mμ and log ε = 1.3, $\lambda_{max.2}$ = 280 mμ and log ε = 1.2 in hexane. Henri, "Études de Photochimie," Paris, 1919, reported the same values in ethanol.

(8) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, pp. 80, 88.

(9) Jenkins, THIS JOURNAL, **55**, 703 (1933).

(10) Hatt, Pilgrim and Hurran, *J. Chem. Soc.*, 93 (1936).

(11) Schönberg and Kraemer, *Ber.*, **55**, 1174 (1922).

(12) Brass, Willig and Hanssen, *ibid.*, **63**, 2613 (1930).

(13) Tiffeneau and Lévy, *Bull. soc. chim.*, [4] **49**, 725 (1931).

(14) Kuhn, Birkofer and Moller, *Ber.*, **76**, 900 (1943).

(15) Irvine, *J. Chem. Soc.*, **79**, 668 (1901).

(16) Schönberg and Malchow, *Ber.*, **55**, 3746 (1922).

(17) Irvine and Moodie, *J. Chem. Soc.*, **91**, 536 (1907).

(18) Vorländer, *Ber.*, **44**, 2455 (1911).

150 ml. of acetic acid was heated to boiling, and 48% hydrobromic acid was added in portions until the solution became turbid. Boiling was continued for two hours, after which the mixture was cooled and poured into water. The crude product (15.6 g.) was recrystallized five times from nitroethane.

The absorption spectra measurements were made with a Beckman quartz spectrophotometer model DU using a 1-cm. quartz cell and a hydrogen discharge tube as the ultraviolet source. Ninety-five per cent. ethanol was used as the solvent throughout. In Table I are reported the physical, analytical and spectrographic data for the compounds studied, and in Figs. 1 through 5, the ultraviolet absorption curves for these compounds.

Discussion

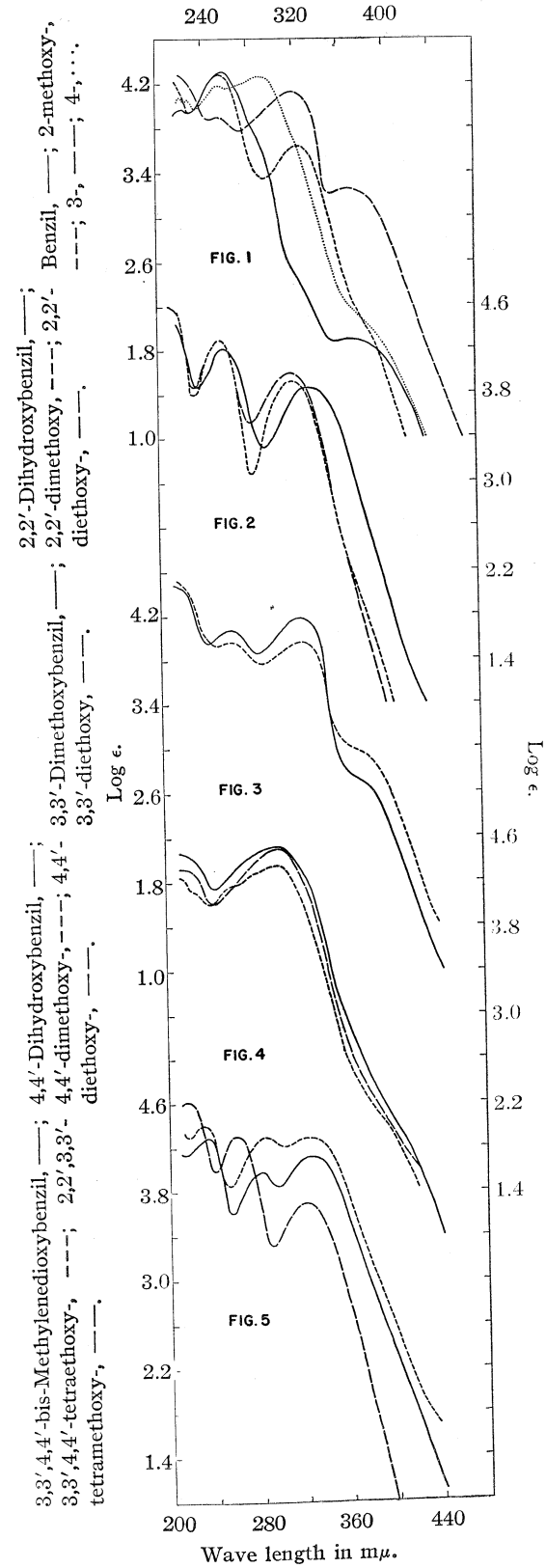
Macroscopic examination of the colors of the 4,4′-disubstituted benzils in the crystalline state shows that the diethoxy compound is colorless whereas the dihydroxy and dimethoxy compounds are definitely yellow. Microscopic examination of the crystals of these compounds, as obtained from aqueous ethanol, indicates that 4,4′-dimethoxy- and 4,4′-diethoxybenzil crystals are orthorhombic, although probably not isomorphous because of the different orientation of the index ellipsoid axes with respect to the prism axis. 4,4′-Dihydroxybenzil crystals are monoclinic.[19]

In all three compounds, the resonance configurations should be similar, which would lead us to expect that the absorption spectra should be similar. This is, in fact, the case, as the ultraviolet absorption determination shows. All three compounds are characterized essentially by one high-intensity absorption peak at 300 mμ (Fig. 4). This is a similar bathochromic shift of 30–40 mμ (compared to benzil) to that observed with the *p,p′*-disubstituted benzalazines.[20] In the wave length region above 410 mμ, the curves for the 4,4′-disubstituted benzils are also similar and resemble closely that of benzil. The prediction from these absorption curves that all of the ethanolic solutions should be yellow is verified simply by visual examination. Since the diethoxy compound is similar to the dimethoxy and dihydroxy compounds in ultraviolet absorption and visible absorption in solution, the lack of color in the 4,4′-diethoxybenzil solid is related to the crystalline habit of the material and is not an effect directly attributable to the electron-donating property of the ethoxyl group, as has been proposed. This seems to be another example of the relatively well-known fact that the color of crystals does not indicate necessarily the color of the molecules in solution.

The inconsistency between color of solid and color of solutions is not exhibited by the corresponding 2,2′-disubstituted benzils. 2,2′-Diethoxybenzil and 2,2′-dimethoxybenzil are colorless as solids and colorless in solution; 2,2′-dihydroxybenzil is pale yellow as a solid and yellow in ethanol solution. As would be expected

(19) The authors are indebted to Miss E. J. Weichel for the crystallographic and optical analyses.

(20) Blout and Gofstein, THIS JOURNAL, **67**, 13 (1945).

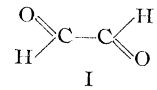


Figs. 1–5.—Absorption spectra of benzils.

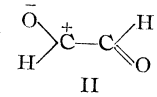
because of their similar electronic configurations, the first two compounds exhibit similar absorption maxima at 254 and 318 mμ; the dihydroxy compound likewise has a maximum at 257 mμ, but the second maximum has shifted to 332 mμ (Fig. 2). The end absorption, above 380 mμ, is less for 2,2′-diethoxybenzil and 2,2′-dimethoxybenzil (colorless in solution) than it is for benzil, while the end absorption of 2,2′-dihydroxybenzil (yellow in solution) is similar to that of benzil. The spectral determination is thus, in this case, consistent with visual examination of the solids and solutions.

While comparison of light absorption of different benzils is warranted, similar comparison of absorption of aromatic 1,2-diketones with that of aliphatic 1,2-diketones has less meaning. Since the time when Robinson proposed the common basis for the yellow color of benzil and glyoxal and for the lack of color of 4,4′-diethoxybenzil and ethyl oxalate,[3] the spacial configuration of the dicarbonyl groups in these molecules has been elucidated. The accumulated evidence indicates that the dicarbonyl system in benzil has a skew configuration, whereas the carbonyl groups in glyoxal and biacetyl have a coplanar, *trans* configuration. The conclusion that the benzil molecule has a skew structure, in which the two benzoyl units lie in planes approximately at right angles to each other, has been reached from X-ray examination of crystals by Knaggs and Lonsdale,[21] from dipole moment measurement of benzil in solution by Caldwell and LeFèvre,[22] and from parachor determination by Gibling.[23] For glyoxal and biacetyl, LuValle and Schomaker[24] have found that the electron diffraction, dipole moment, and chemical data indicate uniformly that both molecules are planar with the *trans* configuration and that rotation about the C—C bond (1.47 ± 0.02 Å.) connecting the adjacent carbonyls is restricted. Observations by Gaydon[25] on the spectrum resulting from a Tesla discharge through glyoxal vapor are best explained on the assumption that the glyoxal molecule has the planar, *trans* form. The bond orders in glyoxal, as calculated by the method of molecular orbitals,[26] are also consistent with the molecular structure of glyoxal as advanced by LuValle and Schomaker.

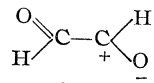
The exact chemical state of glyoxal can be considered most adequately as a resonance hybrid of a number of contributing structures (I, II, III, IVa, IVb). The fact that structures IVa and IVb contribute to the ground state of the molecule is evidenced by the shortened distance, 1.47 Å., between the carbonyl carbon atoms.



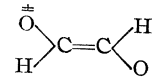
I



II



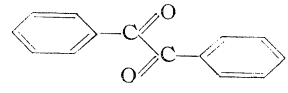
III



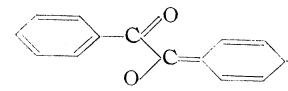
IVa,b

It has been suggested[27,28] that the absorption (and therefore the visible yellow color) of such an aliphatic 1,2-dicarbonyl compound is due to excitation of the electronic oscillations represented mainly by the formulas IVa and IVb.

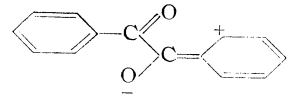
In the benzil molecule, structures of type IV should make much less contribution to the resonance hybrid because the molecule is skew and will resist the coplanarity demanded by such contributing structures. The more likely resonance structures for benzil are indicated by formulas V-X. The absorption spectra observations are consistent with the known differences



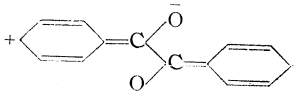
V



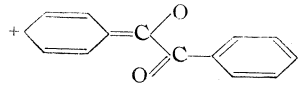
VI



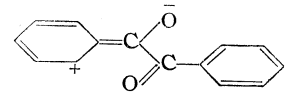
VII



VIII



IX



X

in the structure of glyoxal and benzil. The wave length (450 mμ) and magnitude (log ϵ = 0.50)[29] of absorption by glyoxal[5] are not commensurate with the wave length (259, 370 mμ) and magnitude (log ϵ = 4.31, 1.89) of absorption by benzil (Fig. 1). The "dicarbonyl" absorption has been greatly modified in the benzil molecule.

Since we must consider the 1,2-dicarbonyl systems in the aliphatic and aromatic compounds as essentially different, we cannot expect hydroxyl or alkoxyl groups on the benzil molecule to have an effect on the absorption spectra analogous to that found in going from glyoxal to oxalic acid and its esters. Because of the skew structure of benzil, the absorbing units must act more or less like individual benzoyl groups (V-X), and the spectral effect of substitution of alkoxyl or hydroxyl groups on benzil should be similar to that of analogous substitution on benzaldehyde or acetophenone. The spectra of such compounds in ethanol have been previously deter-

(21) Knaggs and Lonsdale, *Nature*, **143**, 1023 (1939).

(22) Caldwell and LeFèvre, *J. Chem. Soc.*, 1614 (1939); *Nature*, **143**, 803 (1939).

(23) Gibling, *J. Chem. Soc.*, 661 (1942).

(24) LuValle and Schomaker, THIS JOURNAL, **61**, 3520 (1939).

(25) Gaydon, *Trans. Faraday Soc.*, **43**, 36 (1947).

(26) Coulson, *ibid.*, **42**, 106 (1946).

(27) Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939).

(28) Calvin and Wood, THIS JOURNAL, **62**, 3152 (1940).

(29) Methylglyoxal[6] and biacetyl[7] show maxima of greater intensity.

mined, but in order to facilitate comparison of the ultraviolet absorption maxima of benzaldehydes and benzils, the pertinent data are collected and reproduced in Table II.

TABLE II

SUBSTITUTED BENZALDEHYDES

Compound	λmax. mμ	log ε	mμ	log ε	mμ	log ε
Benzaldehyde[30]	240	4.12	278	3.02	320	1.7
Acetophenone[30]	240	4.12	278	3.02		
Propiophenone[31]	245	4.1	~280	3.05		
o-Hydroxybenzaldehyde[30]	255	4.00	325	3.48		
p-Hydroxybenzaldehyde[30]	221	4.14	284	4.24	~332	2.25
o-Methoxybenzaldehyde[30,32]	253	4.07	319	3.62		
m-Methoxybenzaldehyde[30,32]	252	3.92	314	3.45		
p-Methoxybenzaldehyde[30]			277	4.17		
Piperonal[33]			275	3.8	315	4.0

It can be seen from Tables I and II that the effect of *o*-, *m*- and *p*-hydroxy- and alkoxy-substitution in benzaldehyde are indeed parallel to the effects of analogous substitution in both rings of benzil. In general, such substitution shifts the absorption maxima to longer wave lengths. In both series, *ortho*- and *meta*-substituted compounds exhibit two main peaks and *para*-substituted compounds have essentially one absorption band in the ultraviolet.[34] The wave lengths of the maxima are proximate for the benzaldehyde and benzil analogs. The closest agreement is found for the maxima exhibited by *o*-methoxybenzaldehyde and 2,2′-dimethoxybenzil. The wave lengths of the maxima are practically identical and the extinction coefficients of the 2,2′-dimethoxybenzil maxima are about double those of *o*-methoxybenzaldehyde. Thus, the transitions to the excited states responsible for absorption must be similar for the two compounds. There is also close agreement between the maxima of *o*-methoxybenzaldehyde and 2,2′-diethoxybenzil (Fig. 2) and good agreement between the maxima of *o*-hydroxybenzaldehyde and 2,2′-dihydroxybenzil. The maxima for *m*-methoxybenzaldehyde and 3,3′-dimethoxy- and 3,3′-diethoxybenzil (Fig. 3) differ only by 8–10 mμ in wave length, but the long wave length absorption of benzil (370 mμ) appears as an inflection point (380 mμ) in the 3,3′-dialkoxybenzils, indicating that additional electronic transitions are possible in this molecule. The greatest difference of wave length for comparative maxima is found between *p*-hydroxybenzaldehyde and 4,4′-dihydroxybenzil (15 mμ), between *p*-methoxybenzaldehyde and 4,4′-dimethoxybenzil (21 mμ). The shift of the maxima toward longer wave lengths with these *para*-substituted benzils can be due either to an increase in the number of configurations for the excited state or to an increase in the electron density of such states. Because two adjacent carbonyl groups are not very effective in transmitting conjugation through a molecule, it is difficult to see how the length of the absorbing system can be increased over that which exists in *p*-hydroxy- or *p*-alkoxybenzaldehydes.

When the absorption curves of different benzils are compared, we observe that there is close correspondence between those of 4,4′-dihydroxybenzil and 4,4′-dimethoxybenzil, whereas the longer wave length maximum of 2,2′-dihydroxybenzil undergoes a 14 mμ bathochromic shift compared to that of 2,2′-dimethoxybenzil (*cf.* Figs. 2 and 4). Morton and Stubbs[30] observed a similar displacement of 18 mμ between the absorption maxima of *o*-hydroxybenzaldehyde and *o*-methoxybenzaldehyde in hexane solution. They attributed this to chelation in the *o*-hydroxybenzaldehyde, an explanation which is also admissible for 2,2′-dihydroxybenzil.

As mentioned previously, the long wave length maximum of benzil appears as an inflection point in the absorption curves of 3,3′-dialkoxybenzils (Fig. 3), but is not present in the curves of the 2,2′- or 4,4′-dialkoxybenzils (Figs. 2 and 4).[35] This maximum, present in benzil, either has disappeared or has shifted toward shorter wave length and lost its identity in the 2,2′- and 4,4′-disubstituted compounds.

The absorption curves of the 2-, 3- and 4-alkoxybenzils are intermediate between those of benzil and the corresponding disubstituted benzils (*cf.* Figs. 1, 2, 3, 4), as expected. The curves of 3,3′,4,4′-bis-methylenedioxybenzil and 3,3′,4,4′-tetraethoxybenzil (Fig. 5) are a composite of those of 3,3′- and 4,4′-dialkoxybenzil and that of 2,2′,-3,3′-tetramethoxybenzil (Table I) is a composite of those of 2,2′- and 3,3′-dimethoxybenzil.

Summary

The ultraviolet absorption spectra of benzil and seventeen alkoxy- and hydroxybenzils have been determined.

The absorption maxima and the color of series of *o*-, *m*- and *p*-substituted benzils in ethanol solution show regularities which are not exhibited by these compounds in the crystalline state.

The absorption maxima of the substituted benzils and the correspondingly substituted benzaldehydes have been shown to lie at closely comparable wave lengths. This is consistent with the skew structure of benzil, likewise to be expected for the substituted benzils, and is an in-

(30) Morton and Stubbs, *J. Chem. Soc.*, 1347 (1940).

(31) Zucker and Hammett, THIS JOURNAL, **61**, 2785 (1939).

(32) Valiasko, *J. Russ. Phys.-Chem. Soc.*, **42**, 751 (1910).

(33) Hilmer and Schorning, *Z. physik. Chem.*, **168A**, 81 (1934).

(34) The gross structure of the main ultraviolet absorption bands in the benzil series seems to parallel closely that observed with the similarly substituted benzalazines.[20] In particular, it should be pointed out that in both series the symmetrically *para*-substituted compounds exhibit but a single maximum in the region examined, whereas two main absorption peaks become increasingly evident as one proceeds from the symmetrically substituted *meta* to the symmetrically substituted *ortho* compounds.

(35) The presence of a true inflection point at 380–400 mμ in the 4,4′-dihydroxy- and 4,4′-dimethoxybenzil is certainly open to question.

dication that the excited structures which give the major contribution to absorption are closely related to those which contribute to the absorption of the substituted benzaldehydes.

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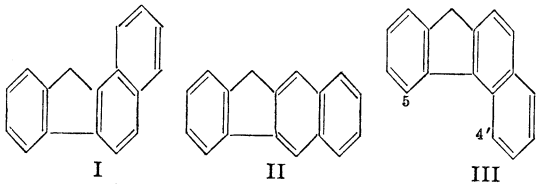
[CONTRIBUTION FROM THE WEIZMANN RESEARCH CENTER, REHOVOTH, ISRAEL, AND THE U. S. BUREAU OF MINES PITTSBURGH, PENNA.]

Structure of the Benzfluorenes and Benzfluorenones

BY MILTON ORCHIN[1] AND ROBERT A. FRIEDEL[2]

Introduction

Of the three possible benzfluorenes, I–III, 1,2-benzfluorene, I, and 2,3-benzfluorene, II, have strikingly similar chemical and physical properties and ultraviolet spectra. 3,4-Benzfluorene, III, is however considerably different from its isomers. The benzfluorenes, I and II, are high melting, difficult to separate and relatively insoluble. They both form unstable pic-



I II III

rates and trinitrobenzene complexes in the ratio of 2 moles of polynitro compound to 1 mole of hydrocarbon. The benzfluorene, III, is much lower melting, relatively soluble, easily separated from its isomers and forms stable molecular complexes in a molar ratio of 1:1.

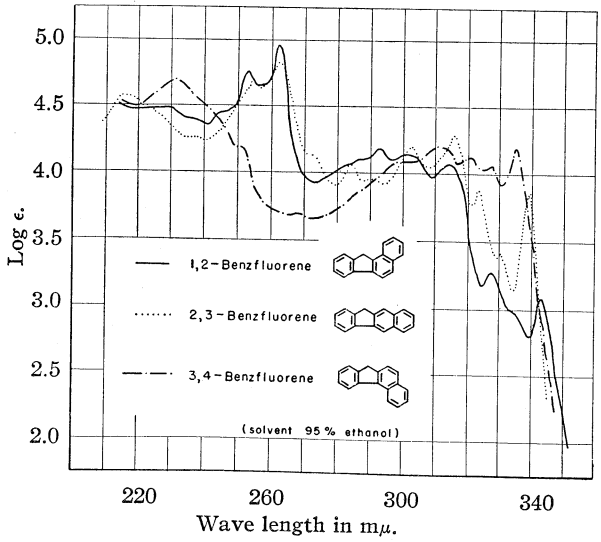


Fig. 1.—Ultraviolet spectra of the benzfluorenes.

Discussion

A possible explanation of the contrasting properties of the benzfluorenes is revealed in a comparison of them with the phenylnaphthalenes. Both I and II may be considered as 2-phenylnaphthalene derivatives while III may be considered as a derivative of 1-phenylnaphthalene. The ultraviolet absorption spectra of the three isomers (Fig. 1) show that although some dissimilarity exists between the spectra of I and II in the 270–300 mμ region, on the whole the spectra of I and II are quite similar and differ from that of III in a manner analogous to the difference in spectra between 1- and 2-phenylnaphthalene.[3] Thus it will be noted that I and II have strong absorption bands in the 260 mμ region, a feature also characteristic of the spectrum of 2-phenylnaphthalene, while the spectrum of the 3,4-benzfluorene, III, exhibits a minimum in this region similar to that shown by 1-phenylnaphthalene.

In 1-phenylnaphthalene there is unquestionably

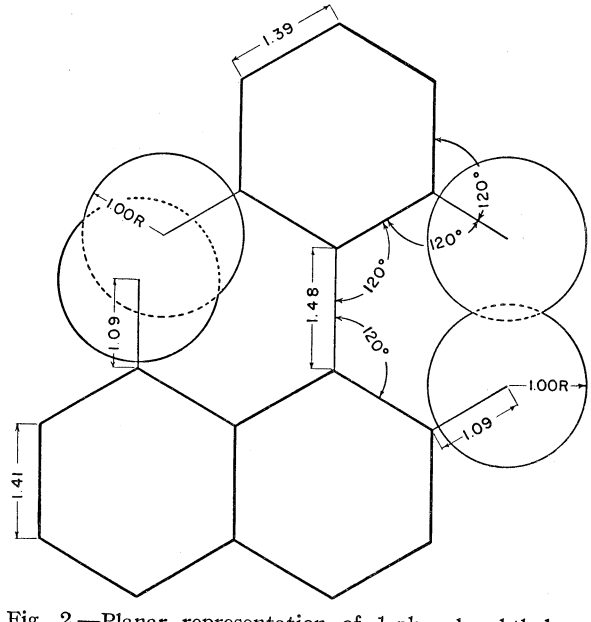


Fig. 2.—Planar representation of 1-phenylnaphthalene.

(1) Present address, U. S. Bureau of Mines, Pittsburgh, Penna. We wish to thank the John Simon Guggenheim Memorial Foundation for a fellowship grant to one of us (M. O.) which helped make this work possible.

(2) Physical chemist, Central Experiment Station, U. S. Bureau of Mines, Pittsburgh, Penna.

(3) Friedel, Orchin and Reggel, THIS JOURNAL, **70**, 199 (1948). The relationship of the spectra of the benzfluorenes and the phenylnaphthalenes has been commented on previously by Jacobs, Craig and Lavin, *J. Biol. Chem.*, **141**, 51 (1941).

steric interference between the hydrogen atoms at the 2′- and 8-positions which inhibits coplanarity. Figure 2 shows the probable extent of the hydrogen overlap at these positions in the planar model. The non-planar structure which is favored because of this interference probably explains the low melting point of 1-phenylnaphthalene as compared to 2-phenylnaphthalene. In view of the spectral resemblance of 3,4-benzfluorene III, to 1-phenylnaphthalene and the relatively low melting point of III, it is of interest to consider the hydrogen overlap in the structure of the latter and to consider also the structure of fluorene.

Cook and Iball concluded from an X-ray crystal study of fluorene, that the fluorene molecule is not planar but that the planes of each six-membered ring are inclined at an angle of 20° to that of the five-membered ring and at about 40° to each other (*cis*-form).[4]

Hughes, LeFèvre and LeFèvre, on the basis of dipole measurements in solution at first proposed a planar model of fluorene.[5a] They pointed out that if it is assumed that the five-membered ring is regular with internal angles of 108°, then the aromatic rings must be distorted 12° from a diphenyl structure and this requires the external angles around the diphenyl linkage to be 132°. These authors later stated[5b] that their measurements did not exclude the possibility of a non-planar structure in which the diphenyl linkage is distorted 8° (irregular pentagon) and the planes of the benzene ring are bent at about 20° either *cis* or *trans*. Figure 3 shows a planar model of 3,4-benzfluorene using angles and carbon to carbon distances which we regard as most probable if fluorene were planar.[6] In such a planar model there is only a minor amount of overlap between hydrogens at 4′ and 5 compared to the overlap in 1-phenylnaphthalene (Fig. 2). This is an additional incentive to favor a non-planar form for fluorene since in either the non-planar model suggested by Cook or inferred by Hughes, LeFèvre and LeFèvre, the interference of the hydrogens in III would be larger and of the magnitude involved in the overlap in 1-phenylnaphthalene. This overlap would cause strain which is additional to that present in the other benzfluorenes, I and II, and may tend to rotate the phenyl ring about the diphenyl linkage (as in the case with 1-phenylnaphthalene) so that the five-membered ring itself may become slightly non-planar. In any case, the postulated hydrogen overlap and the strain which it effects are now proposed to explain the relation between the spectra of 3,4-benzfluorene, III, and 1-phenylnaphthalene on the one hand and the other two benzfluorenes and 2-phenylnaphthalene on the other.

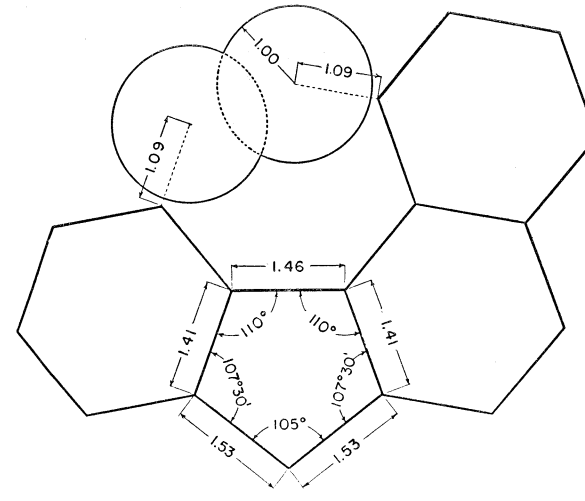


Fig. 3.—Planar representation of 3,4-benzfluorene.

The interesting differences observed with complex compound formation in this series, the data for which are found in Table I, are deserving of comment. The benzfluorenes, I and II, related to 2-phenylnaphthalene, form with 1,3,5-trinitrobenzene (T. N. B.) and with picric acid, complexes containing two moles of the polynitro compound. These complexes dissociate very readily. 2-Phenylnaphthalene also forms a 2:1 T. N. B. and its picrate is so unstable as to elude isolation. On the other hand, 3,4-benzfluorene, III, forms stable, sharp melting complexes with these nitro compounds in a molar ratio of 1:1.[7] These differences may be due to the smaller overall volume of 3,4-benzfluorene as compared to its isomers or they may be related to the strain differences discussed above which tend to make 3,4-benzfluorene less planar than its isomers. It will be noted that all the hydrocarbons in Table I form stable, high melting complexes with 2,4,7-trinitrofluorenone[8] (T. N. F.), in a 1:1 ratio. This fact may be due to some geometrical features of T. N. F. which permits its closer approach to relatively similar hydrocarbons or to the fact that T. N. F. is a relatively large molecule with widely separated positive centers. Observations

(4) Cook and Iball, *Chem. and Ind.*, 467 (1936). These authors point out that the non-planar configuration of fluorene does not necessarily demand the existence of stereoisomeric fluorenes because sufficient elasticity to oscillate may be possessed. Fieser and Joshel, THIS JOURNAL, **62**, 957 (1940), prepared 9-hydroxy-9-methyl-3,4-benzfluorene, which if 3,4-benzfluorene were non-planar, should exist as two racemic mixtures, each of which is resolvable. However, they isolated only one product in 85% yield.

(5) (a) Hughes, LeFèvre and LeFèvre, *J. Chem. Ind.*, **545**, 581 (1936); (b) *J. Chem. Soc.*, 202 (1937).

(6) The planar models of fluorene given by Hughes, LeFèvre and LeFèvre, ref. 5b, and by Pinck and Hilbert, THIS JOURNAL, **59**, 8 (1937), are not drawn accurately to scale. In the latter case, if the model is drawn with the bond lengths indicated and the angles about the diphenyl linkage as 107.5°, the angle at the methylene group is about 104° and not 110°.

(7) Attempts to prepare complexes with 1-phenylnaphthalene were unsuccessful in all cases but melting point–composition diagrams are needed before it can definitely be decided whether compound formation occurs.

(8) (a) Orchin and Woolfolk, THIS JOURNAL, **68**, 1727 (1946); (b) Orchin, Reggel and Woolfolk, *ibid.*, **69**, 1225 (1947).

made in this and other laboratories[9] indicate that in general, T. N. F. is to be preferred over other polynitro compounds for complex compound formation in the polycyclic series.

TABLE I

TABLE OF PROPERTIES

Name	Hydrocarbons M. p., °C.	Picric acid[a] complex	T. N. B. complex	T. N. F. complex	Ketones M. p., °C.	T. N. B. complex
			115	170		
2-Phenylnaphthalene	103	...	2:1	1:1	...	...
		127	145	215		126
1,2-Benzfluorene	186	2:1	2:1	1:1	135	1:1
		122	139	222		124
2,3-Benzfluorene	214	2:1	2:1	1:1	155	1:1
		131	155	192		128
3,4-Benzfluorene	127	1:1	1:1	1:1	160	1:1

[a] The top number under the various complexes is the melting point; below it is the ratio of moles polynitro component to moles of compound.

The ultraviolet absorption spectra of the benzfluorenones (Fig. 4) show an interesting reversal as compared to the parent benzfluorenes. Whereas

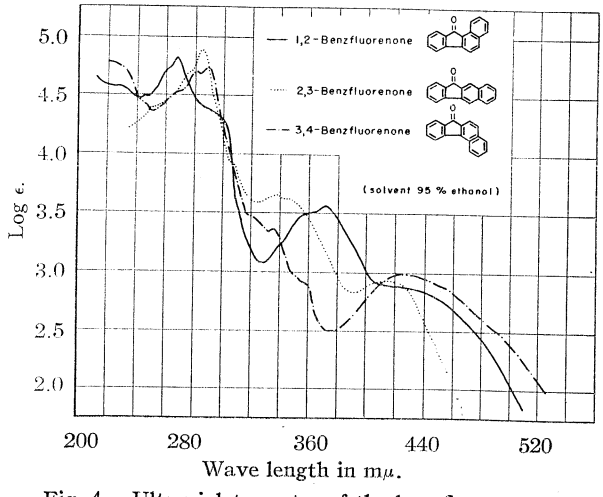


Fig. 4.—Ultraviolet spectra of the benzfluorenones.

in the hydrocarbon series, 3,4-benzfluorene exhibits a spectrum different from that of the other two isomers, in the ketone series 1,2-benzfluorenone has the spectrum which is easily distinguished from that of its isomers. This may be due to interaction between the carbonyl group at position 9 and the hydrogen on carbon 1′ giving rise to weak internal hydrogen bonding and incipient six-membered ring formation. The two main absorption maxima in the spectrum of 1,2-benzfluorenone are located at shorter wave lengths as compared to these maxima in the spectra of its isomers. This indicates less carbonyl contribution in the case of the 1,2-benzfluorenone as indeed would be expected if the oxygen were partially involved in hydrogen bonding. It will be noted from Table I that this ketone is the lowest melting of the isomers.

Acknowledgment.—The authors wish to thank Mr. Martin Michael for expert drafting aid and Mrs. Lois Harnack for assistance with the spectral measurements.

Experimental[10]

1,2-Benzfluorenone.—This compound was prepared on a large scale by a new method which will be reported later.[11] It had a melting point of 134.5–135.0°.

The complex with 1,3,5-trinitrobenzene was prepared in the usual way in ethanol solution and the complex separated as yellow-orange needles, m. p. 125.0–126.0°. Recrystallization from ethanol resulted in a less pure material. The material isolated in the first crop was used for analysis. *Anal.* Calcd. for $C_{23}H_{13}N_3O_7$: C, 62.3; H, 3.0. Found: C, 62.3; H, 3.0.

2,3-Benzfluorenone.—A small sample of this compound was secured from Professor L. F. Fieser.[12] The preparation of a complex with 4 mg. of this material and double the molar proportions of 1,3,5-trinitrobenzene was attempted. The first crops isolated were unchanged trinitrobenzene but later crops consisted of the complex. One recrystallization of the complex gave yellow prisms, softening at 117° and m. p. 124°. Ultraviolet absorption spectra analysis showed this complex to consist of 49 molar per cent. trinitrobenzene and 51 molar per cent. ketone.

3,4-Benzfluorenone.—This compound was also the generous gift of Professor L. F. Fieser.[13]

The complex with 1,3,5-trinitrobenzene was prepared in ethanol; the complex separated in yellow gold needles, which after recrystallization from ethanol had a melting point of 128.0–128.4°. *Anal.* Calcd. for $C_{23}H_{13}N_3O_7$: C, 62.3; H, 3.0. Found: C, 62.3; H, 2.6. The complex was much lighter in color than the ketone itself.

1,2-Benzfluorene, I.—This compound was prepared by reduction of the corresponding benzfluorenone with phosphorus and hydriodic acid, essentially according to the directions of Graebe.[14] Crystallization from ethanol gave small colorless crystals, m.p. 185.4–186.0°.

The picrate has been prepared previously[15] and has been shown to consist of 2 moles of picric acid to 1 mole of hydrocarbon.

The trinitrobenzene complex was obtained from ethanol as small yellow crystals, m.p. 144.0–145.0°. *Anal.* Calcd. for $C_{29}H_{18}N_6O_{12}$: N, 13.1. Found: N, 13.9.

The complex with 2,4,7-trinitrofluorenone separated as red crystals which after crystallization from benzene–ethanol had a melting point of 213.5–215.5°. *Anal.* Calcd. for $C_{30}H_{17}N_3O_7$: C, 67.8; H, 3.2. Found: C, 68.0; H, 3.3.

2,3-Benzfluorene, II.—The properties of this compound have been reported by us previously.[8b]

The picrate was made from the hydrocarbon and picric acid in petroleum ether and recrystallized from petroleum–ether (90–100°) whereupon it separated as yellow-orange crystals, softening at 118° and melting at 121.8–122.5°. *Anal.* Calcd. for $C_{29}H_{18}N_6O_{14}$: C, 51.6; H, 2.7. Found: C, 51.8; H, 3.1.

The complex with 1,3,5-trinitrobenzene was obtained from petroleum ether (90–100°) as bright yellow plates, m.p. 138.0–139.0°. *Anal.* Calcd. for $C_{29}H_{18}N_6O_{12}$: N, 13.1 Found: N, 13.6.

(9) For example, Newman and Hart, THIS JOURNAL, **69**, 298 (1947); Cheronis and Entrikin, "Semimicro Qualitative Analysis," Thomas Y. Crowell, New York, N. Y., 1947, pp. 311, 314.

(10) All melting points corrected. All analyses are microanalyses by Mr. G. L. Stragand, University of Pittsburgh.

(11) We wish to thank Mr. Leslie Reggel for this preparation and for other valuable assistance with a portion of the experimental work.

(12) Fieser and Gates, THIS JOURNAL, **62**, 2335 (1940).

(13) Fieser and Joshel, *ibid.*, **62**, 957 (1940).

(14) Graebe, *Ber.*, **29**, 828 (1896).

(15) Graebe, *Ann.*, **335**, 135 (1904), gives a melting point of 127.5° and Cook and Hewett, *J. Chem. Soc.*, 365 (1934), give a melting point of 124–126°.

In this series of 2:1 complexes it is desirable to avoid the use of ethanol as a solvent. Chloroform or petroleum ether is more satisfactory for the isolation of the unstable complexes.

The 2,4,7-trinitrofluorenone complex has been reported previously[8b] but its analysis did not correspond to any simple molar ratio. This conclusion was reached on the basis of several nitrogen analyses at different laboratories, all of which checked but all of which we have found subsequently to be in error. The carbon and hydrogen analyses showed the complex to be a 1:1 combination. *Anal.* Calcd. for $C_{30}H_{17}N_3O_7$: C, 67.8; H, 3.2. Found: C, 68.1; H, 3.5.

3,4-Benzfluorene, III.—An attempted reduction of 3,4-benzfluorenone with phosphorus and iodine in acetic acid resulted in the almost complete recovery of the ketone. It was then successfully reduced by the Huang-Minlon[16] modification of the Wolff–Kishner reaction. A solution of 0.317 g. of the ketone, 0.5 cc. of 85% hydrazine hydrate, 0.4 g. of sodium hydroxide and 25 cc. of ethylene glycol was refluxed for two hours. During this time the yellow solid became red and gradually went into solution; then all the red color disappeared leaving a clear yellow solution. At the end of the two hours, the condenser was removed and the contents boiled in the open until the temperature in the flask was 200°. The condenser was replaced and the solution refluxed two hours, cooled and poured into ice and hydrochloric acid. The precipitate was dried and crystallized from ethanol. The first crop (0.19 g.) separated as nearly colorless plates tinged with a pink color, m.p. 122.6–124.0°. The second crop (0.05 g.) had about the same melting point. On recrystallization of the first crop from benzene–alcohol a small amount of insoluble material was noted and separated. This melted at 241.5–244.0° and was probably the hydrazone of the benzfluorenone.

(16) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

The soluble fraction gave pure 3,4-benzfluorene, m.p. 126.8–127.4°.[17]

The known mono-picrate[17] was obtained from ethanol as fine red needles, m.p. 131.4–132.2°.

The trinitrobenzene complex was obtained from benzene–alcohol as orange-yellow crystals, m.p. 154.2–155.2°. *Anal.* Calcd. for $C_{23}H_{15}N_3O_6$: C, 64.3; H, 3.5. Found: C, 64.5; H, 3.5.

The trinitrofluorenone complex separated from benzene-alcohol as fine, light red needles, m.p. 191.8–192.8°. *Anal.* Calcd. for $C_{30}H_{17}N_3O_7$: C, 68.8; H, 3.2. Found: C, 67.6; H, 2.9.

2-Phenylnaphthalene and its complex with 2 moles of trinitrobenzene has been described previously[3] as has the complex with trinitrofluorenone.[8b]

Summary

The physical properties and ultraviolet absorption spectra of the three benzfluorenes and the three benzfluorenones were determined and significant features discussed. The molecular complexes formed between these compounds and various polynitro compounds were prepared and studied. In nearly all respects the behavior of 1,2- and 2,3-benzfluorene was similar but 3,4-benzfluorene differed from its isomers. It is proposed that the differences stem from the possibility of hydrogen overlap in the 3,4-benzfluorene molecule which may cause it to assume a less planar structure than its isomers.

(17) Cook, Dansi, Hewett, Iball, Mayneord and Roe, *J. Chem. Soc.*, 1319 (1935), give the melting point of the hydrocarbon as 124–125° and the melting point of its picrate as 130–131°.

PITTSBURGH 13, PENNA. RECEIVED MARCH 25, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

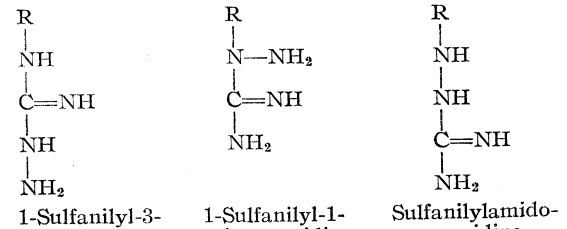
Isomerism of Sulfanilylaminoguanidines[1]

BY ALBERT H. GREER,[1a] DENNIS L. KERTESZ[2] AND G. B. L. SMITH[3]

A sulfanilylaminoguanidine melting at 208–210° was prepared by Winnek, *et al.*,[4] by condensation of N^4-acetylsulfanilyl chloride with S-methylthiourea or with cyanamide, followed by hydrazinolysis or hydrazination and deacetylation. More recently, Owades[5] has obtained the same sulfanilylaminoguanidine by the catalytic hydrogenation of N^4-acetylsulfanilylnitroguanidine and subsequent deacetylation. Prior to this, Kertesz[6] had prepared another sulfanilylaminoguanidine melting at 298–300° by condensing *p*-nitrobenzenesulfonyl chloride with aminoguanidine, and reducing the product by catalytic hydrogenation. We have now prepared a third sulfanilylaminoguanidine melting at 188–190°.

It is evident that three structural isomers of sulfanilylaminoguanidine are possible, as follows

R = sulfanilyl



1-Sulfanilyl-3-aminoguanidine (I) | 1-Sulfanilyl-1-aminoguanidine (II) | Sulfanilylamidoguanidine (III)

The above does not include the tautomeric isomers for which formulas can be written. Isomer I has three tautomers, isomer III has two, and isomer II only one.[4]

The present paper describes the preparation

(1) Abstracted from parts of the theses submitted by Albert H. Greer (M.S. Chem., 1945) and Dennis L. Kertesz (Ph.D., 1941) to the Graduate Faculty of Polytechnic Institute of Brooklyn.

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(2) Present address: Wyeth Inc., Chicago Laboratories, 8134 McCormick Blvd., Chicago, Illinois.

(3) Present address: Chemistry Division, Research Department, U. S. Naval Ordnance Test Station (Inyokern), China Lake, California.

(4) Winnek, *et al.*, THIS JOURNAL, **64**, 1682 (1942).

(5) J. Owades, M.S. Thesis, Polytechnic Institute of Brooklyn, 1944.

(6) D. Kertesz, Ph.D. Thesis, Polytechnic Institute of Brooklyn, 1941.

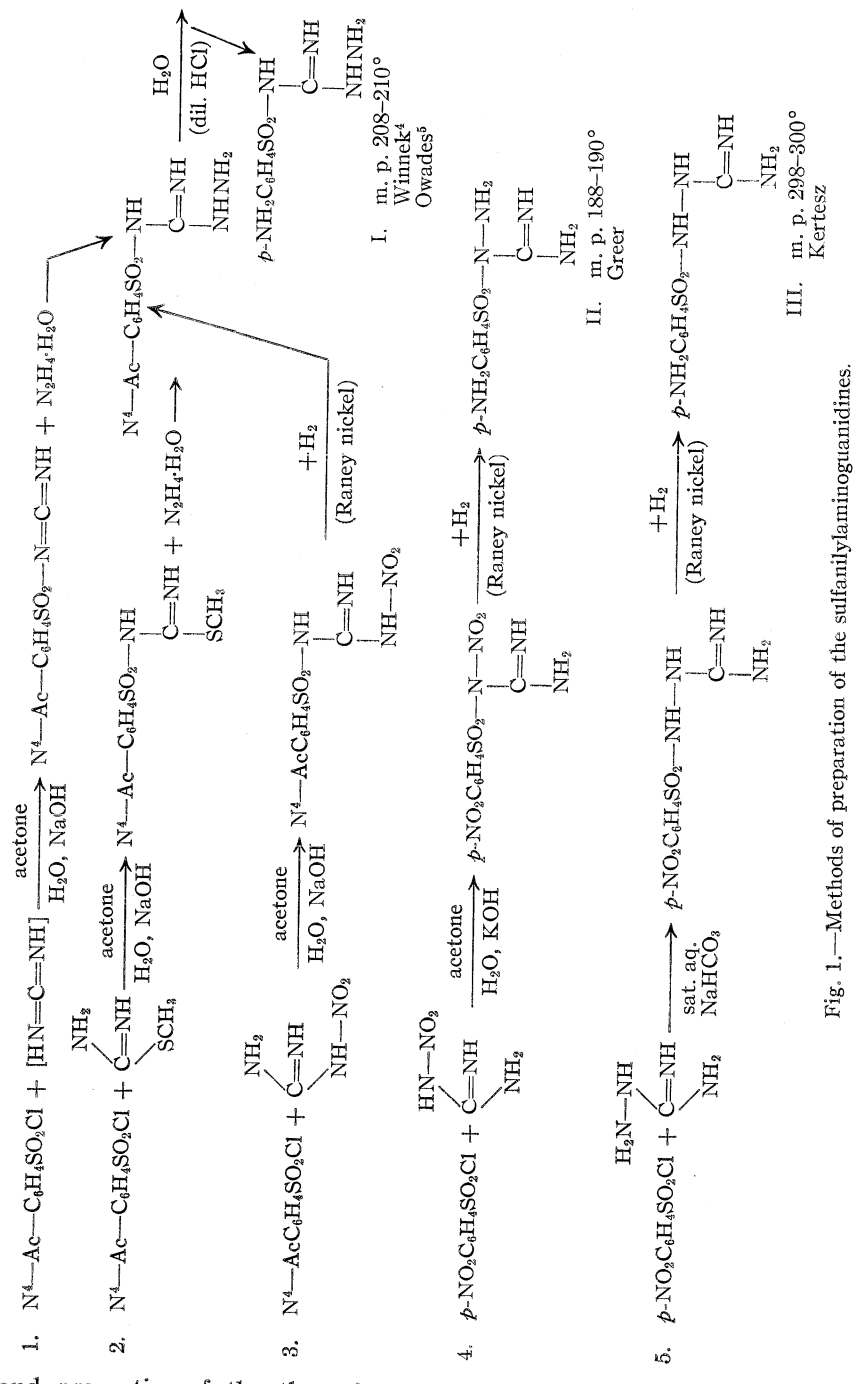


Fig. 1.—Methods of preparation of the sulfanilylaminoguanidines.

and properties of the three isomeric sulfanilylaminoguanidines and deduces therefrom the structural formula applicable to each.

Experimental Part

1-Sulfanilyl-3-aminoguanidine (I) from Nitroguanidine.—Nitroguanidine, 5.2 g. (0.05 mole) was suspended in 60 ml. of acetone, and to this mixture 0.5 g. of potassium hydroxide in 10 ml. of water was added slowly with vigorous stirring. The initial *p*H was approximately 10–11. After the nitroguanidine was dissolved completely, the solution was cooled to 18° and 11 g. (0.05 mole) of N⁴-acetylsulfanilyl chloride was added during a period of thirty minutes. The mixture was stirred for three hours at room temperature by which time a voluminous precipitate had formed. Thirty milliliters of water was added, the precipitate was filtered off, washed with cold water and recrystallized from 80% ethanol, to give 2 g. (13%), of colorless crystals, m. p. 195–198°. This 1-N⁴-acetylsulfanilyl-3-nitroguanidine (6.0 g., 0.02 mole) in ethanol solution was reduced with hydrogen in the presence of Raney nickel catalyst, the catalyst was removed by filtration, and the 1-N⁴-acetyl-sulfanilyl-3-aminoguanidine, obtained by carefully evaporating the solvent, was recrystallized from 70% ethanol; yield, 3.2 g. (57%), m. p. 256–257°. Five grams (0.018 mole) of the acetyl compound was heated for two hours under reflux in a mixture of 30 ml. of ethanol and 5 ml. of 6 *N* hydrochloric acid. On cooling, dilute sodium hydroxide solution was added, I precipitated, was filtered off and recrystallized from ethanol; yield 2.2 g. (53%), m. p. 208–210°.

Isomer I from Aminoguanidine.—Aminoguanidine hydrobromide, 6.2 g. (0.04 mole), was heated in 50 ml. of dry pyridine on a steam-bath. When nearly complete solution had taken place, 9.3 g. (0.04 mole) of N⁴-acetylsulfanilyl chloride was added slowly with stirring. After ten additional minutes on the steam-bath, the mixture was cooled for twenty-four hours. A small residue consisting of unreacted aminoguanidine salt was removed by filtration, the filtrate was evaporated to dryness and the residue was recrystallized from a small quantity of 70% ethanol; yield, 1.5 g. (14%), m. p. 256–257°. The material was identical with the intermediate obtained above, and therefore it was not deacetylated.

1-Sulfanilyl-1-aminoguanidine (II).—Nitroguanidine, 13.8 g. (0.12 mole), was suspended in 180 ml. of acetone and to this was added 18.6 g. of potassium hydroxide dissolved in 30 ml. of water. After the nitroguanidine had dissolved completely, 30 g. (0.13 mole) of *p*-nitrobenzenesulfonyl chloride[7] was added during a period of thirty minutes, while the temperature was maintained at 18°. In a few minutes after the last addition of *p*-nitrobenzenesulfonyl chloride a voluminous mass of yellowish-white crystals appeared. After the addition of 50 ml. of water,

(7) The workers in this Laboratory for many years have prepared *p*-nitrobenzenesulfonylchloride and this substance had a melting point of 67°. Recently, this substance was obtained from Eastman Kodak Company and the melting point was 76°, as most frequently given in the literature. Mixed melting point determination of the two materials gave 76°. Therefore we had been dealing formerly with a thermodynamically less stable polymorph.

the mixture was stirred for three hours at room temperature. The mixture was neutralized with glacial acetic acid; the solid material was removed by filtration and washed with small quantities of water, crystallized four times from 70% ethanol and decolorized with charcoal; yield 18 g. (52%), m. p. 202–203° dec. This 1-*p*-nitrobenzenesulfonyl-1-nitroguanidine in ethanol solution was reduced with hydrogen in the presence of Raney nickel catalyst, using chloroplatinic acid as promotor.[8] After removal of the catalyst, the solvent was evaporated under reduced pressure at 40° to give a light orange oil which crystallized on cooling. The product was dissolved in ethanol, decolorized with carbon, and upon the addition of a small quantity of water, white crystals were formed. Recrystallization from 60% ethanol afforded 8.6 g. (60%) of II, m. p. 188–190°.

Sulfanilylamidoguanidine (III).—Aminoguanidine sulfate ($CN_4H_6 \cdot {}^1/_2H_2SO_4$), 4.92 g. (0.04 mole), dissolved in 20 ml. of water, was added to 100 ml. of a saturated solution of sodium bicarbonate (saturated at 45°), to give a solution of *p*H 8.5. *p*-Nitrobenzenesulfonyl chloride, 5 g. (0.023 mole), was added during a period of thirty minutes to the above solution which had been heated to 55°. The *p*-nitrobenzenesulfonyl chloride dissolved in about two hours and the solution was evaporated to dryness under reduced pressure. The residue was extracted with small portions of hot absolute ethanol first by decantation and finally by repeated washings of the solid material on a Büchner funnel. The alcoholic solution was evaporated under reduced pressure to incipient crystallization and then cooled. The nitro compound was filtered, recrystallized from ethanol, washed with ether and dried over phosphoric anhydride; yield 3 g. (50%), m. p. 298–299° dec. Reduction of this compound by hydrogen in the presence of Raney nickel catalyst yielded 1.7 g. (64%) of III, m. p. 298–300° dec., which was recrystallized from ethanol.

X-Ray Diffraction Measurements.—X-Ray diffraction photographs were taken of the three isomers according to methods outlined by Fankuchen[9] and Buerger.[10] These transmission powder diffraction patterns showed that three distinct crystalline compounds have been formed. Single crystal oscillation patterns about all three axes of the three sets of crystals gave different axial lengths and different cell volumes. The molecular weights were calculated from the cell volumes using the equation.

$$\text{Mol. wt.} = \frac{\text{Volume (Å.}^3) \times \text{density}}{n \times 1.65}$$

where n = number of molecules per unit cell. The density of each set of crystals was determined by the flotation method of solid suspended in a liquid of the same density, Table I.

Isomer I.—The symmetries of the single crystal photographs proved that the crystals must have one of the triclinic symmetries. The space group is therefore P1 or P$\bar{1}$ (C_1^1 or C_i^1). The cell dimensions are d(100) = 9.32 Å., b = 9.75 Å., c = 22.20 Å., volume = 1990 (Å.^{3}). The number of molecules per unit cell is 8.

Isomer II.—The symmetries of the single crystal photographs proved that the crystals must have one of the monoclinic symmetries. The space group is therefore Pm or P2 (C_s^1 or C_2^1). The crystals are elongated with blunt edges and the intermediate refractive index is along the length of the needle axis. The acute bisectrix makes an angle of 14° with the main face of the crystal. The cell dimensions are a = 7.43 Å., b (needle axis) = 5.54 Å., c sine beta = 12.30 Å., volume = 506 (Å.^{3}). The number of molecules per unit cell is 2.

Isomer III.—The symmetries of the single crystal photographs proved that the crystal must have one of the orthorhombic symmetries. The needle crystals had straight extinction and its cross-section contains an angle of 77°. Reflections of the type 0*kl* occur only when l is even and reflections of the type *hk*0 occur only when h is even. The space group is therefore Pcma or Pc-a (D_{2h}^9 or C_{2v}^8). The cell dimensions are a = 7.85 Å., b = 10.00 Å., c = 24.65 Å., volume = 1934 (Å.)^3. The number of molecules per unit cell is 8.

Discussion

Three sulfanilylaminoguanidines, with the empirical and molecular formula, $C_7H_{11}O_2N_5S$, as shown, respectively, by analyses and X-ray molecular weight determination, have been prepared. That these are indeed three different compounds is demonstrated uniquely by mixed melting points and properties (Table I).

TABLE I

PROPERTIES OF THE THREE ISOMERS

Isomer			I	II	III
M. p.			208–210°[a]	188–190°[a]	298–300° dec.[a]
Density at 20°			1.55	1.52	1.57
Crystal system			Triclinic	Monoclinic	Orthorhombic
Molecules/unit cell			8	2	8
Unit cell vol., cu. Å.			1990	506	1934
Space group			P1 or P$\bar{1}$ C_1^1 or C_i^1	Pm or P2 C_s^1 or C_2^1	Pcma or Pc-a D_{2h}^9 or C_{2v}^8
Molecular weight[b]			232.5	231	230
Hydrazine titration			Quant.	Trace	Negative
Analyses, %[d,e]	Calcd.	C	36.67	36.67	36.67
		H	4.83	4.83	4.83
		S	13.98	13.98	13.98
	Found	C	36.78	37.27	36.60
		H	4.77	4.68	4.77
		S	13.00	13.55	13.40
		N	12.08[c]		

[a] Mixed m. p.: I + II, 130°; I + III, 180°; II + III 250–253°; I + II + III, 245–250°. [b] Calcd. 229. [c] Hydrazine nitrogen. [d] 1-*p*-Nitrobenzenesulfonyl-1-nitroguanidine, $C_7H_7O_6N_5S$; Calcd.: C, 29.06; H, 2.43. Found: C, 28.85; H, 2.59. [e] *p*-Nitrobenzenesulfonylamidoguanidine, $C_7H_9O_4N_5S$: Calcd.: C, 32.42; H, 3.49; S, 12.36; N (total nitrogen) (Dumas), 27.01. Found: C, 32.30; H, 3.40; S, 11.00; N, 26.44.

The structural formula (*vide supra*) applicable to each substance can be deduced from the methods of synthesis. The method of Winnek, *et al.*,[4] can give a compound to which only formula I is applicable. The condensation of N^4-acetylsulfanilyl chloride with either amino- or nitroguanidine gives Winnek's compound and therefore formula I is applicable to the product of these con-

(8) Lieber and Smith, THIS JOURNAL, **58**, 2170 (1936).

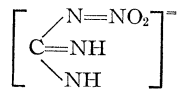
(9) Fankuchen, "Physical Methods of Organic Chemistry," 1st ed., Chapter 14, Interscience Publ., New York, N. Y., 1945, p. 585.

(10) Buerger, "X-Ray Crystallography," 1st ed., John Wiley & Sons, Inc., New York, N. Y., 1942.

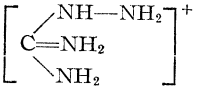
densations. Reduction of the condensation product of *p*-nitrobenzenesulfonyl chloride with nitroguanidine gives a different compound and therefore cannot have formula I. The mode of synthesis of this second compound precludes formula III and therefore formula II is applicable. Reduction of the condensation product of *p*-nitrobenzenesulfonyl chloride with aminoguanidine gives still a third compound and hence it is represented by formula III.

Further evidence for the correctness of the assignment of structural formulas to the three compounds is furnished by two chemical reactions. (1) Determination of hydrazine nitrogen according to the Jamieson method as developed by Smith and Wheat[11] gave a quantitative result in the case of I. For II a slight qualitative reaction was observed which may be attributed to contamination with I. With III no reaction was observed, even when subjected to drastic hydrolytic conditions. (2) When the N^4-acetyl or *p*-nitro intermediates of the three isomers were treated with acidic solution of benzaldehyde only I and II formed benzylidene derivatives. Pellizzari and Cuneo[12] separated two alkylaminoguanidines analogous in structures to II and III by the formation of a benzylidene derivative which formed only with the alkylaminoguanidine corresponding to structure II. It is seen that I and II have a free amino group attached to a nitrogen atom and part of a hydrazine group. In III, however, only an =NH group is present.

The formation of a particular isomer depends upon the *p*H of the medium in which the condensation is effected and also upon the properties of (1) the benzenesulfonyl chloride employed and (2) the compound with which this substance is condensed. When *p*-nitrobenzenesulfonyl chloride is condensed with nitroguanidine, 1-*p*-nitrobenzenesulfonyl-1-nitroguanidine is formed while N^4-acetylsulfanilyl chloride gives 1-N^4-acetylsulfanilyl-3-aminoguanidine. Here the inductive effect of the para-substituent group on the benzene ring may be the determining factor. On the other hand, hydrogen bonding of the nitro group and the (=NH) group may protect the 1- and 2-nitrogen atoms. Further study should prove of interest. The condensation in each case is effected in a very strong alkaline medium (*p*H above 10) and under such conditions the predominating ionic species of nitroguanidine is probably the secondary anion[13]



Aminoguanidine is a moderately strong to strong base. In weakly acidic or weakly alkaline solution the primary aminoguanidonium ion is the predominating species present



The nitrogen atoms connected to the carbon atom are blocked by the stability of the aminoguanidonium ion but in this medium the fourth nitrogen is available for condensation. This condensation has been effected only in a saturated solution of sodium bicarbonate. It has also been found that when N^4-acetylsulfanilyl chloride and aminoguanidine are allowed to react in pyridine, condensation is on the 1- or 2-nitrogen atoms resulting in the formation of 1-N^4-acetylsulfanilyl-3-aminoguanidine.

Acknowledgment.—The authors are indebted to Dr. I. Fankuchen of the Polytechnic Institute of Brooklyn for his assistance in the X-ray analysis of this study.

Summary

The three possible structural isomers of sulfanilylaminoguanidine have been prepared. Mixed melting point determinations, characteristic chemical and physical properties, and X-ray diffraction studies have demonstrated conclusively that these are three distinct compounds. On the basis of their modes of formation formulas have been assigned to each compound. The reasons for the formation of each isomer have been discussed.

BROOKLYN, N. Y. RECEIVED[14] APRIL 16, 1949

(11) Smith and Wheat, *Ind. Eng. Chem., Anal. Ed.*, **11**, 200 (1939).

(12) Pellizzari and Cuneo, *Gazz. chim. ital.*, **24**, I, 222 (1894).

(13) Hahn, Pribyl, Lieber, Caldwell and Smith, THIS JOURNAL, **66** 1223 (1944).

(14) Original manuscript received December 6, 1946.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MISSOURI]

The Reaction of Aryl Carbinols with Aluminum Chloride and Aromatic Hydrocarbons[1]

BY HERBERT E. UNGNADE AND ELBERT W. CRANDALL[2]

Benzyl alcohol and benzhydrol can react with benzene and aluminum chloride to give phenyl substituted methanes.[3,4] This reaction may be interpreted as an alkylation reaction in which these carbinols act as alkylating agents. In the presence of excess aluminum chloride this reaction is entirely suppressed and the same reactants furnish anthracene.

When toluene and diphenylmethane are used in the place of benzene, the two carbinols yield identical mixtures of dimethyl and dibenzylanthracenes, respectively, as the only products. Identical mixtures of such disubstituted anthracenes are also produced from benzaldehyde by reaction with aluminum chloride and the above hydrocarbons.

As an explanation for these reactions it is suggested that benzyl alcohol and benzhydrol can act as carbon monoxide donors when larger amounts of aluminum chloride are used. The hydrocarbon solvent provides the outside rings of the substituted anthracenes while the carbon monoxide from the carbinol furnishes the meso carbons.[5]

A similar explanation has been advanced for the formation of anthracene from aromatic aldehydes.[6]

The proposed mechanism is strengthened by the observation that benzyl alcohol and benzhydrol yield carbon monoxide when stirred with aluminum chloride at 60°, as is the case for benzaldehyde.

Triphenylcarbinol is a by-product in the reaction with benzhydrol only when benzene is used as a solvent. Its formation is favored by lower temperatures (Table I). It is also formed from various substituted aromatic aldehydes, aluminum chloride and benzene[7] and is possibly derived from a reaction between benzene and carbon monoxide. The yields of both anthracene and triphenylcarbinol are increased by adding carbon monoxide to the reaction mixture. Triphenylcarbinol remains unchanged when treated with benzene and aluminum chloride at 60°.

TABLE I

THE REACTION OF BENZHYDROL WITH BENZENE AND ALUMINUM CHLORIDE

Temp., °C.	Moles $AlCl_3$[a]	Triphenylmethane, g.	Triphenylcarbinol, g.	Anthracene, g.	Tar, g.
0	1.0	15.1	0	0	0
0	2.0	1.90	17.1	0	0
0	3.1	0	12.03	8.26	0
60	3.1	0	3.68	4.89	8.64
60[b]	3.1	0	5.94	7.95	9.05

[a] Per mole of benzhydrol. [b] With addition of carbon monoxide gas during the reaction.

Experimental[8]

The Reaction of Benzyl Alcohol with Aromatic Hydrocarbons and Aluminum Chloride.—Benzyl alcohol (19.5 g.), dissolved in 50 cc. of benzene, was added during fifteen minutes to a mixture of 100 cc. of benzene and 56 g. of aluminum chloride. The mixture was stirred for three and one half hours at 60°, then it was decomposed in the usual manner and steam-distilled. The dry non-volatile residue weighed 14.4 g. and gave 57% of crystalline material on vacuum sublimation. Chromatographic adsorption of the sublimate on aluminum oxide from Skellysolve C solution yielded 90.3% of pure anthracene, m. p. 212–214°.

When this reaction was carried out under identical conditions with toluene, the non-volatile product (25.5 g.) yielded 64.7% of sublimate which melted at 213–215° after crystallization from Skellysolve C. It depressed the melting point of anthracene, gave correct analytical values and identical absorption spectra as the mixture of dimethylanthracenes obtained from benzaldehyde, aluminum chloride and toluene.[7]

The non-volatile material from the reaction of benzyl alcohol (25 g.) with diphenylmethane (60 cc.) and aluminum chloride (67 g.) weighed 32.12 g. Vacuum distillation of the crude product at 180–210° (1×10^{-3} mm.) gave 35.5% of distillate which was chromatographically uniform and melted at 191–192° (from Skellysolve C). By analogy with the dimethylanthracenes, this substance may be a mixture of 2,6- and 2,7-dibenzylanthracenes.[9]

Anal. Calcd. for $C_{28}H_{22}$: C, 93.85; H, 6.15. Found: C, 93.99; H, 6.37

The Reaction of Benzhydrol with Aromatic Hydrocarbons and Aluminum Chloride.—The vigorous reaction between benzhydrol, benzene and aluminum chloride was moderated by adding benzhydrol (27.6 g.) slowly during two hours to a mixture of 150 cc. of benzene and aluminum chloride maintained at the specified temperature (Table I). Stirring was continued for one and one-half hours and the mixture was decomposed and steam-distilled. The residue from the steam-distillation was dried by distillation with benzene and weighed. The light colored residues from the reaction at 0° were used directly for the chromatographic separation. The other products were first sublimed at 2 mm.

Adsorption of the mixtures on alumina from Skellysolve C solution permitted a nearly quantitative separation of the constituents. The experimental results are given in Table I.

The reaction of benzhydrol (0.09 mole) with aluminum chloride (0.28 mole) and 150 cc. of toluene yielded 14.96 g. of non-volatile residue which contained 39.7% tar.

(1) Presented in part before the division of Organic Chemistry of the American Chemical Society, Chicago, April, 1948.

(2) In part from the Ph.D. thesis of E. W. Crandall.

(3) Huston and Friedemann, THIS JOURNAL, **38**, 2528 (1916).

(4) Huston and Friedemann, *ibid.*, **40**, 791 (1918).

(5) An alternative explanation is possible for the formation of dimethylanthracenes from benzyl alcohol and toluene, as was pointed out by the referee. Direct condensation of two moles of benzyl alcohol could produce anthracene which could then be methylated by methyl groups from the toluene. An attempt to methylate anthracene with toluene in this manner under the conditions of the reaction, however, yielded only unchanged anthracene and tar.

(6) Hey, *J. Chem. Soc.*, 72 (1935).

(7) Ungnade and Crandall, THIS JOURNAL, **71**, 2209 (1949).

(8) All temperatures uncorrected.

(9) NOTE ADDED IN PROOF.—Oxidation of the mixture of dibenzylanthracenes (1 g.) with chromic oxide (4 g.) in acetic acid (30 cc.) and water (4 cc.) yielded 1.14 g. (98%) of dibenzoylanthraquinone, m. p. 241–242° (from 95% alcohol). *Anal.* Calcd. for $C_{28}H_{16}O_4$: C, 80.70; H, 3.85. Found: C, 80.50; H, 4.04.

The sublimate melted at 215–217° (from Skellysolve C) and was identical with the mixture of dimethylanthracenes obtained previously.

A mixture of benzhydrol (25 g.), diphenylmethane (60 cc.) and aluminum chloride (56 g.) maintained for three hours at 60° yielded 40.43 g. of non-volatile product. Vacuum distillation at 180–210° (1×10^{-3} mm.) yielded 16.0% of dibenzylanthracene, m. p. 191–192°, which was spectroscopically identical with the substance isolated from the benzyl alcohol reaction (Table II).

The Reaction of Benzaldehyde with Diphenylmethane.—Benzaldehyde (25 g.), aluminum chloride (67 g.) and diphenylmethane (70 cc.) gave 55.7 g. of non-volatile product under the same conditions. Dibenzylanthracene, m. p. 190–191°, was obtained from this residue as the only distillable substance. It proved to be identical in all respects with the dibenzylanthracenes described above.

Absorption Spectra.—The ultraviolet absorption spectra of the dimethyl and dibenzylanthracenes were determined in cyclohexane in 0.00128 and 0.00073 molar solutions with a Beckmann spectrophotometer.[10]

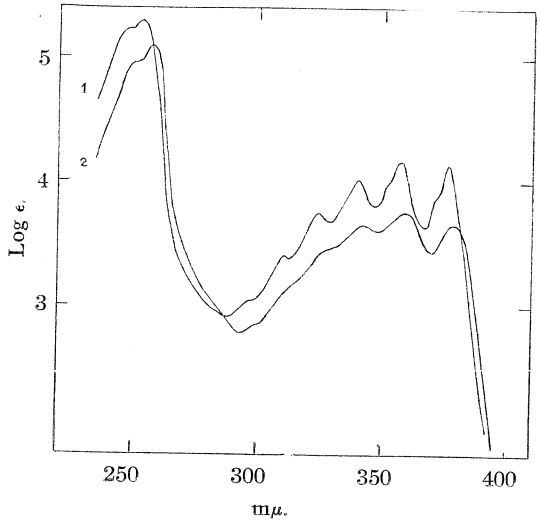


Fig. 1.—Ultraviolet absorption spectra: curve 1, dibenzylanthracenes; curve 2, dimethylanthracenes.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA

Wave length	Log ε λmax. I	II	III	Wave length	Log ε λmin. I	II	III
			Dimethylanthracenes[a]				
257.5	5.029	5.134	5.097	292.5	2.775	2.810	2.790
341.3	3.640	3.655	3.654	349	3.593	3.608	3.594
359	3.751	3.766	3.765	369	3.423	3.444	3.431
379	3.667	3.679	3.673				
			Dibenzylanthracenes[a]				
254	5.312	5.638	5.689	287.5	2.924	2.834	2.997
311	3.423	3.379	3.416	312.5	3.386	3.376	3.412
324	3.769	3.736	3.749	330	3.691	3.664	3.683
340	4.037	4.003	4.012	346	3.822	3.790	3.804
356	4.173	4.146	4.157	367.5	3.654	3.634	3.648
376	4.161	4.130	4.136	380	...	3.756	3.774
381	...[b]	3.895	3.906				

[a] I, product from benzaldehyde, II from benzhydrol, III from benzyl alcohol. [b] This small maximum, which is not present in anthracene, was probably overlooked in the first curve.

One curve each is shown in Fig. 1. Extinction values for maxima and minima of all six substances are listed in Table II. The spectral characteristics of the compounds are in good agreement with the proposed structures. The methylanthracenes exhibit a small hypsochromic effect, slight bathochromic effect and loss of fine structure as compared to anthracene[11] while the benzyl substituents cause general hyperchromic effect, no bathochromic effect and no loss in fine structure.

Summary

Evidence has been presented to show that benzyl alcohol and benzhydrol can act as carbon monoxide donors in the presence of excess aluminum chloride.

COLUMBIA, MISSOURI RECEIVED[12] APRIL 23, 1949

(10) Absorption spectra by Dr. E. E. Pickett, University of Missouri.

(11) Jones, *Chem. Rev.*, **41**, 368 (1947); **32**, 11 (1943).

(12) The first draft of this article was received October 25, 1948.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY, THE DEPARTMENT OF SURGERY OF THE BETH ISRAEL HOSPITAL, BOSTON, AND THE HARVARD MEDICAL SCHOOL]

Preparation of Azo Compounds for the Study of Inhibition of Tumor Growth*

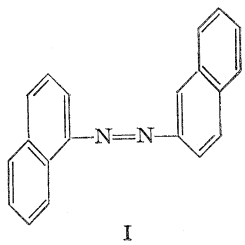
BY ORRIE M. FRIEDMAN, RALPH M. GOFSTEIN AND ARNOLD M. SELIGMAN

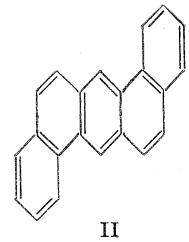
Following the demonstration by Haddow[1] that certain carcinogenic hydrocarbons are able to inhibit the growth of certain tumors in animals, many compounds with a structural resemblance to carcinogenic substances were subjected to this type of bioassay.[2] Isolated instances of inhibition of tumor growth with non-carcinogenic substances were observed, for example, with the unsymmetrical azonaphthalene (I).[2] Haddow suggested that this compound bears a superficial resemblance to the carcinogen, 1,2,5,6-dibenzanthracene (II). However, the only forms in which the unsymmetrical azonaphthalene (I) has features in common with the polynuclear carcinogenic hydrocarbons are the *cis* structures (III) and (IV) which resemble benz- derivatives of both 1,2-benzanthracene and chrysene. The hydrocarbon 1,2,5,6-dibenzphenanthrene, suggested by formula (IV), was found to be an inhibitor of tumor growth.[2] In order to explore further possible relationships between structure of azo compounds and their activity as inhibitors

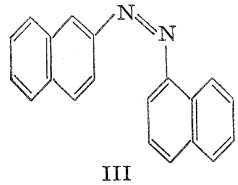
(*) This investigation was aided by a research grant from the National Cancer Institute, National Institutes of Health, Public Health Service.

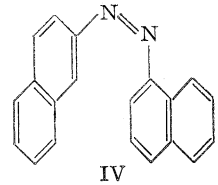
(1) (a) Haddow, *Nature*, **136**, 868 (1935); (b) Haddow and Robinson, *Proc. Roy. Soc.* (*London*), **B122**, 442 (1937); (c) Haddow, Scott and Scott, *ibid.*, **B122**, 477 (1937); (d) Haddow, *J. Path. Bact.*, **47**, 567 (1938); (e) Haddow and Robinson, *Proc. Roy. Soc.* (*London*) **B127**, 277 (1939).

(2) Badger, Elson, Haddow, Hewett and Robinson, *Proc. Roy. Soc.* (*London*), **B130**, 255 (1941).

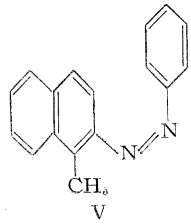

I

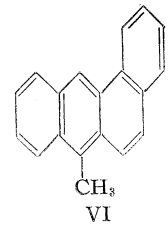

II


III


IV

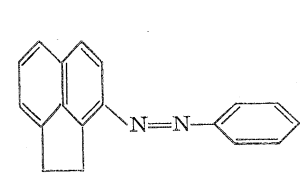
of tumor growth,[3] about twenty-five azo compounds were prepared. When written in the hypothetical *cis* configuration, most of them bear a spatial resemblance to a carcinogenic polynuclear hydrocarbon. As an example the *cis* structure is written for 2-benzeneazo-1-methylnaphthalene (V) and may be compared with the potent carcinogen 10-methyl-1,2-benzanthracene (VI). This azo compound was prepared by the method previously described.[4] No presumption is made as to the actual existence of these substances in the *cis* form, although there is evidence

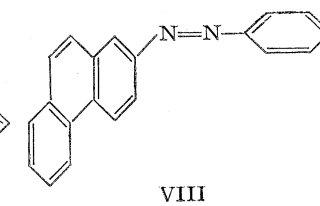

V

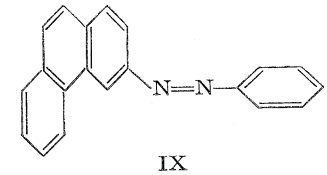

VI

that conversion of the *trans* to the *cis* form can be effected to a significant degree by exposure to ultraviolet light.[5]

The novel method of Michaelis and Petou[6] for the preparation of 1-benzeneazonaphthalene by the action of phenylhydroxylamine on 1-thionylaminonaphthalene proved useful for the preparation of 3-benzeneazoacenaphthene (VII), 2-benzeneazophenanthrene (VIII), and 3-benzeneazophenanthrene (IX). The required 3-aminoacenaphthene was prepared by catalytic reduction of 3-nitroacenaphthene, described by Morgan,[7] and its structure was confirmed by comparison with the amine obtained from 3-acetoacenaphthene[8] by a Hoffmann rearrangement. The thionylamino compounds were prepared by the reaction of thionyl chloride with the respective

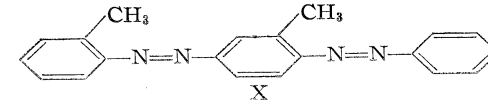

VII

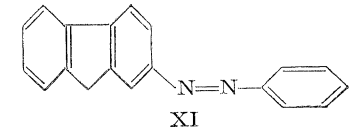

VIII


IX

amines. The products thus obtained were treated with phenylhydroxylamine in benzene. Heat was evolved and a black tarry by-product deposited as a sludge.[6] The products were obtained pure although in rather small yield after chromatographic treatment on alumina.

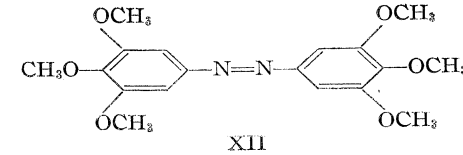
Use was made of the condensation of phenylamines with nitrosobenzene in acetic acid for the preparation of 2-benzeneazo-5-(*o*-tolueneazo)-toluene (X). This method worked well for the preparation of 2-benzeneazofluorene (XI). The reaction followed a different course with amines of naphthalene, acenaphthene, anthracene and phenanthrene. Products deep purple in color were produced, and although some were obtained in crystalline form after chromatographic separation they were not characterized further.

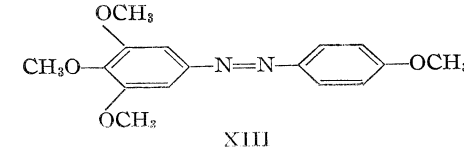

X


XI

Azo-3,4,5-trimethoxybenzene (XII) was prepared by reaction of 3,4,5-trimethoxybenzene diazonium chloride with an excess of cuprous chloride in aqueous solution under conditions described by Borgoslovski.[9]

The diazo coupling reaction was used for the preparation of 3,4,5,4′-tetramethoxyazobenzene (XIII) and 1-(3,4,5-trimethoxybenzeneazo)-


XII


XIII

(3) Seligman, Milden, Sweet, Mollomo, Gofstein and Friedman, to be published.

(4) Bargellini and Silvestri, *R. A. L.*, **57**, 16 II, 261 (1907).

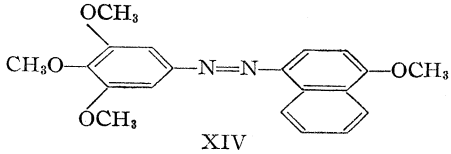
(5) Gortner and Gortner, THIS JOURNAL, **32**, 1294 (1910); Hartley, *Nature*, **140**, 281 (1937); *J. Chem. Soc.*, 633–642 (1938); Cook, *ibid.*, 876 (1938); Cook, Jones and Polya, *ibid.*, 1315 (1939); Cook and Jones, *ibid.*, 184 (1941).

(6) Michaelis and Petou, *Ber.*, **31**, 995 (1898).

(7) Morgan, *J. Soc. Chem. Ind.*, **49**, 413–21 (T) (1930).

(8) Fieser and Hershberg, THIS JOURNAL, **61**, 1275 (1939).

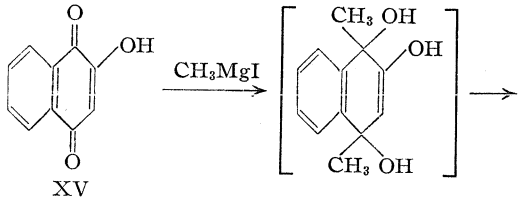
(9) Borgoslovski, *J. Gen. Chem. (U. S. S. R.)*, **16**, 193 (1946).



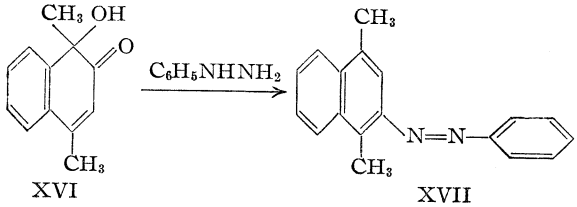
XIV

4-methoxynaphthalene (XIV). 3,4,5-Trimethoxybenzenediazonium chloride was coupled with phenol and α-naphthol, respectively. The products were converted to the corresponding methyl ethers with dimethyl sulfate.

2-Benzeneazo-1,4-dimethylnaphthalene (XVII) was prepared according to Bargellini[10] from



XV



XVI XVII

1,4-dimethyl-1-hydroxy-2-ketodihydronaphthalene (XVI) by condensation with phenylhydrazine. The dihydronaphthalene derivative (XVI) which had been prepared previously[11] by oxidation of 1,4-dimethylnaphthol-2 obtained by degradation of santonous acid, was prepared from the 2-hydroxy-1,4-naphthoquinone (XV) by reaction with excess methylmagnesium iodide.

The authors are grateful to Professor Louis F. Fieser for his helpful interest.

Experimental[12]

3-Aminoacenaphthene (a) From 3-Nitroacenaphthene.—The required 3-nitroacenaphthene was prepared according to Morgan[4] by nitration of acenaphthene in acetic anhydride. The nitro compound (10 g.) suspended in 100 cc. of pure alcohol with 0.5 g. of Adams catalyst was shaken under 30 pounds pressure of hydrogen for four hours. The yellow nitro compound dissolved leaving a nearly colorless solution with a strong blue fluorescence. When the solution was filtered and concentrated to small volume the amine separated in nearly pure form, 8.1 g. (95%), m.p. 82–83°.

(b) From 3-Acetoacenaphthene.[12a]—This preparation was carried out to obtain a reference sample of 3-aminoacenaphthene. The oxime of 3-acetoacenaphthene was rearranged in ether with phosphorus pentachloride to give a 50% yield of the acetylamino derivative, m. p. 192–193°. On acid hydrolysis the acetyl amine gave a product m. p. 82–83° which did not depress the melting point of the material obtained in (a).

3-Benzeneazoacenaphthene (VII).—3-Aminoacenaphthene (8.5 g.) in 100 cc. of benzene was treated with 3.6 g. of thionyl chloride. After five hours under reflux the solution was filtered and the benzene removed at reduced pressure. The residue, washed with petroleum ether, was treated with 11 g. of phenylhydroxylamine in 100 cc. of dry benzene, heat being evolved as a tarry sludge deposited. After being allowed to stand for twelve hours the mixture was filtered. The filtrate was chromatographed on alumina. The orange band eluted with benzene gave 1.7 g. (13%) of red crystals obtained as red needles after several recrystallizations from 70% alcohol, m. p. 99–100°.

Anal. Calcd. for $C_{18}H_{14}N_2$: C, 83.70; H, 5.46. Found: C, 83.55; H, 5.42.

2-Benzeneazophenanthrene (VIII).—The required 2-aminophenanthrene was prepared according to Bachmann and Boatner[13] from 2-acetylphenanthrene. A mixture of 12 g. of the amine and 10 cc. of thionyl chloride in 120 cc. of dry benzene was refluxed at slightly reduced pressure for twelve hours. At this time the heavy precipitate initially formed appeared to have gone into solution. The excess thionyl chloride and solvent were removed by distillation at reduced pressure and the dark residue thoroughly extracted with a mixture of equal volumes of chloroform and petroleum ether. When distilled to dryness the extract left 8.5 g. of the thionylamino compound as an orange-colored crystalline material. This product in 100 cc. of dry benzene was treated with 12 g. of phenylhydroxylamine in 150 cc. of dry benzene. The mixture became warm immediately and deposited a gray amorphous powder. After twelve hours the reaction mixture was filtered. When concentrated and cooled the filtrate deposited 3 g. of crude crystalline product. This material after three recrystallizations from benzene was obtained as lustrous golden orange platelets, 2.5 g. (15%), m. p. 143–144°.

Anal. Calcd. for $C_{20}H_{14}N_2$: C, 85.07; H, 5.00. Found: C, 84.98; H, 5.11.

3-Benzeneazophenanthrene (IX).—The required 3-aminophenanthrene was prepared according to the method of Bachmann and Boatner[13] from 3-acetylphenanthrene. The amine (6 g.) was dissolved in 100 cc. of dry benzene and 2.2 g. of thionyl chloride added. After heating for twelve hours under slightly reduced pressure, the dark solution was filtered and the benzene removed under reduced pressure. The residue was dissolved in petroleum ether and filtered. The petroleum ether was removed at reduced pressure leaving an orange crust of material. This was then treated with a solution of 6.4 g. of phenylhydroxylamine in 100 cc. of benzene. The solution became very warm and turned a bright red depositing a black tarry sludge. After filtration the benzene solution was chromatographed on an alumina column 20 × 2 cm. The orange band was eluted with benzene and the eluate rechromatographed. After removal of the benzene a red crystalline residue remained. This was taken up in alcohol and water added at the boiling point. On cooling and scratching a crystalline material deposited, m. p. 139–140°. Recrystallization is best from ethanol–acetone to give long orange needles.

Anal. Calcd. for $C_{20}H_{14}N_2$: C, 85.07; H, 5.00. Found: C, 84.96; H, 5.04.

2-Benzeneazo-5-(*o*-tolueneazo)-toluene (X).—Nitrosobenzene[14] (1.4 g.) in 30 cc. of glacial acetic acid was added to a cooled solution of 3.0 g. of 2-(3-tolylazo)-5-aminotoluene in 60 cc. of glacial acetic acid. On standing at room temperature for three days the mixture deposited 2.4 g. (60%) of crystalline product, m. p. 104–106°. The material was crystallized from chloroform–alcohol as fine orange-brown needles, m. p. 105–106°. It is soluble in hot chloroform; insoluble in methanol, ethanol or acetone.

Anal. Calcd. for $C_{20}H_{18}N_4$: N, 17.81. Found: N, 17.99.

(10) Bargellini, *Gazz. chim. ital.*, **37**[2], 1407 (1907).

(11) Cannizzaro, *ibid.*, **76**[1], 26 (1896).

(12) Microanalyses by Shirley R. Katz, all melting points are corrected.

(12a) Provided through the courtesy of Professor Louis F. Fieser.

(13) Bachmann and Boatner, THIS JOURNAL, **58**, 2097 (1936).

(14) "Organic Syntheses," Coll. Vol. I, p. 455.

2-Benzeneazofluorene (XI).—The required 2-aminofluorene was prepared by reduction of 2-nitrofluorene with calcium chloride and zinc dust according to Diels.[15] The amine (5 g.) in 25 cc. of acetic acid was treated with 3 g. of nitrosobenzene[13] in 25 cc. of glacial acetic acid. The mixture was kept at 0° for twelve hours during which a crystalline material deposited. After recrystallization from 95% alcohol the product formed yellow leaflets, 4 g. (54%), m. p. 173–174°.

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.41; H, 5.18. Found: C, 84.39; H, 5.22.

3,4,5-Trimethoxy-4′-hydroxyazobenzene.—The required 3,4,5-trimethoxyaniline was prepared in 65% yield from 3,4,5-trimethoxybenzoic acid amide[16] according to "Organic Syntheses"[17] by treatment with sodium hypochlorite. The amine (7.0 g.) in 47 cc. of 13% hydrochloric acid was diazotized at 0° by the addition of 2.3 g. of sodium nitrite in a small amount of water. The clear diazonium salt solution diluted to 50 cc. with ice-water was used as a stock solution. An aliquot (43 cc.) of the stock solution was mixed with an ice-cooled solution of 2.0 g. of phenol and 3.0 g. of sodium hydroxide. After fifteen minutes the mixture was acidified. The product was separated on a filter and after recrystallization from methanol–water was obtained as golden-orange needles, 2.5 g. (79%), m. p. 165–166°.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.47; H, 5.59. Found: C, 62.70; H, 5.78.

3,4,5,4′-Tetramethoxyazobenzene (XIII).—An aqueous solution of 2.5 g. of the above azo-phenol and 0.4 g. of sodium hydroxide heated on the steam-bath and vigorously shaken, was treated with small portions alternately of dimethyl sulfate and aqueous alkali so that the solution was kept as nearly as possible slightly alkaline. The treatment was carried on for about one hour when methylation appeared complete. The product, which separated during the course of the reaction, was collected on a filter and washed with alkali and water. After a few recrystallizations from methanol–water the substance was obtained as glistening orange platelets, 1.5 g., m. p. 106–107°.

Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00. Found: C, 63.80; H, 6.06.

1-(3,4,5-Trimethoxybenzeneazo)-4-methoxynaphthalene (XIV).—An aliquot (65 cc.) of stock solution of trimethoxybenzenediazonium chloride, corresponding to 3.0 g. of 3,4,5-trimethoxyaniline, was mixed in the cold with an aqueous solution of 4.5 g. of α-naphthol and 3.0 g. of sodium hydroxide. The dark red mixture that resulted was acidified with hydrochloric acid. The gummy precipitate, separated on a filter, was dissolved without purification in a minimum of aqueous alkali and treated with methyl sulfate as described in the preparation of (XIII). The methylated product dissolved in benzene was purified by passage over activated alumina in a tower 12 cm. × 1 cm. The orange band eluted with benzene gave a product obtained as orange platelets after two recrystallizations from chloroform–methanol, 2.5 g. (45%), m. p. 152–153°. The substance is soluble in chloroform, acetone and benzene; almost insoluble in methanol.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72. Found: C, 68.23; H, 5.94.

Azo-3,4,5-trimethoxybenzene (XII).—An aliquot (65 cc.) of the stock solution of 3,4,5-trimethoxybenzenediazonium chloride was added over a period of five minutes to a vigorously stirred ice-cooled solution of cuprous chloride prepared according to Borgoslovski[9] from 12 g. of copper sulfate in 100 cc. of hot water by addition of a mixture of 5 g. of hydroxylamine hydrochloride and 4 g. of potassium hydroxide in aqueous solution. Finally just sufficient ammonium hydroxide was added so that a clear cuprous chloride solution resulted. A precipitate formed with the addition of the diazonium salt. Stirring was continued for one hour after which the product was separated on a filter and washed with methanol. The yellow powder remaining crystallized nicely as orange needles from chloroform–methanol, 1.5 g. (50%), m. p. 217–218°.

Anal. Calcd. for $C_{18}H_{22}O_6N_2$: C, 59.65; H, 6.12. Found: C, 59.56; H, 6.30.

1,4-Dimethyl-1-hydroxy-2-ketodihydronaphthalene (XVI).[11]—A solution of 10 g. of 2-hydroxy-1,4-naphthoquinone[18] in 450 cc. of warm dry benzene was slowly added over a period of one hour to a refluxing solution of methyl Grignard prepared from 12 cc. of methyl iodide in 500 cc. of dry ether and 250 cc. of dry benzene. The addition precipitated an orange solid which rapidly turned gray. After heating under reflux for an additional twenty-four hours the mixture was decomposed with excess saturated ammonium chloride solution. The benzene–ether layer, extracted three times with 10% sodium carbonate and washed with water, was distilled to remove the solvent. From the red oily residue, by distillation at reduced pressure, there was obtained 2.2 g. of crude product as gummy crystals, b. p. 130–160°, 2 mm. A small sample crystallized from ethyl acetate–benzene as almost colorless granules, m. p. 103–105° (m. p. 104–105° reported by Cannizzaro).[11]

2-Benzeneazo-1,4-dimethylnaphthalene (XVII).[10]—The azo compound was prepared according to Bargellini[10] from the crude hydroxy ketone (XVI) in solution in 80 cc. of methanol by addition of 1.8 g. of phenylhydrazine hydrochloride in 40 cc. of water to which a few drops of hydrochloric acid was added. The mixture turned orange in color and soon began to deposit clusters of orange crystals. After forty-eight hours the reaction mixture was filtered. The product crystallized as beautiful large orange-red needles from methanol, 1.8 g. (48%), m. p. 82.5–83° (reported by Bargellini,[10] 83–84°).

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.05; H, 6.16. Found: C, 82.99; H, 6.33.

Summary

The synthesis of eight new azo compounds is described: 3-benzeneazoacenaphthene, 2-benzeneazophenanthrene, and 3-benzeneazophenanthrene by reaction of the appropriate thionylamino compounds with hydroxylamine; 2-benzeneazo-5-(*o*-tolueneazo)-toluene and 2-benzeneazofluorene by the use of nitrosobenzene; azo-3,4,5-trimethoxybenzene by the action of cuprous chloride on the diazonium salt; and 3,4,5,4′-tetramethoxyazobenzene and 1-(3,4,5-trimethoxybenzene)-azo-4-methoxynaphthalene by the diazo coupling reaction. There is also described a new method of preparation of 1,4-dimethyl-1-hydroxy-2-ketodihydronaphthalene, an intermediate in the preparation of 2-benzeneazo-1,4-dimethylnaphthalene.

CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 29, 1949

(15) Diels, "Organic Syntheses," Coll. Vol. II, p. 447.

(16) Graebe and Suter, *Ann.*, **340**, 227 (1905).

(17) "Organic Syntheses," Coll. Vol. II, p. 45.

(18) Kindly supplied by Dr. Russell H. Brown.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Analogs of Pteroylglutamic Acid. IV. Replacement of Glutamic Acid by Other Amino Acids

BY WILLIAM B. WRIGHT, JR., DONNA B. COSULICH, MARVIN J. FAHRENBACH, COY W. WALLER,[1] JAMES M. SMITH, JR., AND MARTIN E. HULTQUIST

Variations in the structure of pteroylglutamic acid (I)[2] have given substances of widespread interest. Hutchings, *et al.*,[3] synthesized pteroylaspartic acid, the first analog of pteroylglutamic acid to be isolated in pure form and adequately characterized. It showed pteroylglutamic acid antagonist activity in a number of species. Previous communications from this Laboratory described the synthesis of the N^{10}-alkyl,[4] 4-amino[5] and 9-methyl[6] derivatives of pteroylglutamic acid. The present paper describes a number of analogs prepared for preliminary screening experiments in which the glutamic acid moiety is replaced by other amino acids. Also described are some of the corresponding 4-aminopteroyl derivatives which contain an amino group in the 4-position of the pteridine ring.

Synthesis was accomplished by the method of Waller, *et al.*,[7] in which 2,4,5-triamino-6-hydroxypyrimidine, 2,3-dibromopropionaldehyde, and the N-(*p*-aminobenzoyl)-amino acid are brought together in water at an acid *p*H. For the 4-amino derivatives,[5] 2,4,5,6-tetraminopyrimidine[8] was substituted for the triaminohydroxypyrimidine. Usually one-half equivalent of iodine or sodium dichromate was added during the condensation.

TABLE I

N-(*p*-NITROBENZOYL)-AMINO ACIDS, NO_2—C$_6$H$_4$—CO—R

R = Amino acid	Recrystallization solvent	M. p., °C. (cor.)	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
β-Alanine	Water	163.8–165.0	77	$C_{10}H_{10}N_2O_5$	50.41	50.4	4.23	4.23	11.76	11.5
ε-Aminocaproic acid	Dilute alcohol	147.5–148.5	67	$C_{13}H_{16}N_2O_5$	55.71	55.6	5.76	5.94	10.00	10.1
Diethyl aminomalonate	Alcohol	135–136	60	$C_{14}H_{16}N_2O_7$	51.85	52.1	4.97	4.80	8.64	8.71
Isoleucine (*dl*)	Dilute alcohol	186–187	74	$C_{13}H_{16}N_2O_5$	55.71	55.6	5.76	5.61	10.00	10.1
Methionine (*dl*)	Dilute alcohol	170–171	62	$C_{12}H_{14}N_2O_5S$[a]	48.30	48.6	4.73	4.68	9.40	9.61
Sarcosine	Water	140–141	71	$C_{10}H_{10}N_2O_5$	50.41	50.3	4.23	4.40	11.76	11.6
Tryptophan (*dl*)	Dilute alcohol	196.5–197.5	40	$C_{18}H_{15}N_3O_5$	61.16	60.9	4.28	4.18	11.90	12.3

[a] Calcd.: S, 10.75. Found: S, 10.7.

TABLE II

N-(*p*-AMINOBENZOYL)-AMINO ACIDS, NH_2—C$_6$H$_4$—CO—R

R = Amino acid	M. p., °C. (cor.)	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Alanine (*dl*)[a]	192.5–194.0	75	$C_{10}H_{12}N_2O_3$	57.67	57.6	5.81	5.84	13.46	13.6
β-Alanine[f]	151.8–153.2	60.5	$C_{10}H_{12}N_2O_3$	57.67	57.6	5.81	5.8	13.46	13.3
ε-Aminocaproic acid	132.0–133.0	80	$C_{13}H_{18}N_2O_3$	62.39	62.4	7.25	7.15	11.20	11.2
Aminomalonic acid·H_2O	150 (decarb.)	99	$C_{10}H_{12}N_2O_6$	46.86	46.6	4.72	5.00	10.94	11.0
Diethyl ester	122.0–123.0	93	$C_{14}H_{18}N_2O_5$	57.15	57.2	6.16	6.23	9.52	9.53
Isoleucine (*dl*)	189.0–191.0	85	$C_{13}H_{18}N_2O_3$	62.39	62.7	7.25	7.54	11.20	11.2
Phenylalanine (*dl*)[b]	195.0–196.0	70	$C_{16}H_{16}N_2O_3$	67.56	67.3	5.67	5.82	9.86	9.67
Serine (*dl*)[c]	192[d]	91	$C_{10}H_{12}N_2O_4$	53.55	53.8	5.40	5.50	12.50	12.6
Threonine (*dl*)[d]	192.0–193.0	45	$C_{11}H_{14}N_2O_4$	55.44	55.7	5.92	6.20	11.76	11.8
Tryptophan (*dl*)	199.0–201.0	92	$C_{18}H_{17}N_3O_3$	66.85	66.8	5.30	5.34	13.00	13.2
Valine (*dl*)[e]	196.0–197.0	55	$C_{12}H_{16}N_2O_3$	61.00	61.3	6.83	6.73	11.86	11.8

[a] N-(*p*-Nitrobenzoyl) derivative, m. p. 192.5–194°; Colles and Gibson, *J. Chem. Soc.*, 101 (1928). [b] N-(*p*-Nitrobenzoyl) derivative, m. p. 169.5–170°; Karrer and Christoffel, *Helv. Chim. Acta*, **27**, 623 (1944). [c] N-(*p*-Nitrobenzoyl) derivative, m. p. 195.5–196.0°; Ross and Green, *J. Biol. Chem.*, **137**, 110 (1941); Fischer and Jacobs, *Ber.*, **39**, 2943 (1906). [d] N-(*p*-Nitrobenzoyl) derivative, Siro Maeda, *et al.*, *C. A.*, **33**, 2948 (1939). [e] N-(*p*-Nitrobenzoyl) derivative, m. p. 170–172°; ref. (*b*) above. [f] Prepared by zinc and acid reduction.

(1) Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

(2) Angier, *et al.*, *Science*, **103**, 667 (1946).

(3) Hutchings, *et al.*, *J. Biol. Chem.*, **170**, 323 (1947).

(4) Cosulich and Smith, THIS JOURNAL, **70**, 1922 (1948).

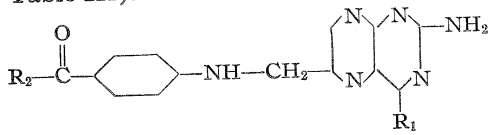
(5) Seeger, Smith and Hultquist, *ibid.*, **69**, 2567 (1947).

(6) Hultquist, Smith, Seeger, Cosulich and Kuh, *ibid.*, **71**, 619 (1949).

(7) Waller, *et al.*, *ibid.*, **70**, 19 (1948).

(8) Traube, *Ber.*, **37**, 4545 (1904).

In certain cases 1,1,3-tribromoacetone,[9a] the tetraminopyrimidine, and N-(*p*-aminobenzoyl)-amino acid were used, in a modification of the method of Hultquist and Dreisbach.[9b] The following were purified by methods similar to those described for pteroylglutamic acid and its analogs[6,9,10]: pteroylalanine (II), pteroyl-β-alanine (III), pteramidomalonic acid (IV), 4-aminopteramidomalonic acid (V), and 4-aminopteroylserine (VI). The remainder of the analogs described herein were examined as the crude reaction products (see Table III).



R_1 = OH
I, R_2 = —NHCH(COOH)CH_2CH_2COOH
II, R_2 = —NHCH(CH_3)COOH
III, R_2 = —$NHCH_2CH_2$COOH
IV, R_2 = —NHCH(COOH)$_2$

R_1 = —NH_2
V, R_2 = —NHCH(COOH)$_2$
VI, R_2 = —NHCH(CH_2OH)COOH

In the course of this work a number of N-(*p*-nitrobenzoyl)-amino acids and N-(*p*-aminobenzoyl)-amino acids were prepared which have not been reported in the literature. Data on these compounds are given in Tables I and II.

The biological properties of these pteroylglutamic acid derivatives have been examined by Dr. E. L. R. Stokstad and Dr. B. L. Hutchings of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York. The details of this work will be published elsewhere.

Experimental

N-(*p*-Nitrobenzoyl)-amino Acids.—The serine and threonine derivatives were prepared by the method of Fischer and Jacobs.[11]

The other compounds were prepared as described below. One-tenth mole of the amino acid and 0.2 mole of 1*N* sodium hydroxide solution were mixed and cooled to 0–10°. One-tenth mole of *p*-nitrobenzoyl chloride was added and the mixture was stirred at 0–10° for one-half hour and then allowed to warm slowly to room temperature. The total reaction time was one and one-half to three hours. The unreacted *p*-nitrobenzoyl chloride was filtered off. The filtrate was cooled in an ice-bath as dilute acid was added until the mixture was at *p*H 2–3. After additional cooling, the product was filtered, washed with water, and dried overnight at 50–60°. The crude products were purified by recrystallization from the solvents indicated. An initial extraction with boiling ether removed much of the impurity from the alanine, phenylalanine and ε-aminocaproic acid derivatives.

In the case of cystine, 0.4 mole of 1*N* sodium hydroxide and 0.2 mole of *p*-nitrobenzoyl chloride were used and the bis derivative was obtained. The product was insoluble in alcohol and was purified by dissolving with cold dilute alkali, treating with Darco, and precipitating by addition of dilute acid (see Table I).

N-(*p*-Aminobenzoyl)-amino Acids.—The N-(*p*-nitrobenzoyl)-amino acids in alcohol solution were reduced catalytically using palladium on activated charcoal as a catalyst (see Table II).

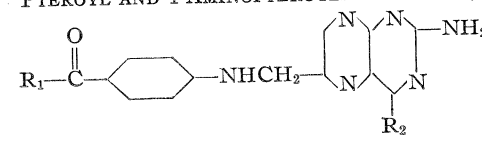
The N-(*p*-aminobenzoyl) derivatives of cystine, methionine and sarcosine were not isolated and characterized. The reduction solution was used directly in the reaction with dibromopropionaldehyde and 2,4,5-triamino-6-hydroxypyrimidine (see Table III).

Diethyl *p*-Nitrobenzamidomalonate.—Diethyl isonitrosomalonate was prepared in 82% yield, and reduced to diethyl aminomalonate by the method of Cerchez.[12] The product was treated directly without isolation with *p*-nitrobenzoyl chloride in a modification of the method of Redemann and Dunn[13] for the preparation of diethyl benzamidomalonate. An example of our procedure is described in detail below.

To 200 g. (1.06 moles) of diethyl isonitrosomalonate dissolved in 1600 ml. of ether was added the aluminum amalgam prepared from 48 g. of aluminum foil. Efficient cooling with an ice-bath was required to control the initial reaction. When the reaction had subsided, 300 ml. of water was added dropwise over a five-hour period to the refluxing mixture. The mixture was filtered and the precipitate washed with ether. To the combined filtrates were added 100 g. of pyridine and 500 ml. of water. A solution of 110 g. (0.6 mole) of *p*-nitrobenzoyl chloride in 400 ml. of ether was then added over a one-half hour period at reflux temperature. After heating under reflux for one hour longer, 1000 ml. of water was added, and the precipitate was filtered. It was recrystallized once from 1400 ml. of 2B alcohol to yield 83 g. (24%) of diethyl *p*-nitrobenzamidomalonate which melted at 135.5–136.5°. The ether layer was washed with water and then combined

TABLE III

PTEROYL AND 4-AMINOPTEROYLAMINO ACIDS,



R_1	R_2 = OH Purity,[a] %	R_2 = OH Biological activity,[b] %	R_2 = NH_2 Purity,[a] %	R_2 = NH_2 Biological activity,[b] %
Alanine (*dl*)	Analytical	0[c]		
Alanine (*dl*)	20.7	0	14.5	0
β-Alanine	Analytical	+2.46		
ε-Aminocaproic acid	27.0	0	11.5	.....
Aminomalonic acid	Analytical	+0.007	66.4	−0.1
Aminomalonic acid	17.4	0	14.0	.....
Cystine (*l*) (*bis*)[d]	22.5	0		
Isoleucine (*dl*)	8.7	.....	5.4	.....
Methionine	25.0	+		
Phenylalanine (*dl*)	13.0	0	5.5	.....
Sarcosine	20.4	+	18.3	.....
Serine (*dl*)			Analytical	−0.174
Serine (*dl*)	18.3	0	22.8	.....
Threonine·H_2O (*dl*)	19.0	.....	22.4	.....
Tryptophan (*dl*)	7.8	.....	8.3	.....
Valine (*dl*)	13.8	0	11.0	0

[a] "Analytical" denotes an analytically pure sample. Per cent. values were determined by the chemical assay method of Hutchings, *et al.* (see ref. 14), and have been corrected for an inert diluent (barium sulfate) present in the crudes. [b] Determined for *S. faecalis* R; + = growth activity as compared to pteroylglutamic acid at 100; — = antagonist activity of N^{10}-methylpteroylglutamic acid for half-maximum inhibition of the growth of *Streptococcus faecalis* R. Values for other compounds are reported in terms of the standard. See ref. 3. [c] 0 = no activity, either as growth-promoter or antagonist. [d] bis-N-(*p*-Nitrobenzoyl)-cystine, Yoshikuni Inoue, *C.A.*, **24**, 341 (1930).

(9) (a) Watson and Yates, *J. Chem. Soc.*, 1207 (1932); (b) Hultquist and Dreisbach, U. S. Patent 2,443,165 (1948).

(10) Stokstad, *et al.*, THIS JOURNAL, **70**, 8 (1948); Mowat, *et al.*, *ibid.*, **70**, 1097 (1948).

(11) Fischer and Jacobs, *Ber.*, **39**, 2942 (1906).

(12) Cerchez, *Bull. soc. chim.*, [4] **47**, 1279 (1930).

(13) Redemann and Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

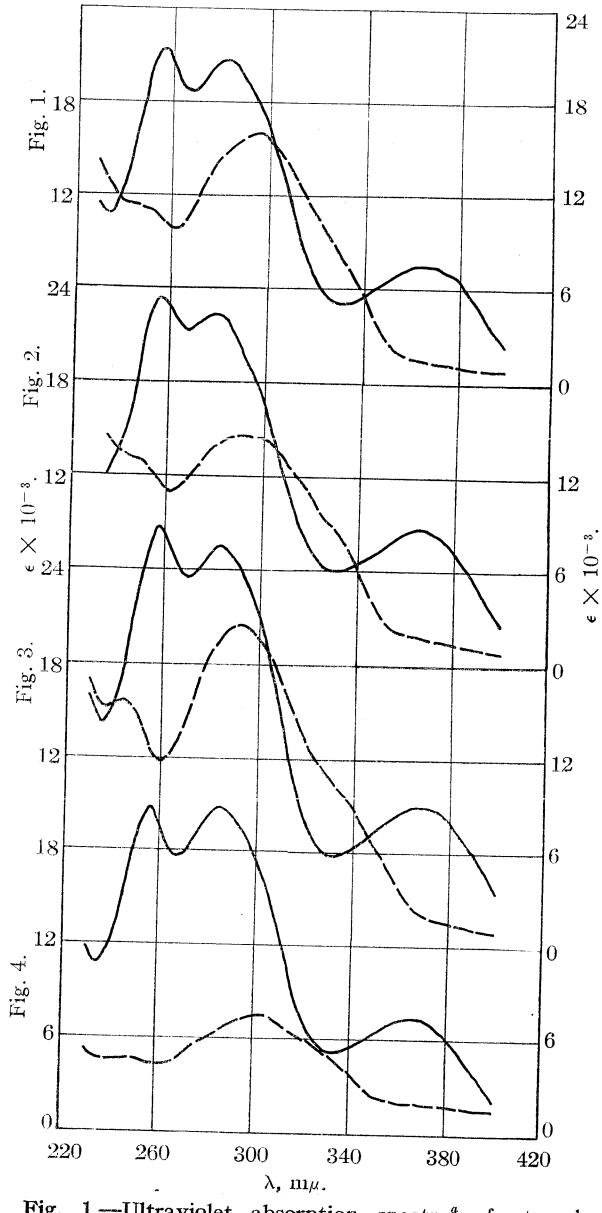


Fig. 1.—Ultraviolet absorption spectra[a] of pteroylalanine: ——— in 0.1 *N* sodium hydroxide; ---------- in 0.1 *N* hydrochloric acid.

Fig. 2.—Ultraviolet absorption spectra[a] of pteroyl-β-alanine: ——— in 0.1 *N* sodium hydroxide; ---------- in 0.1 *N* hydrochloric acid.

Fig. 3.—Ultraviolet absorption spectra[a] of 4-aminopteroylserine: ——— in 0.1 *N* sodium hydroxide; ---------- in 0.1 *N* hydrochloric acid.

Fig. 4.—Ultraviolet absorption spectra[a] of pteramidomalonic acid: ——— in 0.1 *N* sodium hydroxide; --------- in 0.1 *N* hydrochloric acid.

[a] ε is the molecular extinction coefficient as defined by $I = I_0 10^{-\epsilon cl}$ where c is the concentration in moles/liter and l is the cell length in centimeters. Transmittancy (I/I_0) measurements of 10 mg./l. solutions were made in 1 cm. cell at mμ intervals on a Model DU Beckman spectrophotometer using a solvent filled cell in the reference position. Additional data were obtained at 2 mμ intervals at maxima, minima and points of inflection.

with the above alcohol filtrate. Evaporation until precipitation began yielded an additional 60 g. (18%) which melted at 132.0–135.0°.

Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 52.1; H, 4.80; N, 8.71.

Diethyl *p*-Aminobenzamidomalonate.—Catalytic hydrogenation of 9.72 g. (0.03 mole) of diethyl *p*-nitrobenzamidomalonate suspended in 200 ml. of 2B alcohol, using a palladium on activated charcoal catalyst, yielded 8.2 g. (93%) of diethyl *p*-aminobenzamidomalonate in the form of long white needles which melted at 122–123°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.15; H, 6.16; N, 9.52. Found: C, 57.2; H, 6.23; N, 9.53.

***p*-Aminobenzamidomalonic Acid.**—A mixture of 5.88 g. (0.02 mole) of diethyl *p*-aminobenzamidomalonate and 50 ml. (0.10 mole) of 2 *N* sodium hydroxide solution was stirred for two hours. The reaction was acidified with 50 ml. (0.10 mole) of 2 *N* hydrochloric acid, cooled in an ice-bath for three hours, filtered, and the precipitate dried overnight at 40°. The product, 4.7 g. (99%), was almost insoluble in water, alcohol, acetone and ether. A portion which was redissolved in *N* sodium hydroxide solution, filtered, acidified with *N* hydrochloric acid and allowed to stand at room temperature precipitated as clusters of white needles. These were dried for analysis at room temperature in vacuum over phosphorus pentoxide. The dried sample contained one mole of water of crystallization, lost water or decarboxylated at about 150°, and did not melt completely at 250°.

Anal. Calcd. for $C_{10}H_{10}N_2O_5 \cdot H_2O$: C, 46.86; H, 4.72; N, 10.94; H_2O, 7.04. Found: C, 46.6; H, 5.00; N, 11.0; H_2O, 8.08.

Pteroylalanine (II).—Pteroylalanine was prepared by a modification of the method of Waller[7] from 2,4,5-triamino-6-hydroxypyrimidine, 2,3-dibromopropionaldehyde, and N-(*p*-aminobenzoyl)-alanine; 0.5 equivalent of iodine or sodium dichromate was added as oxidant during the condensation. Pteroylalanine was purified and isolated as the magnesium salt by known methods[6,9b,10] (see Table III).

Anal. Calcd. for $C_{17}H_{15}N_7O_4Mg \cdot H_2O$: C, 48.19; H, 4.04; N, 23.15; Mg, 5.74. Found: C, 48.6; H, 3.69; N, 23.5; Mg, 5.89.

Pteroyl-β-alanine (III).—This compound was prepared from N-(*p*-aminobenzoyl)-β-alanine by the method of Waller,[7] modified as for II above, and purified by known methods.[6,9b,10] The purity was 77.9% by chemical assay.[14] Final purification was accomplished as follows: The sample (400 mg.) was dissolved in 10 ml. of dilute sodium hydroxide; the sodium salt was precipitated by the addition of 10 ml. of 10 *N* sodium hydroxide. The crystalline sodium salt was filtered off and recrystallized from 40 ml. of 5 *N* sodium hydroxide. It was converted to the free acid by solution in 20 ml. of water, acidification with 5 ml. of concentrated hydrochloric acid, and dilution to 40 ml. volume. The product which was filtered off was recrystallized by dissolving in 10 ml. of 6 *N* hydrochloric acid and diluting to 35 ml. The final product was collected, washed with water, alcohol and ether and dried fifteen hours at 100° (1 mm.). The purity by chemical assay was 98% (see Table III).

Anal. Calcd. for $C_{17}H_{17}O_4N_7$: C, 53.3; H, 4.44; N, 25.6. Found: C, 52.94; H, 4.74; N, 25.30.

Pteramidomalonic Acid (IV).—This compound was prepared from *p*-aminobenzamidomalonic acid by the method of Waller,[7] modified as for II above and purified and characterized as the magnesium salt by known methods.[6,9b,10]

Anal. Calcd. for $C_{17}H_{12}N_7O_6Mg_{1.5} \cdot 2H_2O$: C, 42.29; H, 3.34; N, 20.32; Mg, 7.56. Found: C, 42.0; H, 3.56; N, 20.4; Mg, 7.78.

4-Aminopteramidomalonic Acid (V).—This compound was prepared by the method of Waller, *et al.*,[7] from 2,4,5,6-tetraaminopyrimidine, 2,3-dibromopropionaldehyde, and

(14) Hutchings, *et al.*, *J. Biol. Chem.*, **168**, 705 (1947).

p-aminobenzamidomalonic acid, modified as for II above (see Table III). Also, V was synthesized by a variation of the procedure employed by Hultquist and Dreisbach using 1,1,3-tribromoacetone.[9] The crude product prepared by the latter method contained about 30% of the desired compound, as estimated by the chemical assay of Hutchings, *et al.*[14] The crude was dissolved in 5% sodium carbonate solution at a concentration of 6 g. of V per liter, filtered, and the filtrate was acidified to *p*H 4 and cooled several hours at 2°. The precipitate was collected on the filter and washed with ice water, and then crystallized (at 5 g./l.) three times from hot 0.1 *N* hydrochloric acid. The material thus obtained had a chemical assay[14] of 66.4%.

4-Aminopteroylserine (VI).—This compound was synthesized from N-(*p*-aminobenzoyl)-serine by the method of Waller, *et al.*,[7] as modified for II above (see Table III) and also by a variation of the procedure of Hultquist and Dreisbach,[9] as indicated above for V. The crude material was heated at 60° with lime in water at a concentration of VI of 1 g./l. The solution was filtered and the filtrate was adjusted to *p*H 10.5–11.0 with aqueous zinc chloride. Insolubles were removed by filtration and the solution was acidified to *p*H 4, and the precipitated material was collected on the filter. It was extracted with 0.1 *N* hydrochloric acid at 80°. The residue was dissolved in dilute sodium hydroxide and reprecipitated with acid at 80°; after cooling to 10° the yellow, partially crystalline product obtained was filtered and dried. It showed a chemical assay[14] of about 70%. It was purified further by repeating the process above and then extracting with 0.1 *N* hychloric acid and reprecipitating three times more.

Anal. Calcd. for $C_{17}H_{18}O_4N_8 \cdot 3H_2O$: C, 45.1; H, 5.35; N, 24.7; H_2O, 11.9. Found: C, 45.3; H, 5.15; N, 24.7; H_2O, 9.9.

The hot 0.1 *N* hydrochloric acid extracts contain additional 4-aminopteroylserine which can be recovered by cooling and reworking as above.

Other Pteroyl- and 4-Aminopteroylamino Acids.—These were prepared by the method of Waller[7] from the N-(*p*-aminobenzoyl)-amino acids. One-half an equivalent of iodine or sodium dichromate was added during the condensation.

Acknowledgment.—We are indebted to Mr. Kenneth H. Collins for technical assistance in this investigation, to Miss Ruth Abbott for the ultraviolet absorption spectra studies, and to Mr. O. Sundberg and co-workers for the microanalyses.

Summary

1. The N-(*p*-nitrobenzoyl) derivatives of β-alanine, ε-aminocaproic acid, diethyl aminomalonate, isoleucine, sarcosine and tryptophan, have been prepared.

2. The N-(*p*-aminobenzoyl) derivatives of the following amino acids have been prepared: alanine, β-alanine, ε-aminocaproic acid, aminomalonic acid, isoleucine, phenylalanine, serine, threonine, tryptophan, and valine.

3. Pteroyl derivatives of alanine, ε-aminocaproic acid, aminomalonic acid, isoleucine, phenylalanine, sarcosine, serine, threonine, tryptophan, valine, β-alanine, cystine and methionine have been prepared as crude reaction products. With the exception of the last three, the corresponding 4-aminopteroylamino acids also have been prepared.

4. Pteroylalanine, pteroyl-β-alanine, pteramidomalonic acid, and 4-aminopteroylserine have been purified.

BOUND BROOK, NEW JERSEY
RECEIVED FEBRUARY 7, 1949

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Fatty Acid Amides. II.[2] Amides as Derivatives for the Identification of Some Long-Chain Unsaturated Fatty Acids

BY DANIEL SWERN, JEANNE M. STUTZMAN AND EDWARD T. ROE

Four techniques are usually employed for the identification of long-chain unsaturated fatty acids. They are (a) rigorous purification of the acid, followed by comparison of its properties with those of the acid with which it is presumed to be identical, (b) cleavage of the acid by any one of several well-known procedures, followed by identification of the fragments, (c) preparation of relatively high melting derivatives involving the ethylenic system, and (d) preparation of derivatives involving the carboxyl group.[3] The relatively high solubility of unsaturated fatty acids in organic solvents, their tendency to form crystalline mixtures of invariant composition, and the need for extremely low temperatures in their isolation and purification render the first technique time-consuming and impractical, and often it does not produce a product of sufficiently high purity, particularly when complex mixtures of fatty acids are employed as the starting material. The second technique is time-consuming, and in addition the severe conditions sometimes required to cleave the chain may cause isomerization. Furthermore, this technique may not give definitive results because of poor yields of cleavage products and the fact that the stereochemical nature of the parent acid cannot be deduced after the molecule is degraded. The third technique, which is the one most widely used, generally involves the formation of brominated or hydroxylated products. Although quantitative

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) For the first paper in this series, see THIS JOURNAL, **71**, 2215 (1949).

(3) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1940; McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945; Wild, "Characterization of Organic Compounds," University Press, Cambridge, England, 1947.

TABLE I

CHARACTERISTICS OF AMIDES OF SOME UNSATURATED ACIDS

Number	Acid	Unsubstituted amide: M. p., °C.	Iodine no.[a] Calcd.	Iodine no.[a] Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	Oleic[b]	76	90.2	90.2	76.8	77.0	12.5	12.4	4.97	4.91
2	Elaidic	90[c]	90.2	90.2	76.8	77.1	12.5	12.7	4.97	4.91
3	Linoleic									
4	Ricinoleic									
5	10-Hendecenoic	87.0–87.5[d]	138.5	135.7[e]	..	..	..	..	7.64	7.53

[a] One-half hour Wijs method. [b] Data taken from the paper by Roe, Scanlan and Swern.[2] [c] Emeljanoff and Albitzky[9] give 93–94°. [d] Jones and Pyman, *J. Chem. Soc.*, **127**, 2588 (1925), give 87°. [e] Micro-hydrogenation no. 8: Calcd. 183.3; found 183.9.

TABLE II

CHARACTERISTICS OF N-SUBSTITUTED AMIDES OF SOME UNSATURATED ACIDS

No. from Table I	N-(2-Hydroxyethyl)-amide: M. p., °C.	Iodine No.[a] Calcd.	Iodine No.[a] Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	N(*n*-Dodecyl)-amide: M. p., °C.	Iodine No.[a] Calcd.	Iodine No.[a] Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	63–64[b]	78.0	78.0	73.8	74.4	12.1	12.1	4.31	4.38	53.5–54.0	56.4	56.1	80.1	79.8	13.2	12.9	3.11	3.07
2	87	78.0	78.1	73.8	73.7	12.1	12.2	4.31	4.19	75.0–75.5[c]	56.4	56.2	80.1	80.1	13.2	13.3	3.11	3.06
3	39.0–39.5	156.9	157.5	74.3	74.3	11.5	11.3	4.33	4.13	45.5–46.0	113.4	114.2	80.5	80.6	12.8	12.9	3.13	3.00
4	54.5–55.0	74.3	74.8	70.3	70.4	11.5	11.7	4.10	4.25	56.0–57.0	54.5	54.3	77.4	77.2	12.8	13.0	3.01	2.90
5	67.0–67.5[d]	111.7	111.4	68.7	68.5	11.1	11.5	6.16	6.05	61.5–62.5	72.2	69.6[e]	78.6	78.3	12.9	12.8	3.98	4.02

[a] One-half hour Wijs method. [b] Hydroxyl: calcd., 5.22; found, 5.18. [c] Harber, *Iowa State Coll. J. Sci.*, **15**, 13 (1940), gives 73.5–74.0°. [d] Széki, *Math. naturw. Aus. ungar. Akad. Wiss.*, **54**, 807 (1936), gives 70.5°. [e] Micro-hydrogenation No. 8: Calcd., 351.6; found, 356.4.

hydroxylation of mono-unsaturated acids is conveniently carried out,[4] and this technique has some promise for identification purposes, the impossibility of regenerating the parent acid from the derivative by any simple procedure is a disadvantage. Furthermore, poly-unsaturated acids cannot be hydroxylated in good yields by any of the methods known at present, and the products obtained consist of mixtures of isomers difficult or impossible to separate. Poly-unsaturated acids are usually identified as polybromo acids, and the disadvantages of this technique have already been pointed out.[5] The fourth technique, however, appears to have none of the drawbacks of the others. This technique has been explored somewhat,[5,6,7] but the emphasis has been primarily on the preparation of esters, which not only have relatively low melting points, but in esters of poly-unsaturated acids do not give the calculated analytical values.

Amides are among the highest melting fatty acid derivatives, and although considerable reliable data are available on the long-chain saturated acids, the literature on amides of unsaturated fatty acids is generally incomplete and often unreliable. This paper describes the preparation and some of the properties of the unsubstituted, the N-(2-hydroxyethyl)-, and the N-(*n*-dodecyl)-amides of linoleic, ricinoleic, 10-hendecenoic (undecylenic) and elaidic acids. The results are summarized in Tables I and II (the characteristics of the corresponding amides of oleic acid, taken from a previous paper,[2] are included for comparison).

The unsubstituted amides of oleic,[2] 10-hendecenoic and elaidic acids, and the N-(2-hydroxyethyl)- and N-(*n*-dodecyl) amides of oleic, linoleic, ricinoleic, 10-hendecenoic and elaidic acids were readily prepared in good yield. They were white, crystalline solids which had the calculated analytical characteristics. N-(2-Hydroxyethyl)-hendecenamide had a strong pepper-like taste. We were unable to purify linoleamide, and this amide, as well as N-(2-hydroxyethyl)-linoleamide, rapidly became rancid and dark at room temperature. They were soon converted to viscous, brown oils, although all operations on these and the other amides described were conducted in an atmosphere of nitrogen, and the samples were stored under nitrogen. These two amides undoubtedly undergo rapid oxidation and polymerization in the presence of small quantities of oxygen. N-(*n*-Dodecyl)-linoleamide, however, was much more stable than the other linoleamides, and after storage for several months it was only pale yellow and slightly rancid. The amides of the monounsaturated acids were stable, provided that they were not heated in air. It was essential to dry the amides in an atmosphere of nitrogen, otherwise incorrect analytical values were obtained. Some difficulty was experienced in obtaining theoretical iodine values on purified 10-

(4) Swern, Billen, Findley and Scanlan, THIS JOURNAL, **67**, 1786 (1945).

(5) Kass, Nichols and Burr, *ibid.*, **64**, 1061 (1942).

(6) Drake and Bronitsky, *ibid.*, **52**, 3715 (1930).

(7) Kimura, *J. Soc. Chem. Ind. Japan*, **37**, 154B (1934).

hendecenamide and N-(*n*-dodecyl)-hendecenamide, even though the elemental analyses were correct. The iodine values obtained on these two compounds were usually about two to three units lower than the calculated values, but microhydrogenation numbers were satisfactory.[8] It has been reported that elaidamide melts at 93–94°,[9] but the highest melting point we were able to obtain was 90°, even though we worked with carefully purified materials. The melting points of oleamide (76°) and elaidamide (90°) differ significantly and are readily duplicated, even though widely different preparative reactions are employed. This is good evidence that the conventional reactions for preparing amides[2] do not cause *cis–trans* isomerization.

In the hydrolysis of N-(*n*-dodecyl)-amides to the acid and amine hydrochloride by refluxing with constant boiling hydrochloric acid, approximately twelve hours reflux time was required, and acid fractions with iodine numbers only about one-third or one-fourth those calculated were obtained. The hydrolysis of the unsubstituted or 2-hydroxyethyl amides, however, was complete in about one hour when a large excess (about 500%) of constant boiling hydrochloric acid was employed, and the iodine numbers of the acid fractions were over 90% of those calculated.

In view of the low melting points and relative instability of the linoleamides, no attempt was made to prepare the corresponding amides of linolenic and eleostearic acids, since these would be expected to have even lower melting points and to be less stable.

Experimental[9a]

Materials Used.—Linoleic acid, iodine number 180.3, was prepared by the debromination of 9,10,12,13-tetrabromostearic acid, m. p. 115.0–115.3°, with zinc dust in diethyl ether solution.[10] Methyl ricinoleate, b. p. 196–199° (2.3–2.5 mm.), $n^{30}D$ 1.4598, iodine number 81.3, was prepared from castor oil by methanolysis, followed by fractional distillation through a Vigreux column 3 feet long and 1 inch in diameter.[11] 10-Hendecenoic acid, m. p. 24.3–24.5°, b. p. 180° (26.5 mm.), iodine number 137.2, was prepared[12] from the purest commercial grade by fractional distillation, and crystallization from petroleum naphtha, hexane fraction, at −20°. Elaidic acid, m. p. 44°, was prepared from oleic acid by isomerization with powdered selenium.[13] Monoethanolamine and dodecylamine were the purest commercial grades, and they were distilled before use through efficient fractionating columns.

Preparation of Derivatives. Unsubstituted Amides.—Linoleic, 10-hendecenoic and elaidic acids were converted to the corresponding acid chlorides by reaction with oxalyl chloride in benzene solution, as described by Bauer.[14] After removal of benzene and excess oxalyl chloride, the acid chlorides were added dropwise to a large excess (500–900%) of ice-cold concentrated aqueous ammonium hydroxide, with stirring. The crude amides were separated from the aqueous layer and dissolved in a suitable solvent (petroleum naphtha was employed for linoleamide, and 95% ethanol was employed for 10-hendecenamide and elaidamide; 4 to 5 ml. of solvent per gram of solute), treated with activated carbon and filtered. The filtrates were cooled to 0 to 5° (room temperature in the case of elaidamide), and the amides which precipitated were filtered off and washed with cold solvent. Linoleamide was obtained as a white solid which could not be completely purified. Additional manipulation caused both the melting point and iodine number to decrease. On standing, the product, which contained 0.44% of chlorine, rapidly darkened and became rancid, and it was soon converted to a brown viscous oil. 10-Hendecenamide and elaidamide were white crystalline solids, which were purified by recrystallization from 95% ethanol at 15 to 25°. They were stable at room temperature. Since ricinoleic acid is difficult to purify and is reported to be unstable, no attempt was made to prepare ricinoleamide from it.

N-(2-Hydroxyethyl)-amides.—Linoleic, 10-hendecenoic and elaidic acids, and methyl ricinoleate were refluxed with a 50% molar excess of monoethanolamine (methyl ricinoleate, one hour reflux; the others, two hours). The cooled reaction mixtures were dissolved in petroleum naphtha, 95% ethanol, petroleum naphtha and acetone, respectively (3 to 8 ml. of solvent per gram of solute). The solutions were treated with activated carbon and filtered. The filtrates were cooled (N-(2-hydroxyethyl)-elaidamide, 25°; N-(2-hydroxyethyl)-linoleamide, 0°; the others, −20°) to precipitate the amides, which were filtered off and washed with cold solvent. The products were then recrystallized to constant melting point (N-(2-hydroxyethyl)-elaidamide from 95% ethanol at 10°). N-(2-Hydroxyethyl)-linoleamide was unstable.

N-(*n*-Dodecyl)-amides.—Linoleic, 10-hendecenoic and elaidic acids, and methyl ricinoleate were heated at 230° with a 1% molar excess of *n*-dodecylamine (methyl ricinoleate, three-hour reaction period; the others, thirty-five minutes). The cooled reaction mixtures were dissolved in 95% ethanol (4 to 5 ml. of solvent per gram of solute), the solutions were treated with activated carbon and filtered. The filtrates were cooled to 0° (N-(*n*-dodecyl)-elaidamide was crystallized at 25°), and the precipitated amides were filtered off and washed with cold solvent. The products were then recrystallized to constant melting points.

Acknowledgment.—The authors are indebted to Jane Dixon and Mary Jane Welsh of the Analytical and Physical Chemistry Division of this Laboratory for the carbon, hydrogen and nitrogen analyses.

Summary

N-(2-Hydroxyethyl)- and N-(*n*-dodecyl)-linoleamides, ricinoleamides, elaidamides and 10-hendecenamides, as well as the unsubstituted amides, elaidamide and 10-hendecenamide, have been prepared and characterized. These amides are suitable derivatives for the identification of the parent unsaturated acids. Linoleamide could not be completely purified. This compound, as well as N-(2-hydroxyethyl)-linoleamide, was unstable at room temperature, both being rapidly converted to dark-brown viscous oils.

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(8) Ogg and Cooper, paper presented at the meeting-in-miniature of the Philadelphia Section of the American Chemical Society, January 20, 1949.

(9) Emeljanoff and Albitzky, *J. Russ. Phys.-Chem. Soc.*, **31**, 106 (1899).

(9a) All operations were conducted in an atmosphere of nitrogen.

(10) Frankel and Brown, THIS JOURNAL, **65**, 415 (1943).

(11) Kass and Radlove, *ibid.*, **64**, 2253 (1942).

(12) Jordan and Swern, *ibid.*, **71**, 2377 (1949)

(13) Bertram, *Chem. Weekblad*, **33**, 3 (1936)

(14) Bauer, *Oil and Soap*, **23**, 1 (1946)

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

The Preparation of Quinolinic and Cinchomeronic Acids by Ozone Oxidation

BY ALBERT F. LINDENSTRUTH AND CALVIN A. VANDERWERF

In an attempt to develop a convenient synthesis for quinolinic and cinchomeronic acids, a study was made of the ozone oxidation of quinoline, 8-hydroxyquinoline and isoquinoline. Mainly out of theoretical interest, the investigation was later extended to include 6-aminoquinoline, 6-nitroquinoline, 6-fluoroquinoline, and 6-fluoro-8-aminoquinoline.

The manufacture of pyridine carboxylic acids by the action of ozone on pyridine derivatives has been claimed previously,[1] but details concerning the ozonolysis, isolation, and characterization procedures are lacking. Quinolinic acid has been prepared by the oxidation of quinoline with hydrogen peroxide in the presence of copper sulfate and sulfuric acid,[2] of quinoline and quinoline derivatives carrying substituents in the benzene ring with alkaline permanganate[3] and of 8-hydroxyquinoline with fuming nitric acid,[4] as well as by the electrolytic oxidation of quinoline.[5] Cinchomeronic acid is commonly obtained by oxidation of isoquinoline with alkaline permanganate[6] and of quinine hydrochloride with nitric acid.[7]

Our studies have shown that with quinoline, one mole of ozone was readily fixed, whereupon further addition of ozone to form a diozonide was considerably slower.[8] In all cases, the addition compound formed was usually stable, resisting decomposition, even under drastic conditions, by the reagents commonly employed for decomposing ozonides. Only when 30% hydrogen peroxide[9] or concentrated nitric acid was used, could traces of the desired product, quinolinic acid, be obtained. Upon strong heating, samples of the addition compound liberated ozone and quinoline.

Quinoline derivatives bearing one or more substituents in the benzene ring added ozone less rapidly than quinoline itself, particularly if the substituents were electron-withdrawing in nature. All gave quinolinic acid as the only identifiable product, in poor yield if the substituents were electron-withdrawing, in good yield if they were electron-releasing. Ozone oxidation of 8-hydroxyquinoline, for example, consistently gave 90–95% yields of quinolinic acid, whereas the yields with 6-nitroquinoline for corresponding ozonization times were less than 6%. In the cases of those compounds which gave only low yields of acid, almost half of the starting material could be recovered by steam distillation of the ozonized reaction mixture. These results substantiate the observation that the pyridine ring in quinoline is much more resistant to oxidation than the benzene ring. Because it gave a clean, facile reaction, hydrogen peroxide in acid solution was utilized in the decomposition of the substituted quinoline ozonides.[10] Decomposition, in every case, could be accomplished merely by treatment with hot water, but the reaction was slower and the yields of acid somewhat lower.

Ozone added relatively slowly to isoquinoline forming diozonides. The diozonide formed by the attack of ozone on the benzene nucleus was reactive in comparison with the unsubstituted quinoline diozonide, decomposing directly in solution to yield cinchomeronic acid, if small amounts of water were present. Treatment of the remaining ozonated solution with 30% hydrogen peroxide[11] yielded phthalic acid and small amounts of cinchomeronic acid, indicating that, in marked contrast to its action on quinoline, ozone attacked both the benzene and pyridine rings. Cinchomeronic and phthalic acids prepared in this manner were obtained together in yields of 45 and 50%, respectively.

Experimental Details

Ozonizer.—The source of ozone was a Type T-12 ozonator purchased from Ozone Processes, Inc., Philadelphia, Pa., designed for operation on a 115-volt, 60 cycle a. c. current. At an oxygen rate of 20 liters per hour, the weight concentration of ozone produced was 9–10%.

Ozonization of 8-Hydroxyquinoline.—A solution of 72.5 g. (0.5 mole) of 8-hydroxyquinoline in 400 ml. of glacial acetic acid was subjected to a stream of 9–10% ozonized oxygen at 20 l. per hour, for forty-eight hours at room temperature. During the early stages of the ozonization the solution turned dark brown and the temperature rose to 35°. After twenty-four hours, the solution turned a light yellow color and the temperature dropped to that of the room. Then 110 g. of 30% hydrogen peroxide[12] was added cautiously to the ozonated solution. The resulting solution was refluxed for two hours and then concentrated almost to dryness. The yellow

(1) British Patent 17,003, January 26 (1914).

(2) Stiks and Bulgach, *Ber.*, **65B**, 11 (1932).

(3) Hoogewerff and Van Dorp, *Ann.*, **204**, 84 (1880); Kirpal, *Monatsh.*, **22**, 361 (1901); Guha and Maller, *Current Sci. (India)*, **13**, 206 (1944).

(4) Sucharda, *Ber.*, **58**, 1727 (1925).

(5) Kulka, THIS JOURNAL, **68**, 2472 (1946).

(6) Hoogewerff and Van Dorp, *Rec. trav. chim.*, **4**, 285 (1885).

(7) Kirpal, *Monatsh.*, **23**, 239 (1902).

(8) Ozonized oxygen of known ozone concentration was employed, and ozone absorption was followed by systematic titration of the effluent gases. The curve obtained by plotting time *vs.* ozone concentration flattened when ozone was no longer absorbed by the reacting solution. The fact that no quinoline could be obtained upon distillation of the reaction product in basic solution indicated that all of the quinoline had been converted to the ozonide.

(9) Henne and Hill, THIS JOURNAL, **65**, 752 (1943).

(10) Only starting material and tarry oxidation products could be isolated after similar treatment of any of the substituted quinolines themselves.

(11) Similar treatment of isoquinoline yielded, in addition to starting material, only tarry oxidation products from which no pure compound could be isolated.

(12) When decomposition of the ozonide was effected by use of water, rather than of hydrogen peroxide, the yields were slightly over 70%. The ozonized solution was concentrated under vacuum to one-fifth its original volume, an equal volume of water added, and the mixture refluxed for four hours.

solid obtained was recrystallized from hot water yielding 76 g. (92%) of quinolinic acid, which decomposed at 190.0–191.2° into a black solid (nicotinic acid), which remelted at 229.2–230.4°. The melting point was not depressed when the product was mixed with an authentic sample of quinolinic acid. If small amounts of water were present some quinolinic acid precipitated during the ozonization.

Ozonization of Quinoline.—The ozonization was conducted as described above. The solvent was removed under vacuum and the resulting product refluxed in turn with water, concentrated sodium hydroxide solution, concentrated hydrochloric acid, glacial acetic acid and zinc, stannous chloride and hydrochloric acid, 30% hydrogen peroxide and concentrated nitric acid. Traces of quinolinic acid were isolated only in the last two cases as well as upon low pressure catalytic hydrogenation with 5% palladium on charcoal and subsequent treatment with 30% hydrogen peroxide. The addition compound, upon steam distillation in a basic solution, did not produce any unreacted quinoline. Attempts to distill the compound under low pressures failed, the majority of the material forming a tar, while, to a lesser extent, quinoline and ozone were regenerated. The ozone was detected by the formation of a sodium hydroxide ozonate,[13] which results from the action of ozone on solid sodium hydroxide and which liberates oxygen when placed in an acid solution.

Ozonization of Isoquinoline.—A solution of 20.0 g. (0.155 mole) of isoquinoline in 200 ml. of glacial acetic acid was ozonized as previously described. Best results were obtained if a small amount of water was added to the solvent; cinchomeronic acid (11.4 g., 44.5%), m. p. 259–260°, then precipitated from solution during the ozonization. The solid material was separated by filtration and the filtrate refluxed with 35 g. of 30% hydrogen peroxide for two hours. Evaporation to dryness (or continuous ether extraction) of the resulting solution yielded 12.8 g. (49.5%) of phthalic acid, melting at 204–205°, and small amounts of cinchomeronic acid. The yield of cinchomeronic acid was lowered to 10% when the ozonization time was reduced to twelve hours.

Ozonization of Other Quinolines.—6-Amino-, 6-fluoro-8-amino-, 6-fluoro- and 6-nitroquinoline yielded 65, 44, 15 and 6%, respectively, of quinolinic acid when ozonized as previously described. Tarry oxidation products were also formed and, in the last two cases, almost half of the quinolines were recovered unchanged.

(13) A study of sodium hydroxide ozonates is being conducted in this Laboratory by Mr. Thomas Whaley.

Summary

1. Preparation of quinolinic acid in 90–95% yield and of cinchomeronic acid in 45% yield by ozone oxidation of 8-hydroxyquinoline and isoquinoline, respectively, is described.

2. Studies on the oxidation by ozone of quinoline, 6-aminoquinoline, 6-fluoroquinoline, 6-nitroquinoline, and 6-fluoro-8-aminoquinoline are also reported.

LAWRENCE, KANSAS RECEIVED JANUARY 21, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF QUEENS COLLEGE]

The Chemical Effects Accompanying Hydrogen Bonding. II. Alkylation of the Oximes of 2-Hydroxy-5-methylbenzophenone

BY A. H. BLATT AND S. ARCHER[1]

The chemical effects of hydrogen bonding were examined in a study of the acyl derivatives of the oximes of 2-hydroxy-5-methylbenzophenone where it was shown that the isomeric bonded (I) and non-bonded (II) oximes behaved similarly on acylation, but that their acyl derivatives showed striking differences in behavior.[2] We have examined the alkylation of these same oximes and find that the differences in behavior show up in the alkylation reaction rather than in the chemistry of the alkylation products.

The generalization in the chemical literature which describes the alkylation of ketoximes in alkaline solution with alkyl halides or dimethyl sulfate is that mixtures of O- and N-alkyl derivatives are formed.[3] The generalization is not applicable to the alkylation of the oximes I and II. The bonded oxime I in normal sodium methoxide solution with methyl iodide (ratios of oxime, alkyl halide, base = 1, 1.5, 1) furnishes the O-methyl ether III in 77–83% yield.[4] None of the N-methyl ether V is obtained. The non-bonded oxime II under the same conditions furnishes the N-methyl ether VI in 83–90% yield. None of the isomeric O-methyl ether IV is obtained. The course of the alkylation is completely controlled by the presence or absence of bonding and it seems reasonable to suggest that the bonding operates by freezing the configuration shown in I and thus preventing the rear-ward approach to the nitrogen atom which would lead to the N-ether V. A scale model of the oxime I shows this clearly. A similar model of the isomeric oxime shows that the oximino group cannot be accommodated to the atomic dimensions involved in IIa and that some rotation about the bond between the substituted phenyl group and the carbon atom of the C=N group is necessary to accommodate the oximino group. In arrangements such as II in which this rotation has taken place the nitrogen atom is relatively accessible to rear-ward approach.

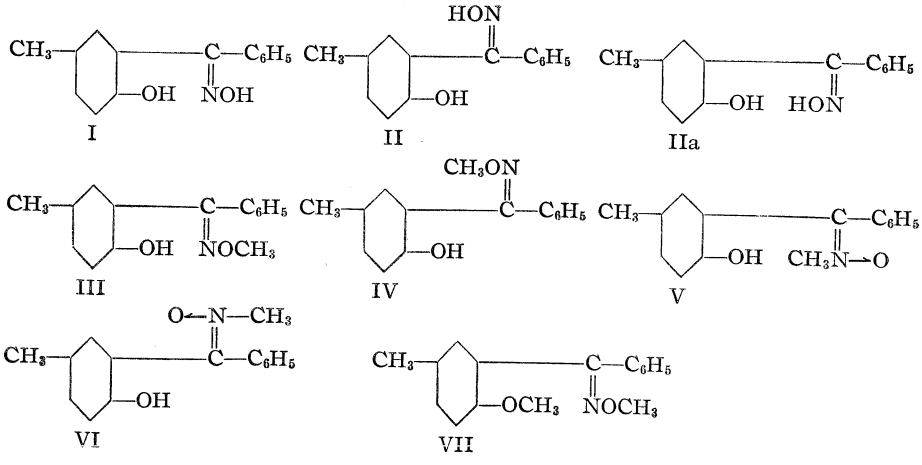
In the alkylation of the non-bonded oxime II, variations in the ratio of oxime to base and to alkylating agent as well as variations in the concentration of the base were without effect. The only product obtained was the N-ether VI. In the alkylation of the bonded oxime I, by con-

(1) Present address: Sterling–Winthrop Research Institute, Rensselaer, New York.

(2) Blatt, THIS JOURNAL, **60**, 205 (1938).

(3) Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1932, Vol. 3, p. 1035.

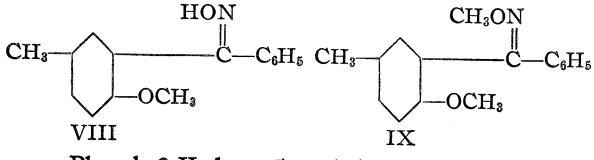
(4) The evidence for the configuration and structure of the alkylation products is to be found in the experimental section.



trast comparable variations in the concentration and molar ratios of the reactants did determine the nature of the alkylation product. The principal product was usually the O-ether III. If, however, a large excess of base and alkylating agent was used, the O-ether III was accompanied by the dimethyl ether VII. The dimethyl ether presumably results from further alkylation of the monomethyl ether III; in fact, the most convenient method of preparing VII is by alkylation of the monomethyl ether III with methyl iodide and sodium methoxide. When the concentration of the sodium methoxide was increased from 1 to 2 *N*, the monomethyl ether III and the dimethyl ether VII were again formed, but the principal product was the N-methyl ether V. This seems to be the result of the formation of the phenoxide ion which would destroy the bonding in I; then the oxime behaves in normal fashion to yield a mixture of N-methyl and O-methyl derivatives.

Experimental

In addition to the alkylations, a number of experiments were run in order to establish the structure and configuration of the alkylation products; and to prepare the reference compounds VIII and IX which were not obtained by alkylation. These experiments are described first and are followed by a description of the alkylation reactions.



***syn*-Phenyl 2-Hydroxy-5-methylphenyl Ketoxime O-Methyl Ether (III).**—This ether is most conveniently prepared from the ketone and methoxyamine. When 6.7 ml. of concd. hydrochloric acid diluted to 15 ml. with water was added to a solution of 10.6 g. of 2-hydroxy-5-methylbenzophenone and 3.7 g. of methoxyamine in 50 ml. of alcohol and the reaction mixture was boiled for four hours, an oil separated. The oil was redissolved by the addition of hot alcohol. On cooling, 7.5 g. of the ether crystallized; yield, 62%. The ether crystallizes from methyl alcohol in stout plates which melt at 94–95°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: OCH_3, 12.9. Found: OCH_3, 13.1.

The ether is sparingly soluble in methyl and ethyl alcohols, moderately soluble in ligroin and very soluble in acetone, benzene, chloroform and ether. The structure of the compound is established by its method of preparation; the configuration follows from the fact that the material shows no hydroxyl group absorption in the infrared. We are indebted to Dr. Oliver Wulf for examining the infrared absorption spectrum.

The ether does not form an acetyl derivative when its solution in acetic anhydride is warmed for ten minutes. It undergoes no shift of configuration and is recovered unchanged after treatment at room temperature or at the boiling point with aqueous potassium hydroxide solutions ranging in concentration from 10 to 40% of potassium hydroxide. Similarly, the ether was recovered unchanged after 1.3 g. in 13 ml. of 3 *N* sodium methoxide was kept at room temperature for fourteen days.

***syn*-Phenyl 2-Methoxy-5-methylphenyl Ketoxime O-Methyl Ether (VII).**—To a solution of 0.23 g. of sodium in 10 ml. of methanol, was added 1.2 g. of *syn*-phenyl 2-hydroxy-5-methyl ketoxime O-methyl ether (III) and 1 ml. of methyl iodide. After twenty-four hours at room temperature, the precipitate of dimethyl ether (VII) was filtered; 1.05 g., 80%. The filtrate on dilution with water furnished a mixture of starting material and dimethyl derivative—see below.

The dimethyl ether (VII) crystallizes from methanol or ligroin in hemispherical clusters of fine needles which melt at 91–92°.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; OCH_3, 24.3. Found: C, 74.8; H, 6.4; OCH_3, 23.7.

An equimolar mixture of the dimethyl ether (VII) and monomethyl ether III melts fairly sharply at 67–68°. (*Anal.* Calcd. for a mixture of $C_{15}H_{15}NO_2$ (III) and $C_{16}H_{17}NO_2$ (VII): OCH_3, 18.6. Found: OCH_3, 18.5.) This mixture often crystallizes from solutions containing both ethers. The mixture can be separated into its components by careful crystallization from methyl alcohol. The first crop consists of the characteristic plates of the monomethyl ether III. After they have been separated, the filtrate is evaporated to dryness and the residue taken up in ligroin. From this solvent the dimethyl ether VII crystallizes first.

The structure of the dimethyl ether follows from its method of preparation. It has been assigned the same configuration as the monomethyl ether III because that ether undergoes no change in configuration in sodium methoxide solution.

***anti*-Phenyl 2-Methoxy-5-methylphenyl Ketoxime (VIII).**—To prepare this oxime 4.5 g. of 2-methoxy-5-methylbenzophenone was dissolved in 20 ml. of alcohol and 2.0 g. of hydroxylamine hydrochloride in 5 ml. of water was added. The solution was boiled for two hours and diluted with 10 ml. of water. The crude oxime, which crystallized as the solution cooled, weighed 4 g., 83%. In a parallel experiment using hydroxylamine hydrochloride and excess sodium hydroxide the yield of crude oxime was 93%. For analysis the oxime was crystallized from ethanol. The pure product melts at 162–163°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: OCH_3, 12.9. Found: OCH_3, 13.2.

The structure and configuration of the oxime were established by a Beckmann rearrangement. When 1.7 g. of

the oxime suspended in 30 ml. of absolute ether was treated with an equal weight of phosphorus pentachloride, the oxime dissolved to furnish a yellow solution. After an hour and a half the reaction mixture was poured onto ice and water and left until the ether had evaporated. The yield of crude product was quantitative. For analysis the material was crystallized from ethanol. It was obtained as stout matted needles which melted at 90.5–91.5°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: OCH_3, 12.9. Found: OCH_3, 13.1.

The rearrangement product to be expected from the oxime VIII is 2-methoxy-5-methylbenzanilide, described as melting at 96°.[5] We prepared a sample of this anilide by methylating 2-hydroxy-5-methylbenzanilide with sodium methoxide and methyl iodide. The synthetic product melted at 93–94° and a mixture of the synthetic product and rearrangement product melted at 92.5–93.5°.

The oxime VIII does not furnish a copper derivative when its ethereal solution is shaken with aqueous copper acetate. When it is warmed with acetic anhydride, the oxime furnishes an acetate which melts at 104–105° after recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{17}NO_3$: OCH_3, 10.95. Found: OCH_3, 10.75.

***anti*-Phenyl 2-Methoxy-5-methylphenyl Ketoxime O-Methyl Ether (IX).**—A solution of 2.5 g. of methoxyamine hydrochloride in 5 ml. of water was added to 4.5 g. of 2-methoxy-5-methylbenzophenone in 20 ml. of ethanol. The reaction mixture was boiled for two and one-half hours during which time an oil separated. Water was added and the reaction mixture was left in the ice-chest overnight. The solid thus obtained was crystallized from methanol and furnished 3.3 g. of the dimethyl ether IX which melted at 67–68°; yield, 66%.

Anal. Calcd. for $C_{16}H_{17}NO_2$: OCH_3, 24.3. Found: OCH_3, 24.6.

The dimethyl ether is related configurationally to the oxime VIII by its preparation from that oxime. When 1.2 g. of the oxime VIII in 10 ml. of methanol containing 0.23 g. of sodium was treated with 1 ml. of methyl iodide, the reaction mixture furnished, after twenty-four hours, 0.8 g. of the dimethyl ether IX; yield, 63%.

Alkylation of the Oximes I and II.—The alkylations were run unless otherwise specified on 4.5 g. (0.02 mole) quantities of oxime. The oxime was dissolved in sodium methoxide solution, the alkylating agent added and the reaction mixture left stoppered for eighteen to twenty-four hours at room temperature. Any solid was removed by filtration, then water was added to the filtrate and the organic material extracted with ether. In experiments where an excess of base was used the reaction mixtures were acidified.

When 1 mole of the bonded oxime I was treated with 1 mole of 1 or 1.3 *N* sodium methoxide and 1.5 to 2 moles of methyl iodide, the product obtained in 77–83% yield was the oxime O-methyl ether III. From 1 mole of oxime, 2 moles of 1 *N* sodium methoxide and 1 mole of methyl iodide, the principal product was the non-bonded oxime II; 70% of the oxime I which was not converted into its stereoisomer II appeared as the monomethyl ether III. From 1 mole of oxime, 3 moles of 1 *N* sodium methoxide and 4 moles of methyl iodide, the yield of crude alkylation product was very satisfactory; but the product was a mixture of the ether III and the dimethyl ether VII and more than half of the material was lost in the fractional crystallization, so that the yields of III and VII were 30 and 5%, respectively. When the concentration of the base was increased to 2 *N*, the N-methyl ether V appeared as a product. From 1 mole of oxime, 4 moles of sodium methoxide and 3 moles of methyl iodide, the yield of N-methyl ether was 50%; the filtrates furnished a mixture of the monomethyl ether III and the dimethyl ether VII.

***syn*-Phenyl 2-hydroxy-5-methylphenyl ketoxime N-methyl ether (V)** is obtained as small cubes by recrystallization from methyl or ethyl alcohol. It is almost insoluble in ether. The melting point of the material, 180–181°, varies with the rate of heating.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.65; H, 6.3. Found: C, 74.6; H, 6.1; methoxyl, negative.

The structure of the N-ether was established by its ready hydrolysis. Boiling with methyl alcohol and hydrochloric acid for twenty minutes brought about complete hydrolysis to 2-hydroxy-5-methylbenzophenone.

The experiments with methyl *p*-toluenesulfonate paralleled those with methyl iodide and need not be described in detail. The ester is so readily hydrolyzed, however, that in the runs using 1 mole of ester and 2 to 4 moles of sodium methoxide only unreacted oxime was obtained. In a single run using diazomethane the only product obtained was unchanged oxime.

The non-bonded oxime on alkylation furnished only the N-methyl derivative VI. This material, ***anti*-phenyl 2-hydroxy-5-methylphenyl ketoxime N-methyl ether,** crystallizes from methyl or ethyl alcohol in splendid yellow cubes which melt at 142–143°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.65; H, 6.3. Found: C, 74.9; H, 6.2; methoxyl, negative.

The N-methyl derivative turns purple on exposure to light. It is hydrolyzed by twenty minutes of boiling in a solution of 7 parts of methanol and 1 part of concd. hydrochloric acid to 2-hydroxy-5-methylbenzophenone (85% yield) and N-methylhydroxylamine hydrochloride.

From 1 mole of the non-bonded oxime II, 1 mole of sodium methoxide and 1.5 or 2 moles of methyl iodide the yield of N-ether VI was 83–90%. The same ether, VI, was the only product isolated from 1 mole of oxime, 2 moles of 1 *N* sodium methoxide and 1 mole of methyl iodide, and from 1 mole of oxime, 4 moles of 1 *N* sodium methoxide and 2.5 moles of methyl iodide. In these experiments the yields were not so good and oily products were also formed.

Alkylation of the non-bonded oxime with methyl *p*-toluenesulfonate and sodium methoxide and with diazomethane also furnished only the N-methyl ether VI.

Summary

The behavior on alkylation of the bonded and non-bonded oximes of 2-hydroxy-5-methylbenzophenone was studied. The non-bonded oxime furnished only the N-ether, *anti*-phenyl 2-hydroxy-5-methylbenzophenone ketoxime N-methyl ether, regardless of the ratios of oxime to alkylating agent and base. On the other hand, the nature of the products formed when the bonded oxime was alkylated did depend on the concentrations of the reactants. When one mole of base and two moles of iodide were used only *syn*-phenyl 2-hydroxy-5-methylphenyl ketoxime O-methyl ether was obtained. Increasing the quantities of base and methyl iodide resulted in the appearance of the dimethyl ether, *syn*-phenyl 2-methoxy-5-methylphenyl ketoxime O-methyl ether. With a very large excess of base and alkylating agent another product, namely, *syn*-phenyl 2-hydroxy-5-methylphenyl ketoxime N-methyl ether was encountered also.

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[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1287]

The Apparent Ionization Constants and Ultraviolet Spectra of *o*-, *m*- and *p*-Chloro- and *p*-Sulfamyl-DL-phenylalanine

BY JUDD C. NEVENZEL,[1] WESLEY E. SHELBERG[2] AND CARL NIEMANN

At least four problems under investigation in these Laboratories, *i.e.*, the enzymatic synthesis of acylated α-amino acid amides,[3] the specificity and kinetics of chymotrypsin action,[4] the development of metabolic antagonists of the natural α-amino acids,[5] and the relation between chemical structure and thyroxine-like activity[6] have required the use of nuclear substituted phenylalanines or their analogs[7] and it thus has become imperative to have at hand more information regarding the physical and chemical properties of these compounds than is presently available. In this communication we wish to report observations relative to the apparent ionization constants and ultraviolet absorption spectra of the three isomeric nuclear substituted monochloro-DL-phenylalanines and of *p*-sulfamyl-DL-phenylalanine.

The apparent ionization constants of phenylalanine and the above four nuclear substituted phenylalanines, in 0.1 formal aqueous sodium chloride at approximately 25°, are given in Table I. It appears that the earlier values[8,9] for the pK'_{CO_2H} of phenylalanine are either too high (2.58) or too low (1.83) since the former is inconsistent with values reported for alanine and its derivatives[10] and the latter with values now available for additional derivatives of phenylalanine. A nuclear chlorine atom, irrespective of its position, was found to increase the acid strength of the ammonium group in phenylalanine by approximately 0.2 of a pK unit whereas a *p*-sulfamyl group caused an increase of approximately 0.5 of a pK unit. In contrast the above nuclear substituents had relatively little effect upon the acid strength of the carboxyl group.

An attempted independent determination of the acid ionization constant of the sulfamyl group in *p*-sulfamyl-DL-phenylalanine by a spectroscopic technique[11] was not successful and the assignment of the first, second, and third ionization constants found by titration, to the carboxyl, ammonium, and sulfamyl groups, respectively, was necessarily based upon comparison with representative values for other compounds containing these functional groups.[10]

The principal features of the ultraviolet absorption spectra of phenylalanine, the three isomeric nuclear substituted monochlorophenylalanines, and *p*-sulfamylphenylalanine are given in Table II. The spectrum of phenylalanine is in agreement with that reported by Smith[12] with the exception that the band in the 250-260 mμ region was found to have a fine structure not seen in Smith's curves. The replacement of any one of the nuclear hydrogen atoms by a chlorine atom, or of the *p*-hydrogen atom by a sulfamyl group, produced the expected[13] batho- and hyperchromic effects.

Experimental

***o*-Chloro-DL-phenylalanine (I).**[14]—Simultaneous reduction and hydrolysis[15] of 77 g. of 2-phenyl-4-(*o*-chlorobenzal)-5-oxazolone,[16,17] m. p. 159–161° (cor.) gave after successive recrystallizations from aqueous-ammonia and aqueous-methanol (90% methanol) 16 g. of I, long silky needles, m. p. 241–242°, dec. In contrast to phenylalanine and the other substituted phenylalanines described in this communication, I did not form well-defined crystals when recrystallized from water.

Anal. Calcd. for $C_9H_{10}O_2NCl$ (199): C, 54.3; H, 5.0; N, 7.0. Found: C, 54.6; H, 5.3; N, 6.8.

***m*-Chloro-DL-phenylalanine (II).**[18]—Reductive hydrolysis[15] of 109.5 g. of 2-phenyl-4-(*m*-chlorobenzal)-5-oxazolone,[18,19] m. p. 166–166.8° (cor.), gave after recrystallization from aqueous-ammonia 25.3 g. of II, colorless platelets, m. p. 239–241°, dec.

Anal. Calcd. for $C_9H_{10}O_2NCl$ (199): C, 54.3; H, 5.0; N, 7.0. Found: C, 54.3; H, 4.9; N, 7.1.

***p*-Chloro-DL-phenylalanine (III).**[20]—Proceeding as described above, 110 g. of 2-phenyl-4-(*p*-chlorobenzal)-5-oxazolone, m. p. 196–197° (cor.) gave 42.6 g. of III, colorless platelets, m. p. 258–259°, dec., after recrystallization from aqueous-ammonia.

Anal. Calcd. for $C_9H_{10}O_2NCl$ (199): C, 54.3; H, 5.0; N, 7.0. Found: C, 54.4; H, 5.4; N, 7.0.

***p*-Sulfamyl-DL-phenylalanine (IV).**—*p*-Formyl-benzenesulfonamide (V), m. p. 115–116° (cor.), was prepared by the oxidation of *p*-toluenesulfonamide with chloramine-

(1) Department of Chemistry, Ohio State University, Columbus, Ohio.

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T.[21-23] From 2 kg. of chloramine-T sufficient anilide was obtained to permit the isolation of 150 g. of twice recrystallized V. V gave a phenylhydrazone, yellow leaflets, m. p. 237–238° (cor.) after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{13}O_2N_3S$ (275): C, 56.8; H, 4.8; N, 15.3; S, 11.6. Found: C, 56.9; H, 4.8; N, 15.2; S, 11.6.

A mixture of 18.5 g. of V, 17.9 g. of hippuric acid, 16.5 g. of sodium acetate, and 100 ml. of acetic anhydride was heated on a steam-bath for three hours, the reaction mixture cooled, the precipitate collected and washed with acetic acid and ethanol to give 40 g. of crude 2-phenyl-4-(*p*-sulfamylbenzal)-5-oxazolone (VI). Thirty grams of crude VI was dissolved in 50 ml. of 5 *N* methanolic sodium hydroxide and 100 ml. of water, the solution heated to boiling, chilled and acidified with 5 *N* hydrochloric acid. The crystalline precipitate was collected, recrystallized from aqueous ethanol and dried to give 19.5 g. of crude α-benzamido-*p*-sulfamyl-cinnamic acid (VII), m. p. 194–195° (cor.) with preliminary sintering at 150°. The crude VII was recrystallized twice from hot water to give VII, sheaves of colorless needles, m. p. 197.5–198.5° (cor.) with preliminary sintering at 150°. VII was dried at 100° prior to analysis.

Anal. Calcd. for $C_{16}H_{14}O_5N_2S$ (346). C, 55.5; H, 4.1; N, 8.1. Found: C, 55.0; H, 4.0; N, 8.1.

A suspension of 150 g. of VII, m. p. 197.5–198.5°, in 600 ml. of ethanol was reduced at 30–40 lb. of hydrogen pressure over 20 g. of 5% palladized charcoal, VII dissolving as the hydrogenation proceeded. After removal of the catalyst the ethanol solution was evaporated to dryness, the residue dissolved in 10 liters of hot water, the solution decolorized and allowed to stand for several days at 5°. The gummy precipitate was collected and dried *in vacuo* to give 103 g. of crude N-benzoyl-*p*-sulfamyl-DL-phenylalanine (VIII). One hundred grams of crude VIII was refluxed for two hours with 2 liters of 2.5 *N* hydrochloric acid, the hydrolysate allowed to stand at 5° for several days, the precipitate collected, the filtrate extracted with ether, and the aqueous phase adjusted to *p*H 2.6 with silver carbonate. The precipitate obtained from the chilled hydrolyzate (above) was washed with ether and dried to give 43 g. of crude VIII which was again refluxed with 800 ml. of 2.5 *N* hydrochloric acid for two hours. The hydrolysate was treated as described above and the aqueous phase, adjusted to *p*H 2.6, was combined with the aqueous phase obtained from the first hydrolysate. This solution was concentrated *in vacuo* to 100–150 ml., the concentrate adjusted to *p*H 6 with acetic acid and ammonium hydroxide, and placed in a desiccator over sulfuric acid. After standing for several months the crystalline residue was dissolved in the minimum quantity of hot water, the solution decolorized, an equal volume of ethanol added to the colorless filtrate and the solution allowed to stand several days at 5°. The crystalline precipitate was collected, washed with ethanol and dried to give 16.5 g. of IV, glistening colorless platelets, m. p. 246–251°, dec.

Anal. Calcd. for $C_9H_{12}O_4N_2S$ (244): C, 44.3; H, 4.9; N, 11.5; S, 13.1. Found: C, 44.4; H, 5.2; N, 11.3; S, 13.3.

The α-amino acid nitrogen content[24] of IV was found to be 5.67% which is in good agreement with the calculated value of 5.74%.

The residue remaining after the second hydrolysis described above was alternately recrystallized from aqueous ethanol and water to give VIII, blunt prisms, m. p. 204–205° (cor.).

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Anal. Calcd. for $C_{16}H_{16}O_5N_2S$ (348): C, 55.2; H, 4.6; N, 8.0. Found: C, 55.1; H, 4.6; N, 7.8.

Miscellaneous Preparations.—Synthetic DL-phenylalanine (Winthrop) was recrystallized three times from water. Toluenesulfonamide (IX), m. p. 135.7–137.0° (cor.) was obtained by dissolving crude IX in 5% sodium hydroxide followed by precipitation with dilute hydrochloric acid and recrystallization from aqueous ethanol. Eastman Kodak Co. White Label benzenesulfonamide was used without further purification.

TABLE I

APPARENT IONIZATION CONSTANTS OF NUCLEAR SUBSTITUTED PHENYLALANINES

In 0.1 formal aqueous sodium chloride at approximately 25°

Compound (1)	pK'_{CO_2H} (2)	$pK'_{NH_3^+}$ (3)	$pK'_{SO_2NH_2}$ (4)
Phenylalanine	2.16	9.15	
o-Chlorophenylalanine	2.23	8.94	
m-Chlorophenylalanine	2.17	8.91	
p-Chlorophenylalanine	2.08	8.96	
p-Sulfamylphenylalanine	1.99	8.64	10.26

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF SEVERAL NUCLEAR SUBSTITUTED DL-PHENYLALANINES

Compound	λ (mμ)	ε
Phenylalanine (in water)	232 (min.)	36
	252 (max.)	148
	254 (min.)	142
	258 (max.)	179
	262 (min.)	133
	263 (max.)	137
o-Chlorophenylalanine (in 0.1 formal aqueous sodium chloride)	213 (max.)	8300
	238 (min.)	43
	263	199
	264	200
	266 (max.)	203
	272 (min.)	142
	273 (max.)	144
m-Chlorophenylalanine (in 0.1 formal aqueous sodium chloride)	213 (max.)	8900
	237 (min.)	47
	260	215
	262	220
	267 (max.)	266
	272 (min.)	173
	274 (max.)	201
p-Chlorophenylalanine (in 0.2 formal aqueous sodium chloride or water)	221 (max.)	11200
	240 (min.)	68
	260 (max.)	226
	262 (min.)	214
	267 (max.)	261
	273 (min.)	169
	275 (max.)	182
p-Sulfamylphenylalanine (in 0.1 formal phosphoric acid or solution 0.1 formal in hydrochloric acid and 0.03 formal in sodium chloride)	224 (max.)	13000
	247 (min.)	269
	262	556
	263	558
	267 (max.)	631
	271 (min.)	431
	274 (max.)	527

Potentiometric Determination of Apparent Ionization Constants.—Twenty-ml. aliquots of 0.01–0.02 formal amino acid in 0.05, 0.10 and 0.20 formal aqueous sodium chloride were titrated at 24.4 ± 2.1° with standard 0.2 normal hydrochloric acid or sodium hydroxide using a Beckman Model G *p*H meter equipped with No. 1170 and No. 1190E electrodes. The constants were evaluated analytically[25,26] recognizing over-lapping ionizations in the case of *p*-sulfamyl-DL-phenylalanine and correcting in every instance for the amount of acid or base added which did not react with the amino acid. As a check, several of the constants were also evaluated by the method of Speakman.[27] The reduced data summarized in Table I were obtained from thirty-three independent titrations which revealed no significant dependence of the ionization constants upon ionic strength over the range studied. The values given are believed to be accurate to within 0.05 of a pK unit.

Absorption Spectra.—All spectra were determined with a Beckman Model DU Quartz Spectrophotometer at a temperature of 25 ± 3° and at intervals of 2 mμ or less from the lower limit of the instrument to 280 mμ and then at 10 mμ intervals to 320 mμ.

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Spectrophotometric Titrations.—The procedure of Stenstrom and Goldsmith[11] was employed using solutions approximately 0.001 formal in sulfonamide and adjusted to the desired *p*H maintaining the total ionic strength at approximately 0.12. The values found for $pK'_{SO_2NH_2}$ for benzenesulfonamide were 9.96 ± 0.05 and for *p*-toluenesulfonamide 10.21 ± 0.05.

Summary

The apparent ionization constants and ultraviolet absorption spectra of DL-phenylalanine, *o*-, *m*- and *p*-chloro- and *p*-sulfamyl-DL-phenylalanine have been determined. These nuclear substituents have been found to increase the acid strength of the ammonium group by approximately 0.2 of a pK unit for the chloro-compounds and by 0.5 of a pK unit for the *p*-sulfamido-derivative. Since these substituents effect the acid strength of the carboxyl group to a lesser degree all of the above substituted DL-phenylalanines have apparent isoelectric points which are more acidic than that of the parent amino acid.

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The Viscosities of Binary Liquid Mixtures: Monofluorodichloromethane and Acetone

BY J. R. LACHER, C. H. WALDEN AND J. D. PARK

Viscosity determinations on a binary liquid mixture of a haloform and a solvent containing donor atoms have been carried out by various investigators[1] and it was recognized at once that it presented a case of marked non-ideality of liquid mixtures. However, all of the early investigators in this field failed to arrive at any satisfactory treatment of the experimental results. The activated complex theory proposed by Eyring[2] does present a method of drawing certain conclusions about the viscosity process which may be expressed as follows

$$\eta = \frac{Nh}{V} \exp. \left[\frac{N_1 \Delta F_1^{\pm} + N_2 \Delta F_2^{\pm} - \frac{\Delta F_m}{2.45}}{RT} \right] \quad (1)$$

This formula has been applied to the benzene–phenol binary mixtures.[3] Here V is the average molar volume and $\Delta F_1^{\pm}$ and $\Delta F_2^{\pm}$ are the free energy of activation for the pure components and ΔF_m is the excess free energy of mixing. There is not sufficient information available at this time to calculate ΔF_m for the mixture treated in this paper and hence the validity of this equation cannot be checked. However, the viscosity results on the monofluorodichloromethane–acetone mixture will be discussed qualitatively on the basis of this theory. The mixture chosen for investigation was of special interest, for the heat of mixing has been determined in this Laboratory[4] and the extreme electronegativity of the fluorine atom in monofluorodichloromethane should give results differing from the less electronegative bromoform and chloroform used by others.

Experimental Details.—A Fischer–Irany type viscometer was used in these determinations. It is a modification of the Ostwald type which allows the flow to take place in a closed system. It was housed in an insulated bath equipped with windows to allow one to view the flow of the liquid. The bath was ice water for the 0° determinations and dry ice–acetone for the −40 and −80° runs. It was stirred with an electric stirrer and the temperature was determined within 0.1° with a single junction copper–constantan thermocouple. The binary mixtures were weighed out and their densities determined all in one operation by employing a special pycnometer designed in this Laboratory. It is constructed of metal and capillary tubing and designed to withstand the high vapor pressures encountered in working with certain fluorine-containing compounds at room temperature. The results at −80° are given in Table I for rounded mole fractions. The acetone used was purified by the method of Shipsey and Werner[5] using sodium iodide. Monofluorodichloromethane

(1) O. Faust, *Z. physik. Chem.*, **79**, 97 (1912).

(2) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

(3) J. F. Kincaid, H. Eyring and A. E. Stearn, *Chem. Revs.*, **28**, 301 (1941).

(4) J. R. Lacher, J. J. McKinley and J. D. Park, THIS JOURNAL, **70**, 2598 (1948).

(5) K. Shipsey and E. A. Werner, *J. Chem. Soc.*, **103**, 1255 (1913).

was furnished us through the courtesy of Mr. R. J. Thompson of Kinetic Chemicals, Inc. It was distilled in a twenty-plate column and dried by passing repeatedly over phosphorus pentoxide.

TABLE I

DENSITY OF MONOFLUORODICHLOROMETHANE–ACETONE MIXTURE AT −80°

Mole fraction $CHCl_2F$	Density, g./ml.
0.0000	0.8996
.2500	1.0721
.5000	1.2450
.7500	1.4175
1.0000	1.5862

Discussion.—Three sets of determinations were carried out over a temperature range of 80°. They were 0, −40 and −80°. This constitutes almost the entire temperature range over which it is possible to make these measurements as the boiling point of monofluorodichloromethane is 9° (760 mm.) and the freezing point of acetone is −95°. The values of the viscosity in centipoises as a function of the mole fraction of monofluorodichloromethane at −80° are shown in Fig. 1. From

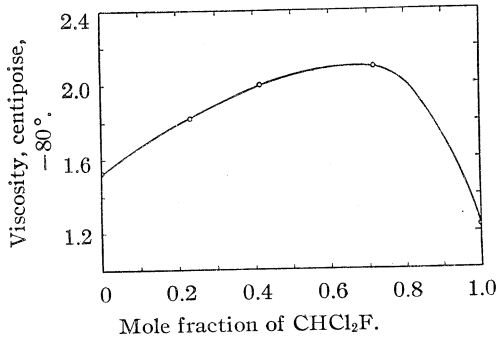

Fig. 1.

curves of this kind, the viscosities at rounded mole fractions were obtained for the three temperatures. The data are given in Table II, column two, three and four. A graph of the logarithm of the viscosity at constant composition against $1/T$ gave excellent straight lines for both the pure components and the various mixtures. This would seem to preclude any strong type of association such as that in water and other hydrogen bonded liquids as these do not give a linear relationship.[2] From the equation first suggested empirically by Arrhenius and derived by both Eyring and Andrade,[2] $\eta = A \exp[-E_{vis}/RT]$ the energy of activation for viscous flow, E_{vis}, may be calculated. The values so obtained are given in Table II, column five. Using the experimental values of the constant A, the entropy of activation for viscous flow, $\Delta S^{\pm}$, was calculated from the following equation also due to Eyring

$$A = \frac{hN}{V} \exp. \left[\frac{-\Delta S^{\pm}}{R}\right]$$

Here N is Avogadro's number, h is Planck's constant and V is the molar volume which is obtainable from the experimental density measurements. The equation assumes $p\Delta v$ is negligible in comparison with $\Delta H^{\pm}$. The entropies so calculated are also given in Table II. They are positive with monofluorodichloromethane having the smallest value. The free energy of activated flow, $\Delta F^{\pm}$, at 233°K. may be readily calculated and the results are given in Table II, column seven.

Figure 2 gives E_{vis}, $\Delta S^{\pm}$ and $\Delta F^{\pm}$ as a function of the mole fraction of monofluorodichloromethane. It is apparent that E_{vis} and $\Delta S^{\pm}$ vary with

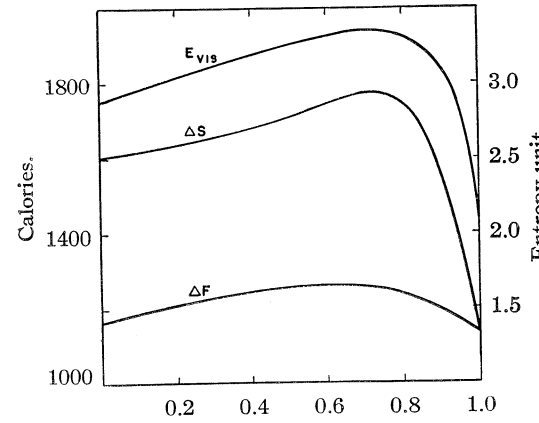

Fig. 2.

the composition in a similar way and have a maximum at about 0.75 mole fraction. The more positive $\Delta S^{\pm}$ is, the greater amount of randomness produced in going to the activated state. It takes less energy for a molecule of monofluorodichloromethane to reach the activated state necessary for viscous flow than it does for pure acetone and the various mixtures, but to reach this state the monofluorodichloromethane molecules undergo a smaller positive entropy change. The variations in E_{vis} and $\Delta S^{\pm}$ tend to counteract each other in $\Delta F^{\pm}$ with the result that the latter function is more nearly independent of the mole fraction.

TABLE II

Mole fraction $CHCl_2F$	Viscosity, centipoise −80°	−40°	0°	E_{vis}, cal.	$\Delta S^{\pm}$, e. u.	$\Delta F^{\pm}$, cal.	$\Delta E_{vap.}$, cal.	$\Delta E_{vap.}/E_{vis}$	ΔF_m, cal.
0.0000	1.526	0.713	0.398	1747	2.499	1165	6577	3.75	...
.2500	1.848	.791	.453	1834	2.659	1214	6568	3.58	−113
.5000	2.042	.869	.487	1889	2.701	1259	6357	3.36	−231
.7500	2.064	.854	.473	1938	2.945	1252	5921	3.05	−242
1.0000	1.232	.664	.412	1441	1.323	1133	5260	3.65	...

Eyring has found that the ratio of the energy of vaporization to the energy of activation for flow, $\Delta E_{vap}/E_{vis}$, gives interesting information.[2] Spherical molecules require a hole one-third the size of the molecule for flow and consequently $\Delta E_{vap}/E_{vis}$ has a value of about three. Polar and elongated molecules have values of this ratio nearer four. In these cases several orientations for viscous flow are possible and the molecules tend to acquire those requiring the least E_{vis}. In making the calculations of the energy of vaporization that of acetone was taken to be 6557 cal./mole[6] and that of monofluorodichloromethane as 5260 cal./mole.[7] The energy of vaporization of the mixtures was calculated from the following equation using heat of mixing data[4]

$$\Delta E_{vap} = N_1 \Delta E_1 + N_2 \Delta E_2 + \Delta H_{mix}$$

The results of these calculations are given in Table II, column eight, together with the ratio, $\Delta E_{vap}/E_{vis}$ in column nine. The ratio is 3.75 for acetone which compares with 3.86 given by Ewell and Eyring[8] for apparently a higher temperature range.

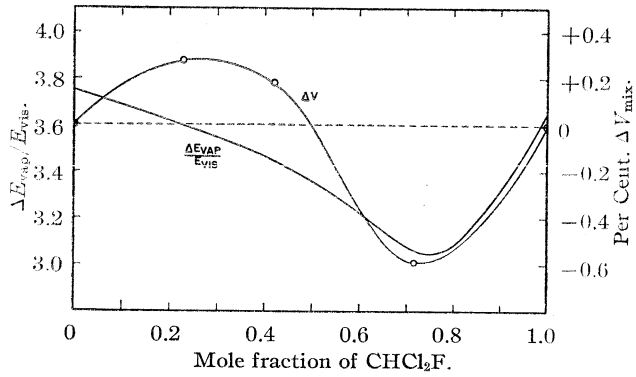

Fig. 3.

The value of 3.65 for monofluorodichloromethane is slightly lower than the value of 3.76 given for chloroform.[8] As is shown in Fig. 3, $\Delta E_{vap}/E_{vis}$ has a minimum value at a mole fraction of about 0.75. The per cent. change in volume which results when one mole of solution is produced from the pure components is also given in Fig. 3. The curve was calculated from density measurements made at −80°. A similar type of curve was noted by Hubbard[9] for chloroform–acetone mixtures. Except for a small initial rise, the volume changes are of the same general form as that given by $\Delta E_{vap}/E_{vis}$. In order to account for the curves in Figs. 2 and 3 we will assume, with Trew,[10] that acetone is a partially associated liquid and that a weak complex forms between acetone and monofluorodichloromethane. Whether this complex forms in a 1:1 ratio is not known. However, Wyatt[11] found from freezing point curves that such was the case with the analogous mixture of chloroform–acetone. When monofluorodichloromethane is added to pure acetone, the association between the acetone molecules decreases and that between the acetone and monofluorodichloromethane increases. The two effects do not balance exactly and E_{vis} and S increase slightly even though there is a slight volume increase on mixing the two pure components. At a mole fraction of 0.75 the volume change has its maximum negative value and for solutions richer in monofluorodichloromethane, E_{vis} and S fall off rapidly. Apparently the monofluorodichloromethane molecules pack in tightly with the acetone–monofluorodichloromethane complexes at this mole fraction. A maximum of activation energy is required to produce viscous flow which, when it takes place, ruptures the closely packed liquid structure and the entropy of activation is also a maximum. The fact that the viscosity is strongly dependent upon the free volume has been previously pointed out by Eyring,[2] Kottler[12] and Batschinski.[13]

Although it is not possible to test the validity of Equation I directly for this mixture, it is possible to determine what value of F_m is required to satisfy the equation when the experimental values of viscosity and free energy of activation for viscous flow are used. The values so obtained are included in Table II, column ten.

Summary

The viscosities of binary liquid mixtures of monofluorodichloromethane and acetone have been measured for several mole fractions and over a temperature range of −80 to 0°. The results are discussed in terms of the activated complex theory of Eyring for viscous flow.

BOULDER, COLORADO RECEIVED FEBRUARY 26, 1949

(6) J. E. Mills, THIS JOURNAL, **31**, 1099 (1909).
(7) Circular no. 2, Am. Soc. Refrigeration Eng., 1926.
(8) R. Ewell and H. Eyring, *J. Chem. Phys.*, **5**, 727 (1937).
(9) J. C. Hubbard, *Z. physik. Chem.*, **74**, 207 (1910).
(10) V. Trew, *Trans. Faraday Soc.*, **28**, 509 (1932).
(11) W. F. Wyatt, *ibid.*, **24**, 429 (1928).
(12) F. Kottler, *J. Phys. Chem.*, **48**, 76 (1944).
(13) A. J. Batschinski, *Z. physik. Chem.*, **84**, 643 (1913).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Dissociation Constants of Some Unsymmetrically Substituted Diphenylselenium Dibromides[1]

BY JAMES D. MCCULLOUGH AND MAX K. BARSH

In earlier communications measurements of the dissociation constants of diphenylselenium dibromide[2a] and some symmetrically disubstituted diphenylselenium dibromides[2b] have been reported. The equilibria involved are of the type

$$R_2SeBr_2 = R_2Se + Br_2$$

Spectrophotometric measurements on carbon tetrachloride solutions of the dibromides at measured temperatures near 25° enabled determination of the concentrations of the species involved. The dissociation constants, $K = (R_2Se)(Br_2)/(R_2SeBr_2)$ were then readily computed and ranged in value from 2.7×10^{-5} for the di-*p*-methoxydiphenylselenium dibromide to 1.1×10^{-2} for the di-*m*-chloro compound. When the values of log K for the symmetrically disubstituted dibromides were plotted against Hammett's[3] substituent constants, σ, a reasonably close approximation to a straight line resulted.

The study of unsymmetrically substituted diphenylselenium dibromides reported in the present communication was undertaken primarily to test a postulate of additivity of the σ value for a substituent on one ring to the σ value for a substituent on the other ring. Additivity of these values is to be expected if pronounced resonance effects are not produced by the combination of substituents. It is conceivable that in the symmetrically disubstituted compounds, the very symmetry of the molecules might either enhance or suppress the effect of the substituents. The additivity postulate was tested by making a single plot of the log K values for all types of dibromides against the sums of the σ values involved.

A second objective of the investigation was a more accurate treatment of the effects of temperature on the equilibria through better control of the temperatures of the solutions at the time of measurement. This has permitted a better evaluation of ΔH and ΔS for the dissociations.

Experimental

Materials.—The selenides used in this investigation were synthesized by the methods of Campbell and McCullough.[4] The identity of these compounds is supported by the methods of synthesis (taken into consideration with the starting materials) and by the equivalent weights of the dihalides as determined by the method of McCullough, Campbell and Krilanovich.[5] Physical constants for the compounds prepared are given in Table I.

TABLE I

PHYSICAL CONSTANTS OF UNSYMMETRICALLY SUBSTITUTED DIPHENYLSELENIDES AND THEIR DIHALIDES

Substituents	Melting points, °C. (uncor.) Selenide	Dichloride	Dibromide	Equivalent weights, g. Dichloride Expt.	Dichloride Theor.	Dibromide Expt.	Dibromide Theor.
m-Cl	[a]	103–104	[a]	168.9	169.2		
p-Cl[b]	[a]		117–118.5			211	213.8
p-CH$_3$, *p'*-Cl	72–73		120			221.9	220.8
m-CH$_3$[b]	[a]	110–111.5	[a]	158.5	159.0		
p-CH$_3$	[a]		137–138			203.6	203.5
p-OCH$_3$	46.3	162–164	[a]	167.7	167.1		

[a] Crystalline solid could not be obtained. [b] New compounds.

Carbon tetrachloride and bromine were of reagent grade and were carefully dried and distilled before use.

Procedure.—The dissociation constants were determined spectrophotometrically using a Beckman Model DU Quartz Spectrophotometer. For those selenides which form stable crystalline dibromides, the method was essentially that described earlier.[1a] Where crystalline dibromides were not obtainable, the selenides (which in these cases were liquid) were purified through several recrystallizations of the dichlorides from carbon tetrachloride. The dichlorides were then reduced by refluxing their carbon tetrachloride solutions for several hours with C. P. zinc dust in excess. The solid phases were then removed by filtration through sintered glass and the carbon tetrachloride distilled off, finally using a pressure of 100 mm. at 40° for two days in order to remove the solvent as completely as possible with minimum decomposition of the selenides. The selenides thus purified are colorless oils. By ordinary reduced pressure distillation they are at best light orange in color, due to decomposition. Solutions of the selenides having known concentrations were made up by weighing the pure liquids. Dibromide solutions were prepared by addition of the required amount of a carbon tetrachloride solution of bromine from a microburet. From this point the procedure was the same as that used when the solid dibromide is obtainable.

Temperature Control.—The temperature of the solutions was held constant within 0.2° by means of a specially built chamber inserted between the main part of the spectrophotometer and the photo-tube compartment. The central segment of the chamber consisted of the absorption-cell compartment furnished with the instrument and was flanked on both sides by brass plates $^7/_{16}$" thick.

(1) Based primarily on research performed under Contract N6 onr-275 between the University of California at Los Angeles and the Office of Naval Research.

(2) (a) J. D. McCullough, THIS JOURNAL, **64**, 2672 (1942); (b) J. D. McCullough and B. A. Eckerson, *ibid.*, **67**, 707 (1945).

(3) L. P. Hammett, "Physical Organic Chemistry," Chapter VII, McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

(4) T. W. Campbell and J. D. McCullough, THIS JOURNAL, **67**, 1965 (1945).

(5) J. D. McCullough, T. W. Campbell and N. J. Krilanovich, *Anal. Chemistry*, **18**, 638 (1946).

TABLE II

EQUILIBRIUM DATA AND THERMODYNAMIC QUANTITIES (25°) FOR DISSOCIATION OF UNSYMMETRICAL DIPHENYLSELENIUM DIBROMIDES

Substituent	Temp., °C.	log K	log K (25°)	σ	ΔF, kcal./mole	ΔH, kcal./mole	ΔS, cal./mole/deg.
p-OCH_3	32.2	−3.91	−4.19	−0.268	5.74	14.4	29
	9.2	−4.76					
p-CH_3	29.5	−3.54	−3.68	− .170	5.15		
m-CH_3	31.5	−3.41	−3.64	− .069	4.98	11.3	21
	23.8	−3.68					
None	30.6	−3.29	−3.42	0	4.69	9.7	17
	9.0	−3.82					
p-CH_3, p'-Cl	30.8	−3.08	−3.26	.057	4.46		
p-Cl	30.8	−2.78	−2.96	.227	4.15	13.1	30
	9.8	−3.48					
m-Cl	32.0	−2.42	−2.64	.373	3.62		

These plates were drilled to fit the instrument and to provide paths for the light beam and for circulation of the thermostating fluid. The thermoregulator was carried in a well in one plate and a thermometer in the other. The thermostating fluid (water in the present case) was circulated from a thermostated bath placed nearby.

Results and Discussion

The temperatures at which the spectrophotometer measurements were made for each dibromide and the corresponding values for log K are given in columns two and three of Table II. For purposes of comparing the dissociation constants of the various compounds it was necessary to compute values for the constants at some fixed temperature, in this case 25°. In the work of McCullough and Eckerson[1b] this correction was made by use of an average value (8.6 kcal./mole) for ΔH for three different dibromides. An average value was used because the observed values showed no correlation with Hammett's sigma values. Actually there should be a linear relationship between ΔH and σ. This follows from the reasonable assumption that ΔS is constant for a given reaction series. With ΔS constant at some fixed temperature, the equation

$$\Delta H = \Delta F + T\Delta S \quad (1)$$

becomes

$$\Delta H = \Delta F + b \quad (2)$$

where b is a constant. Substituting for ΔF, we have

$$\Delta H = -RT \log K + b \quad (3)$$

But log K is a linear function of σ, thus

$$\log_{10} K = \rho\sigma + \log_{10} K^\circ \quad (4)$$

where $\log_{10} K^\circ$ is a constant.

Substituting in equation (3), changing to ordinary logarithms and combining constants leads to the equation

$$\Delta H = -2.30\, RT\rho\sigma + A \quad (5)$$

where A and ρ are constant for a given reaction series.

Attempts to correlate equation (5) with the experimentally determined ΔH values were disappointing. Although the seven experimental values (four from the present work and three from the work of McCullough and Eckerson) show a trend in the right direction, the points are so badly scattered that a significant line cannot be drawn through them. This scattering is considerably greater than can be attributed to experimental errors alone and indicates that ΔS is not constant for the reaction series.

Log K values for 25° were obtained from the values at higher and lower temperatures in those cases where determinations were made at two temperatures. In the three remaining cases, log K (25°) was obtained through use of an average ΔH value of 10.6 kcal. per mole obtained from the seven experimental ΔH values. Errors in log K

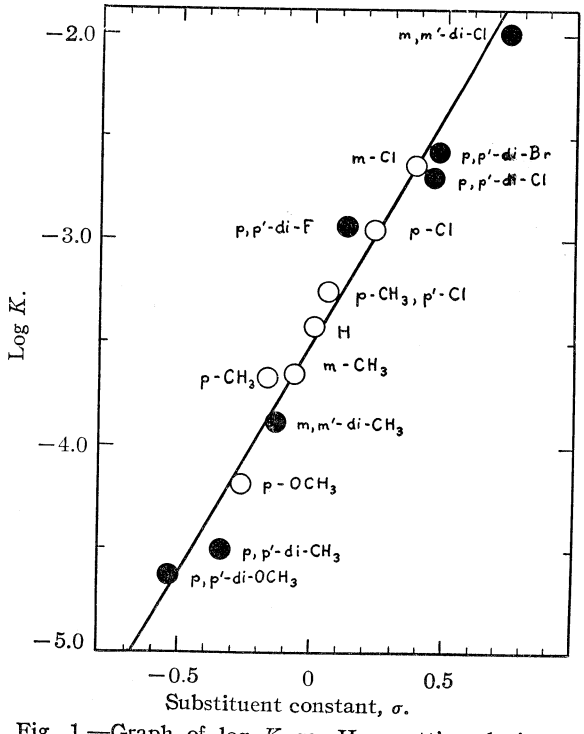

Fig. 1.—Graph of log K *vs.* Hammett's substituent constant for substituted diphenylselenium dibromides: O, present work; ●, McCullough and Eckerson.

caused by this approximate treatment are not large because of the shortness of the temperature intervals involved.

Log K, ΔF, ΔH and ΔS values for the dissociations are given in Table II. In Fig. 1, the log $K(25°)$ values are plotted against the substituent constant, σ. The data from the present work are indicated by open circles while the data of McCullough and Eckerson are indicated by full circles. The sigma values employed for the disubstituted diphenylselenium dibromides are the sums of the two individual sigma values concerned (twice Hammett's sigma values in the cases of the symmetrically disubstituted compounds). The straight line shown is the result of a least squares treatment of all of the data and has a slope, ρ, of 2.2. This indicates a rather high susceptibility of the selenium–bromine bond to changes in electron density on the selenium atom.

The fact that all of the log K values lie reasonably close to a single straight line is convincing evidence of the additivity of the effects of a substituent on the first ring to those of a substituent on the second ring in this type of system.

Summary

1. Dissociation constants for a number of unsymmetrically substituted diphenylselenium dibromides in carbon tetrachloride solution have been determined and the values (as log K) are given in Table II.

2. The values of log K (25°) from the present study have been plotted together with those from an earlier study of symmetrically disubstituted dibromides against Hammett's substituent constant, σ. The fact that all log K values lie reasonably close to a single straight line with slope, ρ, of 2.2 shows that the σ value for a substituent on one ring is additive to that for a second substituent on the other phenyl group.

3. The quantities ΔF, ΔH and ΔS at 25° have been evaluated for the dissociations and are listed in Table II.

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[CONTRIBUTION NO. 61 FROM THE INSTITUTE FOR ATOMIC RESEARCH AND THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Spectrophotometric Studies of Dilute Aqueous Periodate Solutions[1]

BY CARL E. CROUTHAMEL, HOMER V. MEEK, D. S. MARTIN AND CHARLES V. BANKS

The solubility behavior of various sparingly soluble periodates was found to be anomalous as interpreted through the equilibrium constants for the dilute aqueous periodate system as reported in the literature. Thus it was necessary to investigate these equilibria as a possible reason for the anomaly. Reinterpretation of this solubility behavior in light of the results of this investigation will be reported at a later date.

The ionization of periodic acid in aqueous solutions has been studied previously by various authors.[2,3] Giolitti[2a] and Partington and Bahl[3] found evidence of the dibasicity of periodic acid. Dubrisay[2b] found somewhat doubtful evidence of a third replaceable hydrogen. Rothmund and Drucker[4] reported the dissociation constant $K_1 = 2.3 \times 10^{-2}$ for paraperiodic acid, H_5IO_6. Rae[5] ran a conductometric titration of paraperiodic acid with sodium hydroxide and obtained two breaks. The first is in accord with the K_1 value reported by Rothmund and Drucker and from the second break he estimated that K_2 may be of the order of 10^{-6}. The literature generally concurs with the fact that paraperiodic acid, H_5IO_6, is the only solid periodic acid which is capable of existence in equilibrium with aqueous solutions of the acid. Hill[6] estimated a K_3 value of 4.6×10^{-11} using the previously reported values of K_1 and K_2 as a basis for his estimate.

In this study we have confirmed the previously reported value of $K_1 = 2.3 \times 10^{-2}$ and have assigned new values of $K_2 = 4.35 \times 10^{-9}$ and $K_3 = 1.05 \times 10^{-15}$. K_1 was confirmed from spectrophotometric studies, K_2 was estimated from spectrophotometric and potentiometric studies and K_3 was estimated using the method of Hill[6] and was confirmed by spectrophotometric data.

Aqueous solutions of periodate in the absence of interfering ions show an absorption maximum at 222.5 mμ in the ultraviolet region of the spectrum over a limited pH range. Since the start of this investigation MacDonald, Thompsett and Mead[7] reported an absorption maximum at 222 mμ and indicated that Beer's law was obeyed but neglected to mention the critical nature of pH. The full importance of pH is adequately described below.

Experimental

In the spectrophotometric studies a Beckman Quartz Spectrophotometer (Model DU) and a Cary Recording Spectrophotometer (Model 12) were employed. A Beckman Glass Electrode pH Meter (Model H-2) was used in carrying out the potentiometric titrations. Sources of periodate were paraperiodic acid manufactured by the

(1) This document is based on work performed in the Ames Laboratory, Atomic Energy Commission.

(2) (a) Giolitti, *Atti reale Accad. Lincei*, **14**, 217 (1905); (b) Dubrisay, *Compt. rend.*, **157**, 1150 (1913).

(3) Partington and Bahl, *J. Chem. Soc.*, 1088 (1934).

(4) Rothmund and Drucker, *Z. physik. Chem.*, **46**, 850 (1903).

(5) Rae, *J. Chem. Soc.*, 876 (1931).

(6) Hill, THIS JOURNAL, **65**, 1564 (1943).

(7) MacDonald, Thompsett and Mead, *Anal. Chem.*, **21**, 315 (1949).

G. Frederick Smith Chemical Company, Columbus, Ohio, and Baker and Adamson reagent grade potassium metaperiodate. The spectra obtained were found to be independent of the starting material in the absence of interfering substances. Ions which exhibited no interference were perchlorate, sodium and potassium. Ammonium ion exhibited no interference in concentrations attained by adjusting 10^{-4} M potassium metaperiodate up to pH of *ca.* 10.5 with filtered reagent grade ammonia solutions. Nitrate, sulfate and carbonate ions and carboxylate groups definitely interfere.

After originally establishing the nature of the absorption, solutions of both potassium metaperiodate and paraperiodic acid were scanned on the Cary instrument using 1.000 cm. silica cells at various pH values as adjusted with perchloric acid. Figure 1 shows the nature of the variation of the absorption spectra of solutions 1.01×10^{-4} M potassium metaperiodate at various pH values as adjusted by perchloric acid and using the Cary instrument. Figure 2 similarly shows the variation in the alkaline region of 1.05×10^{-4} M potassium metaperiodate at various pH values as adjusted by potassium hydroxide and unlike Fig. 1 these solutions are 10^{-2} M in sodium perchlorate.

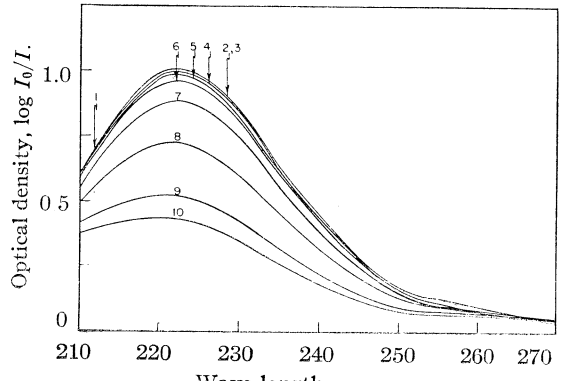

Fig. 1.—Absorption spectra of 1.01×10^{-4} M potassium periodate solutions at pH values: 1, 6.92; 2, 4.78; 3, 3.43; 4, 3.04; 5, 2.80; 6, 2.35; 7, 1.80; 8, 1.35; 9, 1.10.

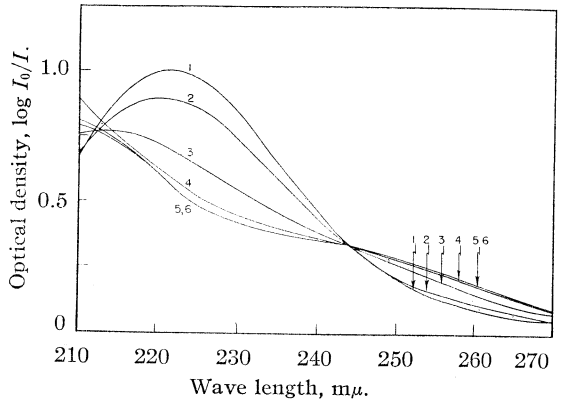

Fig. 2.—Absorption spectra of 1.05×10^{-4} M potassium periodate solutions at pH values: 1, 6.50; 2, 7.50; 3, 8.50; 4, 9.30; 5, 10.15; 6, 10.75.

Isobestic points are apparent at approximately 213 mμ and 244 mμ. Solutions of paraperiodic acid gave absorption curves identical within experimental error when similarly adjusted in pH. Figure 3 is a plot of the optical densities at 222.5 mμ for solutions 1.009×10^{-4} M in potassium metaperiodate at various pH values as adjusted with perchloric acid or sodium hydroxide. The Beckman instrument (0.998 cm. silica cells) was used up to pH 12 but at higher pH the Cary instrument was used because it appears to be better suited to the measurement of very high optical densities. High optical densities at pH values above 12.0 were due to the fact that sodium hydroxide solutions of very high pH even though they contain only relatively small amounts of carbonate nevertheless absorb considerably at 222.5 mμ. The experimental values plotted in Curve 1, Fig. 3, above pH 12.0 represent the difference between optical densities of the periodate solutions at the pH values indicated and distilled water of the same pH values as adjusted by the same sodium hydroxide solution. As indicated on Fig. 3 the series of experimental optical density values above pH 12.0 represent Cary instrument readings converted to equivalent Beckman instrument readings. This was necessitated by the fact that different molecular extinction coefficients, ϵ, were found for the $H_3IO_6^=$ ion on the two instruments. This is explainable by the fact that th molecular extinction coefficient for this ion was determined not at an absorption maximum but at a wave length where the optical density is changing rapidly with wave length. Therefore minor discrepancies in the wave length scales of the two instruments would be reflected quite sensitively in the molecular extinction coefficients obtained for this ion. In the case of the $H_4IO_6^-$ ion no such discrepancy would be expected because the molecular extinction coefficient for this ion was determined at an absorption maximum where optical density is rather insensitive to wave length. Experimental values are in agreement with this explanation. In curve 1, Fig. 3, the ionic strength, μ, varies only as a consequence of the addition of perchloric acid or sodium hydroxide required in adjusting pH. The solutions for Curve 2, Fig. 3, differ from those of curve 1 only in that the former are all 0.0625 M in sodium perchlorate. Differences between curves 1 and 2 are due only to differences in ionic strength and experimental error. Table I lists observed and calculated data corresponding to Fig. 3.

TABLE I

EXPERIMENTAL AND CALCULATED DATA CORRESPONDING TO FIG. 3

pH	$\sqrt{\mu}$	γ_1	γ_2	γ_3	ΣD_i Calcd.	ΣD_i Exptl.
1.0[a]	0.32	0.770	0.359	0.225	0.403	0.405
2.0	.10	.900	.665	.650	.792	0.810
3.0	.033	.970	.885	.900	.983	1.000
4.0	.014	.988	.947	.950	1.013	1.017
5.0	.011	.992	.965	.955	1.014	1.020
6.0	.012	.990	.956	.952	1.013	1.016
7.0	.012	.990	.956	.952	0.996	1.010
8.0	.017	.985	.932	.930	.881	0.875
9.0	.020	.982	.922	.930	.666	.645
10.0	.020	.982	.922	.930	.599	.590
11.0	.035	.968	.872	.880	.591	.585
12.0	.10	.900	.665	.650	.590	.584
13.0	.32	.770	.359	.225	.579	.577
14.0	1.23	.585	.267	.060	.403	.390
1.0[b]	0.40	.740	.307	.150	.408	...
2.0	.27	.795	.405	.300	.811	.840
3.0	.25	.805	.428	.350	.987	.987
4.0	.25	.805	.428	.350	1.013	1.004
5.0	.25	.805	.428	.350	1.013	1.007
6.0	.25	.805	.428	.350	1.012	1.005
7.0	.25	.805	.428	.350	0.986	0.957
8.0	.25	.805	.428	.350	.823	.737
9.0	.25	.805	.428	.350	.637	.603
10.0	.25	.805	.428	.350	.595	.572
11.0	.25	.805	.428	.350	.591	.572

[a] Curve 1. [b] Curve 2.

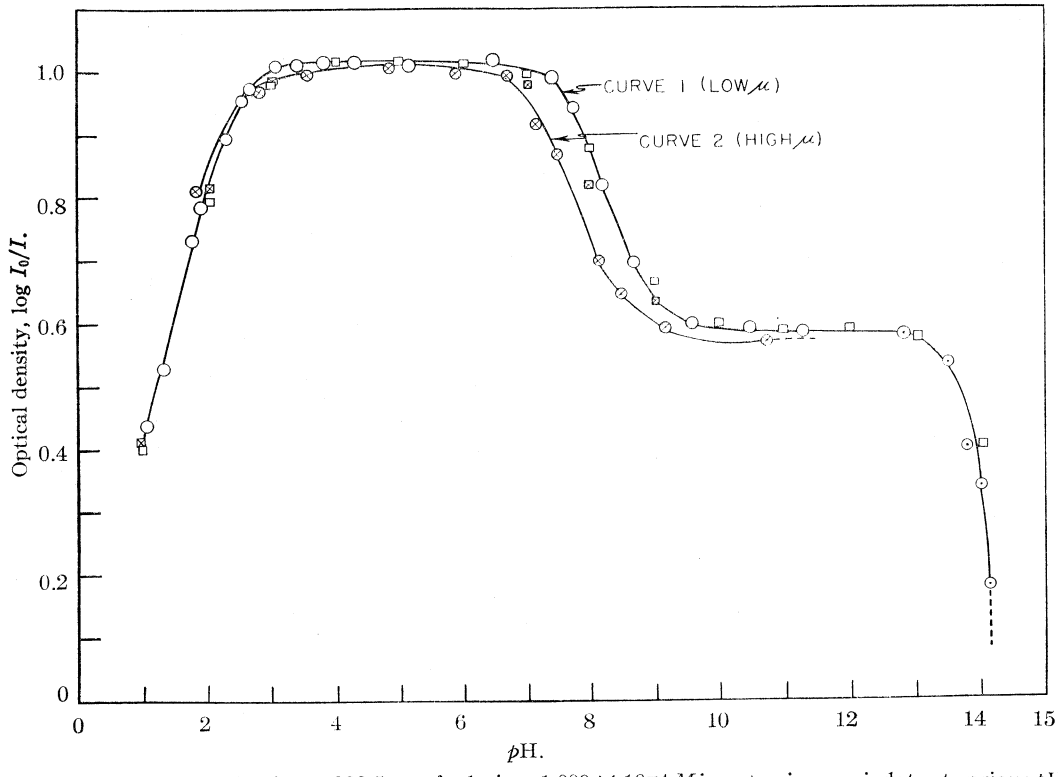

Fig. 3.—Variation of optical density at 222.5 mμ of solutions 1.009×10^{-4} M in potassium periodate at various pH values as adjusted with perchloric acid or sodium hydroxide using the Beckman instrument: curve 1, O, experimental (Beckman); ⊙, experimental, (Cary) converted to Beckman; □, calculated; curve 2, ⊗, experimental (Beckman); ⊠, calculated.

Figure 4 is a plot of the data obtained in the potentiometric titrations of two samples of paraperiodic acid with 0.2232 N potassium hydroxide using the Beckman pH Meter.

Discussion and Calculations

Aqueous solutions of periodate were found to follow Beer's law at given pH values from 1.0 to 10.5 at all wave lengths in the range where appreciable absorption occurs. The equilibria

$$H_5IO_6 \longleftrightarrow H_4IO_6^- + H^+, K_1 = \frac{a_{H^+}a_{H_4IO_6^-}}{a_{H_5IO_6}} \quad \text{Eq. 1}$$

$$H_4IO_6^- \longleftrightarrow H_3IO_6^{=} + H^+, K_2 = \frac{a_{H^+}a_{H_3IO_6^{=}}}{a_{H_4IO_6^-}} \quad \text{Eq. 2}$$

$$H_3IO_6^{=} \longleftrightarrow H_2IO_6^{\equiv} + H^+, K_3 = \frac{a_{H^+}a_{H_2IO_6^{\equiv}}}{a_{H_3IO_6^{=}}} \quad \text{Eq. 3}$$

predict that the ratios of the activities of the various species remain constant at constant pH. Yet deviation from Beer's law might be caused by the variation of the activity coefficients in the solutions studied. In these solutions, however, either the ionic strength was so low that all activity coefficients were nearly 1.0 or the ionic strength was maintained constant by the addition of an electrolyte. In this work the pH value indicated by the glass electrode instrument, calibrated by means of three standard buffers of pH 4, 7 and 10, is taken as $-\log a_{H^+}$. For values less than 1.0 or greater than 12.0 the pH was calculated from the molar concentration of H^+ or OH^- and estimated values of activity coefficients.

However, an equilibrium such as

$$2H_3IO_6^{=} \longleftrightarrow I_2O_9^{==} + 3H_2O, K_4 = \frac{a_{I_2O_9^{==}}a^3_{H_2O}}{a^2_{H_3IO_6^{=}}} \quad \text{Eq. 4}$$

does predict a departure from Beer's law at any pH value at which this equilibrium is of importance, because the activities of the $I_2O_9^{==}$ and $H_3IO_6^{=}$ ions are raised to different powers in the expression for K_4. Therefore this equilibrium is of no importance up to a pH of 10.5 and is probably never appreciably involved in dilute aqueous solutions of periodates. The formulation $K_4I_2O_9 \cdot 9H_2O$ frequently encountered in the literature[8] is probably better represented as $K_2H_3IO_6 \cdot 3H_2O$. Reactions of simple hydration or dehydration of the various periodate species involved in Equations 1, 2 and 3 predict no departure from Beer's law and are not considered in this work. Treatment of the data obtained using only K_1, K_2 and K_3 accounts completely for the variation of the optical densities of the solutions with pH.

A molecular extinction coefficient was estimated for H_5IO_6 using a solution of known periodate concentration and 1.14 M in perchloric acid. Molecular extinction coefficients for $H_4IO_6^-$ and

(8) Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938, p. 59.

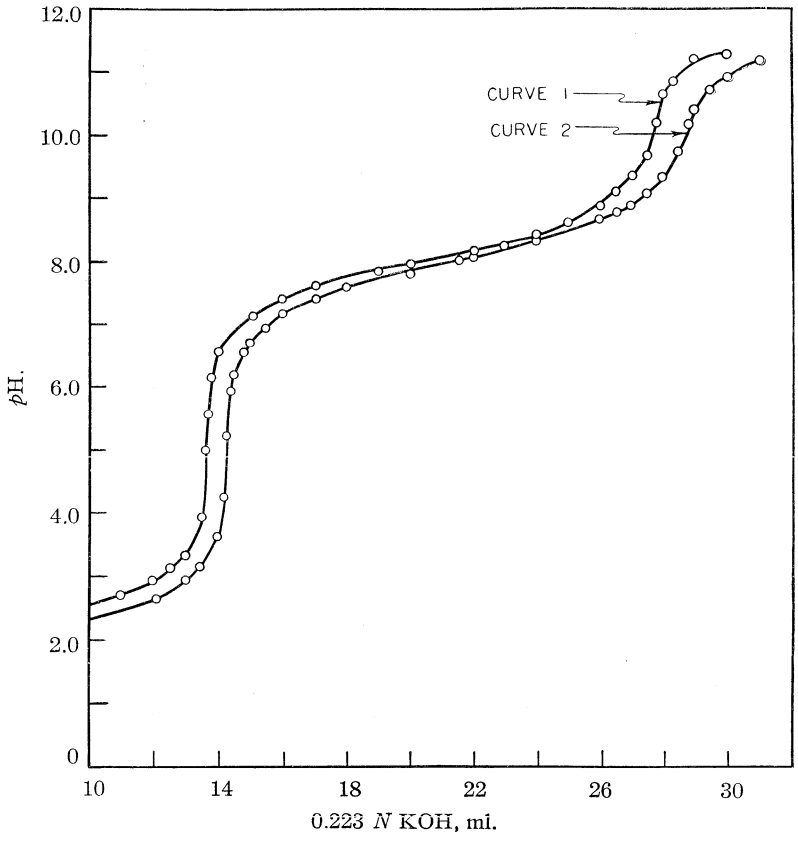

Fig. 4.—Potentiometric titration curves of paraperiodic acid.

$H_3IO_6^=$ were estimated from the wide plateaus obtained in dilute acid and dilute alkaline solution respectively in the plot of optical densities *vs.* *p*H for known concentrations of periodate. Table II lists the molecular extinction coefficients estimated for the various species of periodate using both the Cary and Beckman instruments.

TABLE II

MOLECULAR EXTINCTION COEFFICIENTS AT 222.5 mμ OF THE VARIOUS PERIODATE SPECIES IN DILUTE AQUEOUS SOLUTION

Instrument	$\epsilon_0 \times 10^{-3}$	$\epsilon_1 \times 10^{-3}$	$\epsilon_2 \times 10^{-3}$	$\epsilon_3 \times 10^{-3}$
Beckman	2.18	10.08	5.24	0.00
Cary	2.18	9.97	5.86	0.00

Good agreement was obtained except in the case of $H_3IO_6^=$ and the probable reason for this has already been cited (see Experimental). This is not unexpected since Ewing and Parsons[9] have shown relative discrepancies of half this magnitude among ten Beckman instruments themselves at constant band width.

By substituting $\gamma_0M_0, \gamma_1M_1, \gamma_2M_2$ and γ_3M_3 for the activities of H_5IO_6, $H_4IO_6^-$, $H_3IO_6^=$ and $H_2IO_6^{\equiv}$, respectively, in equations 1, 2 and 3 and solving these equations for the molar concentrations of the various periodate species the following equation may be written for the total periodate concentration, assuming that $\gamma_0 = 1$

$$M_{\text{total}} = M_0 + \frac{K_1M_0}{\gamma_1 a_{H^+}} + \frac{K_1K_2M_0}{\gamma_2 a^2_{H^+}} + \frac{K_1K_2K_3M_0}{\gamma_3 a^3_{H^+}} \quad \text{Eq. 5}$$

The activity coefficients as functions of the ionic strength were estimated in the following manner for all points except for *p*H 14. For γ_1, values of $\gamma_{\pm}$ for aqueous potassium chloride solutions[10] were used. Values for γ_2 were calculated from values of $\gamma_{C_2O_4^=}/\gamma_{Cl^-} \times \gamma_{HC_2O_4^-}$ indicated in the potentiometric evaluation of the second ionization constant of oxalic acid[11] together with the values of γ_1. The activity coefficient, γ_3, was calculated in the conventional manner from values of $\gamma_{\pm}$ reported for various rare earth chlorides.[12] For *p*H of 14, γ_1 was taken from values of $\gamma_{\pm}$ for sodium hydroxide and γ_2 was calculated from values of $\gamma_{\pm}$ for alkaline earth halides tabulated by Harned and Owen.[13] The values of K_1, K_2 and K_3 are quite easily estimated from equation 5 and the following relation for the optical density

$$D = l\left[\epsilon_0M_0 + \frac{\epsilon_1K_1M_0}{\gamma_1 a_{H^+}} + \frac{\epsilon_2K_1K_2M_0}{\gamma_2 a^2_{H^+}} + \frac{\epsilon_3K_1K_2K_3M_0}{\gamma_3 a^3_{H^+}}\right] \quad \text{Eq. 6}$$

since a_{H^+} is known from *p*H measurements, M_{total} is known from chemical analysis, l is the cell thickness in cm. and ϵ_3 is very nearly zero. In this way the values for K_1, K_2 and K_3 which gave the best agreement between experimental and calculated optical density values at low ionic strength were found to be

$$K_1 = 2.30 \times 10^{-2}$$
$$K_2 = 4.35 \times 10^{-9}$$
$$K_3 = 1.05 \times 10^{-15}$$

The value of K_1 thus determined agrees exactly with previously reported values.[4,5] The value of K_2, a new constant, was substantiated from the potentiometric titration data shown in Fig. 4 in the following manner.

From equation 2 it follows that

$$K_2 = a_{H^+} \text{ when } \frac{a_{H_3IO_6^=}}{a_{H_4IO_6^-}} = \frac{\gamma_2M_2}{\gamma_1M_1} = 1 \quad \text{Eq. 7}$$

(9) Ewing and Parsons, *Anal. Chem.*, **20**, 423 (1948).

(10) Shedlovsky and MacInnes, THIS JOURNAL, **59**, 503 (1937).

(11) Pinching and Bates, *J. Research Natl. Bur. Standards*, **40**, 405 (1948).

(12) Robinson, THIS JOURNAL, **59**, 84 (1937); *Trans. Faraday Soc.*, **35**, 1229 (1939).

(13) Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943, p. 567.

Knowing the total quantity of periodate, the volume of solution, how the assumed values for γ_1 and γ_2 vary with ionic strength, and how the ratio of M_2: M_1 varies with ml. of base added, the condition where Eq. 7 is satisfied was evaluated by a series of successive approximations. This condition was found to occur where $\sqrt{\mu}$ was *ca.* 0.25 and

$$\frac{M_2}{M_1} = \frac{\gamma_1}{\gamma_2} = \frac{0.805}{0.428} = 1.88$$

This molar ratio corresponds to *p*H values of 8.24 and 8.26 on curves 1 and 2, respectively, in Fig. 4. This gives a value of $K_2 = 5.6 \times 10^{-9}$ which, in view of the uncertainties involved in γ_1 and γ_2, is in good agreement with the value of $K_2 = 4.35 \times 10^{-9}$ obtained from the spectrophotometric studies.

The value of K_3, also a new constant, agrees, within experimental error, with the value of K_3 obtained from K_1 and K_2 using the method of Hill.[6]

Activity Coefficients.—The magnitudes of the differences between Curves 1 and 2 in Fig. 3 are much greater than predicted differences due to such changes in ionic strength, using normal γ_1 and γ_2 values. This suggests an abnormal decrease of the actual activity coefficients of the $H_4IO_6^-$ and $H_3IO_6^=$ ions, particularly the latter, with increasing ionic strength. For this reason values of K_1 and K_2 were calculated from the data for low ionic strength where errors due to such abnormalities would be very small. Estimates of the actual γ_1 and γ_2 values at the ionic strengths indicated may be made from the magnitudes of the differences between the two curves.

Analytical Significance.—From these studies it is quite obvious that for the analytical determination of periodate (in the absence of interfering substances) spectrophotometrically, *p*H is a very important factor. Inspection of the plot of optical density at 222.5 mμ *versus* *p*H shows clearly that a *p*H of *ca.* 5.0 is the optimum *p*H to use in acid solutions for this determination. For solutions of low ionic strength *p*H values of 5.0 ± 1.5 are quite satisfactory, the optical density not varying appreciably in this region. Concentrations as low as 10^{-7} molar in periodate should be detectable using 5.00-cm. silica cells. In the event that it is desirable to determine periodate spectrophotometrically in alkaline solutions, *p*H values between *ca.* 10.5 and 12.5 are desirable. Such analysis leads to a sacrifice in sensitivity of the method at 222.5 mμ because of the lower molecular extinction coefficient of the $H_3IO_6^=$ ion as compared to that of the $H_4IO_6^-$ ion used in the lower *p*H range. This disadvantage may be eliminated by simply carrying out the analysis at a somewhat lower wave length, *i. e.*, at a wave length nearer to or at which the $H_3IO_6^=$ ion shows an absorption maximum.

Summary

It was shown that most probably any equilibria involving the formation of the dimesoperiodate ion, $I_2O_9^{==}$, is of no importance in dilute aqueous solutions. Three simple equilibria involving stepwise dissociation of paraperiodic acid, H_5IO_6, account completely for the variation of the ultraviolet absorption spectra of dilute aqueous solutions of periodate with *p*H. K_1[4,5] was substantiated and new estimates of K_2 and K_3 were made from spectrophotometric studies. K_2 was substantially confirmed by potentiometric studies and K_3 was confirmed by the method of Hill.[6] Evidence was shown for abnormal activity coefficients of $H_4IO_6^-$ and $H_3IO_6^=$ ions with increasing ionic strength. Recommendations were made for the spectrophotometric determination of periodate in slightly acid and alkaline solutions.

AMES, IOWA RECEIVED APRIL 4, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORQUIMA S. A., SÃO PAULO, BRAZIL]

The Acid Properties of Iron Tetracarbonyl Hydride

BY P. KRUMHOLZ AND H. M. A. STETTINER

It has been shown previously[1] that the reaction between iron pentacarbonyl and alkalies does not produce, as assumed by Hieber,[2] the free iron tetracarbonyl hydride but its monobasic salts. The acid behavior of iron carbonyl hydride could be confirmed later by preparing salts with complex amine cations.[3] Some of them, as shown by Hieber,[4] behave in solution as strong electrolytes. Meanwhile Hieber[4] stated that structures as $[Fe(CO)_4H]^-$ are not stable and only can be stabilized by the formation of salts with complex cations, that the alkaline solutions of the hydride contain aquo salts rather than normal salts not yet prepared,[5] and that the formation of metal derivatives of $Fe(CO)_4H_2$ is by far not as general as it is supposed to be in an ordinary formation of salts.

In order to destroy any doubts regarding the behavior of iron carbonyl hydride as an ordinary acid we tried to determine its dissociation constant[6] by potentiometric titration of its salts with

(1) F. Feigl and P. Krumholz, *Monatsh.*, **59**, 314 (1932).
(2) W. Hieber and F. Leutert, *Z. anorg. Chem.*, **204**, 145 (1932).
(3) F. Feigl and P. Krumholz, *ibid.*, **215**, 242 (1933).
(4) W. Hieber and E. Fack, *ibid.*, **236**, 83 (1938).

(5) The monosodium salts prepared by F. Feigl and P. Krumholz, ref. 1, as alcoholates could not be freed completely from alcohol.

(6) A. A. Blanchard, *Chem. Rev.*, **21**, 3 (1937), assumed that the dissociation constant of cobalt tetracarbonyl hydride should be about 10^{-5}.

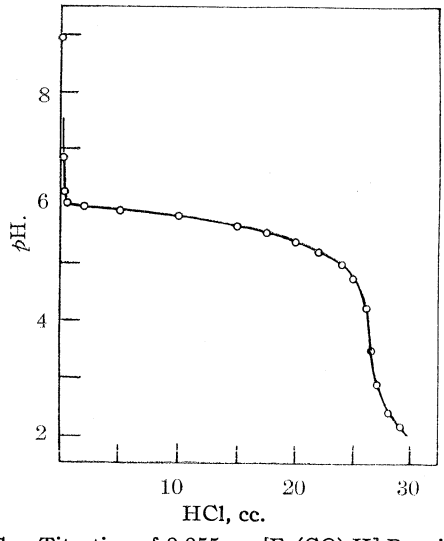

Fig. 1.—Titration of 0.055 m. $[Fe(CO)_4H]_2Ba$ with 0.57 *N* HCl; initial volume 135 cc., $T = 17.5°$.

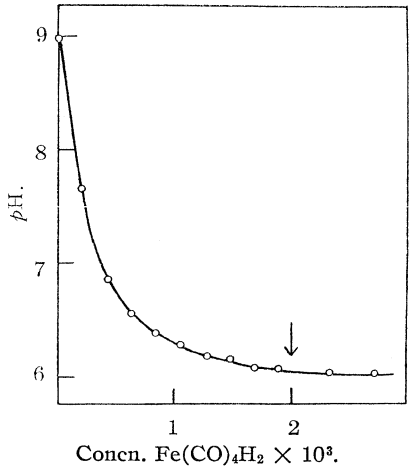

Fig. 2.—Titration of 0.055 m. $[Fe(CO)_4H]_2Ba$ with 0.57 *N* HCl.

HCl. Figs. 1 and 2 show the change of *p*H during the titration of a solution of the barium salt $[Fe(CO)_4H]_2Ba$ obtained by allowing barium hydroxide to react upon an excess of iron pentacarbonyl[1] according to

$$2Fe(CO)_5 + 3Ba(OH)_2 = [Fe(CO)_4H]_2Ba + 2BaCO_3 + 2H_2O \quad (1)$$

Those diagrams represent typical titration curves of salts of a weak acid of low solubility, since, immediately after starting the titration, the initially steep slope of the titration curve turns suddenly flat. At this point the initially clear solution becomes turbid due to the separation of free iron carbonyl hydride (the point where the first visible turbidity appears is indicated by an arrow in Fig. 2). From this part of the titration curve the molar solubility of $Fe(CO)_4H_2$ (at 17.5°) may be calculated as about 1.8×10^{-3}. The *p*H at the endpoint of the titration is 3.60; it corresponds to a thermodynamic dissociation constant[7] of $\approx 3.4 \times 10^{-5}$ (at 17.5°). Computing the dissociation constant from *p*H values at different concentrations of $[Fe(CO)_4H]^-$, and assuming that the concentration of undissociated $Fe(CO)_4H_2$ remains constant, we obtained as mean value $K_1 = 4.15 \times 10^{-5}$ (Table I).

TABLE I

$C_{Fe(CO)_4KH}$	*p*H	$K_1 \times 10^5$
1×10^{-1}	6.00	4.17
7.5×10^{-2}	5.88	4.13
5.3×10^{-2}	5.71	4.31
4.3×10^{-2}	5.63	4.20
2.3×10^{-2}	5.36	4.14
8.4×10^{-3}	4.95	3.92

The titration curve shows furthermore that the reaction between barium hydroxide and excess $Fe(CO)_5$ proceeds to an extent of at least 99.8% according to (1).

Solutions of the mono potassium salt of iron carbonyl hydride prepared by allowing $Fe(CO)_5$ to react with potassium and barium hydroxide in quantities corresponding to the equation

$$Fe(CO)_5 + KOH + Ba(OH)_2 = Fe(CO)_4KH + BaCO_3 + H_2O \quad (2)$$

behave in a similar way.

As iron carbonyl hydride also forms bibasic salts with some heavy metals,[3,8] and as Blanchard[9] recently assumed the formation of a bibasic potassium salt $Fe(CO)_4K_2$, we submitted solutions prepared according to

$$Fe(CO)_5 + 2KOH + Ba(OH)_2 = Fe(CO)_4K_2 + BaCO_3 + 2H_2O \quad (3)$$

to potentiometric titrations. As shown in Fig. 3 the *p*H values in the first moiety of the diagram are lower than the corresponding values of potassium hydroxide of equal concentration (represented by the dotted line in Fig. 3). This proves the formation of the dibasic salt, hydrolyzed to an extent of about 45% in 0.18 molar solution. We computed the second dissociation constant of iron carbonyl hydride from the hydrolytic equilibrium of the bibasic salt according to[10]

$$K_2 = K_{H_2O} \times \frac{C_{K_2X} - (OH^-)}{[C_{KHX} + (OH^-)](OH^-)} \times \frac{\gamma_{bi}}{(\gamma_{mono}^2)}$$

where C_{K_2X} and C_{KHX} represent the analytical concentrations of the bibasic and monobasic salt, $K_{H_2O} = 5.6 \times 10^{-15}$ (at 17.5°) and γ the activity coefficients of the ions.[11] We obtained

(7) Assuming the activity coefficient of $[Fe(CO)_4H]^-$ to 0.75 and γ_H to 0.80 at the ionic strength of 0.15.

(8) H. Hock and H. Stuhlmann, *Ber.*, **61**, 2097 (1928).

(9) A. A. Blanchard and G. W. Coleman, "Inorganic Syntheses," vol. 2, p. 243 (1946).

(10) *Cf.* I. M. Kolthoff and H. A. Laitinen, "*p*H and Electro Titrations," John Wiley and Sons, New York, N. Y., 1941.

(11) The initial ionic strength of the solution is 0.46, diminishing during the titration, mainly due to the disappearance of the bivalent ion $[Fe(CO)_4]^=$, reaching the value of 0.33 at the first equivalence point. We assumed (from known activities of salts of bibasic acids) at the beginning of the titration $\gamma_{mono} = 0.66$ and $\gamma_{bi} = 0.20$ and at the equivalence point $\gamma_{mono} = 0.70$ and $\gamma_{bi} = 0.24$.

the OH^- concentrations by comparing the measured potentials with those of potassium hydroxide solutions containing the same amount of K^+ (as KCl) as the solution of the iron carbonyl salt.[12]

The mean value (Table II) of the second dissociation constant of iron tetracarbonyl hydride at 17.5° thus obtained is $K_2 = 3.7 \times 10^{-14}$.

TABLE II

$C_{Fe(CO)_4K_2}$	$C_{Fe(CO)_4KH}$	(OH^-)	$K_2 \times 10^{14}$
1.8×10^{-1}	θ	7.8×10^{-2}	4.25
1.13×10^{-1}	6.15×10^{-2}	4.5×10^{-2}	3.7
8.2×10^{-2}	9.05×10^{-2}	3.0×10^{-2}	3.8
4.1×10^{-2}	1.27×10^{-1}	1.45×10^{-2}	3.45
1.6×10^{-2}	1.50×10^{-1}	5.5×10^{-3}	3.40

The pH of the second equivalence point is 3.56 corresponding to a value of $K_1 = 3.7 \times 10^{-5}$. The mean value of this constant computed from pH values between the first and the second equivalence point[13] (Table III) is $K_1 = 4.3 \times 10^{-5}$.

TABLE III

$C_{Fe(CO)_4KH}$	pH	$K_1 \times 10^{-5}$
1.47×10^{-1}	6.11	4.45
1.25×10^{-1}	6.04	4.42
9.8×10^{-2}	5.94	4.37
6.3×10^{-2}	5.78	4.06
1.7×10^{-2}	5.20	4.16

The experimental error of the indicated values amounts to ±10%. The assumed values of the activity coefficients, specially of the bivalent ion, may be wrong to an extent of about 10–20%. A further error may be due to differences in the liquid junction potentials, so that the obtained values of the dissociation constants may be uncertain within ± one unit.

For the dissociation constants of iron tetracarbonyl hydride at 17.5° we can assume the approximate values

$$K_1 = 4 \times 10^{-5} \text{ and } K_2 = 4 \times 10^{-14}$$

exact within about ± one unit.

Thus, iron carbonyl hydride as monobasic acid is stronger than acetic acid, while the relation between the two dissociation constants reaches the extremely high value of 1:10^9.

Furthermore, we tried to prepare the solid alkali salts from solutions obtained according to equations (2) and (3). These solutions, if prepared and kept under complete exclusion of oxygen, are only slightly brownish or pink and perfectly stable.

(12) The ionic strength of the potassium hydroxide solution is smaller (initially 0.36) than the ionic strength of the carbonyl solution. As the activity coefficients of OH^- vary less within those limits than the experimental error of the pH measurements, we assumed that equal potentials do not only correspond to equal values of the activities, but also to equal values of the concentrations of OH^-.

(13) Assuming $\gamma[Fe(CO)_4H]^- = 0.70$ at the ionic strength of about 0.30.

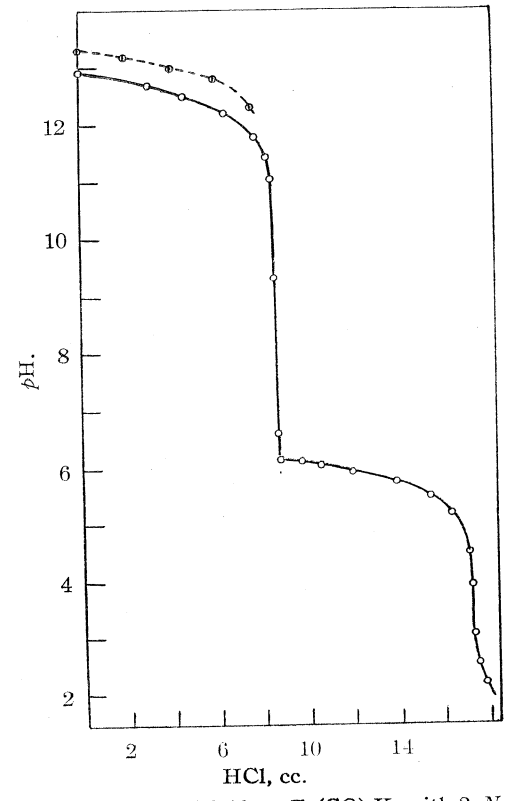

Fig. 3.—Titration of 0.18 m. $Fe(CO)_4K_2$ with 2 N HCl; initial volume 96 cc., T = 17.5°. Dotted line: titration of 0.18 N KOH + 0.18 N KCl with 2 N HCl.

On concentrating the solution of the bibasic salt at a low temperature, colorless crystals appear when the volume is reduced to a few cc. A slightly brownish mass remains when dried over phosphorus pentoxide at 0.5 mm; its analysis corresponds closely to the bibasic anhydrous salt $Fe(CO)_4K_2$. The salt is very soluble in water, producing a brownish solution due to an unavoidable small decomposition. Such a solution reacts with mercuric chloride according to

$$Fe(CO)_4K_2 + 2HgCl_2 = Fe(CO)_4Hg_2Cl_2 + 2KCl \quad (4)$$

yielding 98% of the theoretical amount of the mercuric salt.

These results allow no further doubts as to the existence of the anhydrous salt $Fe(CO)_4K_2$. They also exclude the possibility that the product obtained represents a mixture of $Fe(CO)_4KH$ and potassium hydroxide, specially as a potassium hydroxide solution retains about 2 molecules of water when dried under similar conditions over phosphorus pentoxide.

Treating solutions of the monobasic salt in an analogous way one obtains no separation of crystals, but the residue of the evaporation solidifies over phosphorus pentoxide to a brownish amorphous substance, with analytical data corresponding to the anhydrous salt $Fe(CO)_4KH$. This salt is extremely hygroscopic and, like the

bibasic salt, very sensitive to oxygen. Its brownish solution reacts with mercuric chloride according to

$$Fe(CO)_4KH + 2HgCl_2 = Fe(CO)_4Hg_2Cl_2 + HCl + KCl \quad (5)$$

yielding 97% of the theoretical amount of the mercuric salt, but only 92% of the theoretical amount of hydrogen chloride due to a loss of the very volatile $Fe(CO)_4H_2$ through hydrolysis of the monobasic salt and to a simultaneous formation of $Fe(CO)_4K_2$.

Since at least 97% of the substance consists of $Fe(CO)_4KH$ and $Fe(CO)_4K_2$, as shown by the reaction with mercuric chloride, it seems certain that $Fe(CO)_4KH$, too, exists as an anhydrous salt. It is possible, of course, that the ions $[Fe(CO)_4]^=$ and $[Fe(CO)_4H]^-$ are hydrated in aqueous solution. No further doubt may exist as to the rather peculiar fact that iron tetracarbonyl hydride behaves as an acid forming "normal" salts not only with amine cations but also with alkali metals.

The acidic behavior of iron carbonyl hydride—formation of hydrogen ions (or hydroxonium ions) in aqueous solution—is in contradiction to the easy decomposition of the hydride to molecular hydrogen explained by Hieber[2] with the formulation of $Fe(CO)_4H_2$ as a true hydride with direct iron-hydrogen bond. But this formulation explains hardly the acidic functions of $Fe(CO)_4H_2$. Furthermore, electron diffraction studies by Evans and Lister[14] seems to indicate that the hydrogen atoms are fixed on the oxygen atoms according to the formula $Fe(CO)_2(COH)_2$.

This formulation, especially in the electronic expression like $Fe^{=}:C:::{}^{++}O:H$ or $Fe^{-}::C::{}^{+}O:-H$, might explain the acid behavior of the hydride as the positively charged oxygen atoms must repel protons.[15]

But neither of both formulations is able to explain by itself the experimental facts, that iron carbonyl hydride may lose neutral hydrogen atoms as well as protons.

The structural problems in question will be discussed further in a later paper.

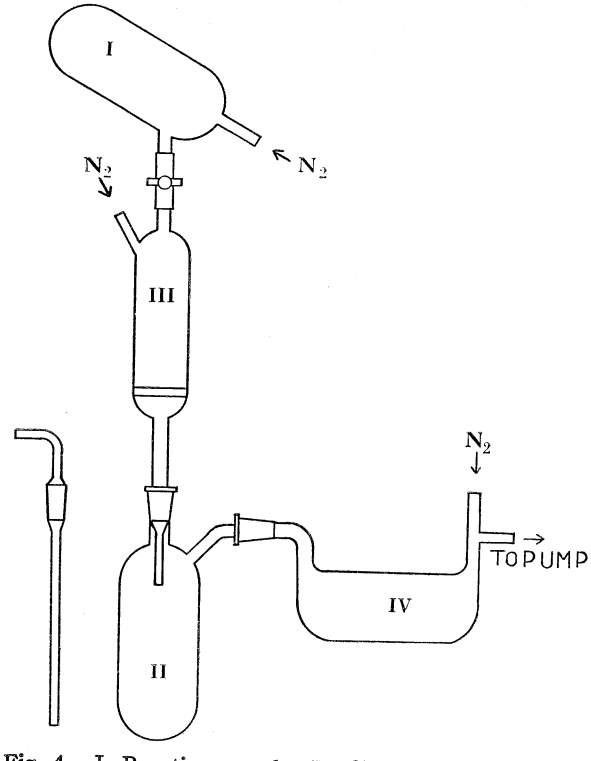

Fig. 4.—I, Reaction vessel; II, filter vessel; III, filter tube; IV, trap.

Experimental Part

Due to the enormous sensitivity of iron carbonyl-hydride and its salts to oxygen, all operations have to be performed under nitrogen absolutely free from oxygen, taking extreme care to exclude air during the manipulations.

We prepared the solutions for the potentiometric titrations in a modified Schlenck apparatus,[1] by shaking for three hours excess $Fe(CO)_5$ with a 0.33 N solution of barium hydroxide, or, according to equations (2) and (3) exact quantities of $Fe(CO)_5$ with solutions containing 0.18 mole of barium hydroxide and 0.18 or 0.36 mole of potassium hydroxide, respectively, in 1000 ml. and filtering the solution from the precipitated barium carbonate. The filtered solution was transferred to a titration vessel consisting of a 500-cc. erlenmeyer flask containing the glass and reference electrodes, buret, thermometer and inlet and outlet tubes for nitrogen. The titrations were performed with hydrochloric acid to 17.5 ± 0.2° after calibrating the glass electrodes with buffer solutions. It is known that glass electrodes show large alkali errors at pH above 10, even in potassium salt solutions. To eliminate these errors we calibrated the electrode in the strongly alkaline range with potassium hydroxide solutions containing the same amount of K^+ (as KCl) as the titrated solution. The reproducibility of the potentials during calibration and over the whole range of the titration —excepting perhaps the immediate proximity of the first equivalence point—was better than 1 mv. In order to obtain this accuracy in the strong alkaline range one has to wash the electrodes before every use for at least six hours in pure water, particularly after being used in acid solutions, and to wait about five minutes before taking the first reading. If oxygen is not entirely excluded, it is impossible to obtain constant readings near the first equivalent point, the liberated $Fe(CO)_4H_2$ being immediately destroyed by oxidation.

As already stated, soon after the first equivalence point, there appears free $Fe(CO)_4H_2$ at first in the form of a milky turbidity, separating later as a yellow oily layer that soon turns deeply red by decomposition. This decomposition however does not influence the titration. Apparently enough hydride always remains to give a saturated solution as shown by the constancy of the potentials, and the fact that calculated values of K_1 are constant within the limits of accuracy over the whole range of titration. Only at a temperature of over 25° does the decomposition become great enough in more acid solutions so that one is no longer able to determine the second equivalence point exactly.

Preparation of the Potassium Salts.—We prepared the solutions of the potassium salts by a procedure similar to that used for the potentiometric titration, using the apparatus shown in Fig. 4. The solution prepared in the

(14) R. V. G. Evans and M. W. Lister, *Trans. Faraday Soc.*, **35**, 681 (1939).

(15) See the similar formulation of carboxyl groups by L. Pauling, "The Nature of the Chemical Bond," 2nd ed., p. 202.

reaction vessel I was filtered through the filter tube into the previously weighed vessel 2 connected with an ice cooled trap. After having exchanged the filter tube for a gas inlet tube, the vessel was immersed in a water-bath at 20° and evaporated at about 5 mm. in a slow stream of nitrogen. After the evaporation the trap was exchanged for one filled with phosphorus pentoxide, and evacuated at less than 0.5 mm. to constant weight.

For analysis the content of the weighed vessel was dissolved in water and decomposed by slow addition of neutral 10% hydrogen peroxide, boiling finally until the iron tetracarbonyl formed had disappeared completely. To prevent loss by volatilization of iron carbonyl the vessel was connected with a wash bottle containing 0.2 *N* alcoholic potassium hydroxide and a small quantity of hydrogen peroxide. The solution filtered from the iron oxide contains the potassium as carbonate. The carbonate was determined by acidimetric titration. The iron was determined in the residue on the filter and in the contents of the washing bottle.

$Fe(CO)_4K_2$.—The solution was prepared from 1 ml. = 0.0074 mole $Fe(CO)_5$ and 40 ml. of a solution containing exactly 0.0074 mole of $Ba(OH)_2$ and 0.0148 mole of KOH. *Anal.* Calcd. for $Fe(CO)_4K_2$: Fe, 22.70; K, 31.78. Found: Fe, 22.89, 23.30, 22.73; K, 31.3, 31.45. 1.316 g. of the dry salt was dissolved in 50 ml. of water freed from air and poured under nitrogen into a saturated solution containing 5 g. of mercuric chloride. The mixture was shaken for thirty minutes to complete the reaction, then filtered, washed with water, dilute hydrochloric acid, alcohol and ether (to remove small quantities of iron tetracarbonyl) and dried *in vacuo*, giving 3.4484 g. of the yellow $Fe(CO)_4Hg_2Cl_2$. *Anal.* Calcd.: Fe, 8.72; CO, 17.51. Found: Fe, 8.65, 8.63; CO, 17.08, 16.98. Calculating the amount of pure mercuric salt from the found CO value the relation $Fe(CO)_4K_2$:$Fe(CO)_4Hg_2Cl_2$ is 1:0.98.

$Fe(CO)_4KH$.—Prepared from 1.5 cc. of $Fe(CO)_5$ (excess) and 40 cc. of a solution containing exactly 0.0074 mole of $Ba(OH)_2$ and 0.0074 mole of KOH. *Anal.* Calcd. for $Fe(CO)_4KH$: Fe, 26.85; K, 18.80. Found: Fe, 27.35, 26.87; K, 18.89.

The reaction of 0.845 g. of this salt with $HgCl_2$ yields 2.5716 g. of the mercuric salt. *Anal.* Found: Fe, 8.54; CO, 17.05. In the filtrate from the mercuric salt we determined the HCl by acidimetric titration. The relation $Fe(CO)_4KH$:$Fe(CO)_4Hg_2Cl_2$:HCl is 1:0.97:0.92 if the salt is calculated as pure $Fe(CO)_4KH$. As the salt contains about 5% $Fe(CO)_4K_2$ this relation is still about 1% nearer to the theoretical amount.

Summary

The dissociation constants of iron tetracarbonyl hydride at 17.5° have been determined to $K_1 = 4 \times 10^{-5}$ and $K_2 = 4 \times 10^{-14}$.

The molar solubility of iron carbonyl hydride at 17.5° is about 1.8×10^{-3}.

The anhydrous salts $Fe(CO)_4K_2$ and $Fe(CO)_4KH$ (the latter containing about 5% of $Fe(CO)_4K_2$) have been prepared.

RECEIVED OCTOBER 21, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Disperse Structure of Manganese Oxides and a Magnetic Method for Studying Depolarizer Action in the Leclanché Cell[1]

BY P. W. SELWOOD, R. P. EISCHENS,[2] MARYLINN ELLIS AND KATHRYN WETHINGTON

The object of this work was to explore the possibility of using magnetic methods for the study of chemical changes occurring *in situ* in the dry cell. Manganese is the only paramagnetic constituent in the cell, and the number of unpaired electrons increases as tetravalent manganese is reduced. Consequently it was considered possible to follow the valence changes of the manganese during cell discharge and recovery by observing changes of magnetic susceptibility.

Magnetically dilute tetravalent manganese has three unpaired electrons and a well established, spin-only, magnetic moment of about 3.9 Bohr magnetons. Similarly, manganese in the oxidation states of three and two has magnetic moments of 4.9 and 5.9, respectively. With adequate magnetic dilution the susceptibility at any one temperature is virtually linear with oxidation state.

Unfortunately, the crystalline transition group oxides are so magnetically concentrated that large interactions occur between adjacent paramagnetic ions. Thus, the susceptibility at 25° for crystalline *pyrolusite* is 27×10^{-6}, that for the crystalline sesquioxide (*bixbyite*) is 89×10^{-6}, but for the monoxide (*manganosite*) it is only 67×10^{-6}. Furthermore, all these substances show large and uncertain values for the Weiss constant, and, at lower temperatures, wide deviations from the Curie–Weiss law.

These effects eliminate the possibility of using crystalline *pyrolusite* as depolarizer in quantitative magnetic studies. Attention was, therefore, turned to supported oxides, which have been shown to approach high magnetic dilution at moderately low concentration.[3]

A series of studies on manganese oxides on various supports showed that the oxidation state of supported manganese was determined in part by the crystal structure of the support, and this observation led to the general principle of valence inductivity, as previously described.[4] It was established that the experiment on the dry cell could be carried out if the manganese depolarizer were supported on high-area titania, in the *rutile* modification.

At this point in the work it was discovered that many laboratory prepared samples of manganese

(1) This paper describes, in part, work performed under contract with the Squier Signal Laboratory, Signal Corps Engineering Laboratories, as part of their program for the improvement of dry cells.

(2) Present address: The Texas Company, Beacon Laboratories, Beacon, N. Y.

(3) Selwood, Hill and Boardman, THIS JOURNAL, **68**, 2055 (1946).

(4) Selwood, *ibid.*, **70**, 883 (1948).

dioxide and practically all natural and commercial samples of manganese dioxide had an astonishing magnetic difference from pure highly crystalline *pyrolusite*. These samples all have high magnetic susceptibilities and are properly considered as magnetically dilute substances. The effect must be related to the attenuated structure possessed by these oxides. The effect has been observed in various other inorganic solids, and appears to offer promise for the structural study of many so-called gels of transition group oxides.

This observation eliminated the necessity for work with supported oxides, fruitful though that study had been. Cells were made with the gel-like manganese dioxides as depolarizers and the magnetic study of such cells was rapidly completed. There are described below, first the magnetic observations on gel-like oxides as compared with highly crystalline samples; and second, the magnetic changes occurring during dry cell discharge. Those oxides of a highly crystalline, magnetically concentrated form we shall continue to designate as "massive" solids in accordance with the terminology used in our earlier papers on supported oxides. Those oxides of an attenuated gel-like structure, as shown by magnetic dilution effects, we shall designate as "disperse" solids.

Preparative Methods[5]

Analytical Methods.—Analyses were performed for total manganese and for active oxygen. Manganese was determined by reaction with standard ferrous sulfate after all of the manganese had been oxidized to permanganate. Solution of the sample was effected by treatment with dilute sulfuric acid containing ferrous sulfate. Oxidation of the manganese from a valence of two to seven was accomplished by sodium bismuthate in nitric acid.

Active oxygen was found by using a known excess of standard ferrous ammonium sulfate in dissolution of the sample. The excess was then titrated with standard permanganate. Active oxygen is then eight times the number of equivalents of ferrous ion oxidized in the dissolution process.

Pyrolusite.—Massive *pyrolusite* was prepared by thermal decomposition of manganous nitrate in accordance with well known procedures.[6] "Reagent grade" manganous nitrate was recrystallized from water and the crystals were heated to 120–125° until the whole mass appeared on the verge of solidifying. A stream of air was directed over the open evaporating dish to facilitate the removal of oxides of nitrogen and of water vapor. Water was added to the mass, and it was stirred and filtered. The solid was dried at 110° for twenty-four hours in air. It was ground to pass through a 150-mesh sieve and reheated at 150° in air for twenty-four hours. The crystals were next washed with 1:1 nitric acid and finally with water to remove the nitric acid. The acid and wash water should both be boiling for best results. Final drying was done at 160° in air for fifty-two hours. The product was dark gray in color.

Analysis gave the following: Calcd. for MnO_2: Mn, 63.19; active oxygen, 18.4. Found: Mn, 63.1; active oxygen, 18.3. The X-ray diffraction pattern agreed in detail with the ASTM index cards. The sample appeared to be as pure as any heretofore obtained.

γ(I) Manganese Dioxide.—The preparation so designated was based on the first of three methods given by Glemser.[7] To a solution of manganous sulfate (50 g. hydrate in a liter of water) there was added 100 ml. of 2 *N* sulfuric acid. The resulting mixture was heated to boiling and 113 g. of ammonium persulfate was added slowly. A black precipitate formed and the supernatant liquid was decanted. Washing was by decantation with temperature of wash liquid 70–80°. This was continued until tests showed that the precipitate was free of sulfate. The precipitate was now filtered and washed with hot water and dried for two days at 60°. Analysis gave Mn, 60.7; "active" oxygen, 16.8. Apparent formula $MnO_{1.95}\cdot 0.25H_2O$. The X-ray diffraction pattern for this preparation was in reasonably satisfactory agreement with that reported by Glemser, as shown.

d (Å.) Reported	Found	$I/I_{max.}$ Found
3.88	4.03	0.5
2.42	2.42	1.0
2.11	2.12	0.6
..	2.06	.3
1.80	1.83	.1
1.62	1.62	.9
1.42	1.40	.5
1.30	..	..

γ-II Manganese Dioxide.—The second of the three methods given by Glemser was used for a preparation designated by us as γ-(II)MnO_2. A solution of 36 g. of manganous sulfate hydrate and 24 g. of potassium nitrate in 2.5 l. of water was heated to boiling. Approximately 1 l. of 2% potassium permanganate solution was now added (until the solution acquired a pink color). The supernatant liquid was decanted and the solid was washed four times with 3-l. portions of water. The product was filtered through asbestos, and washed free of sulfate. The brown product was dried for two days at 60°. Analysis yielded a formula $MnO_{1.96}\cdot 0.81H_2O$. The X-ray diffraction pattern was very similar to that for the γ-(I) preparation, although quite diffuse.

(5) Magnetic and X-ray methods have been described in earlier papers from this Laboratory.

(6) A comparison of preparations and properties for the solid oxides and hydroxides of manganese will appear in a forthcoming paper by Moore, Selwood and Ellis.

(7) Glemser, *Ber.*, **72B**, 1879 (1939).

Gel(I) Manganese Dioxide.[8]—Preparation of a gel form of manganese dioxide was attempted by the hydrolysis of manganese(IV) sulfate. The sulfate was prepared by oxidizing a 55% sulfuric acid solution of manganous sulfate with potassium permanganate. The temperature was kept below 80° because the sulfate decomposes above that temperature in a 55% acid solution. The product was filtered and washed, and hydrolysis was carried out with sodium acetate. The resulting hydrous oxide was filtered, washed and dried at 70° for three days in air. It was very hard, black and shiny, and gave no X-ray pattern. Analysis showed the product to be $MnO_{1.88}\cdot 0.83H_2O$.

Gel II Manganese Dioxide.[7]—Dilute sulfuric acid (1:4) and a 50% solution of sodium permanganate were added slowly to a concentrated solution of manganous sulfate until no more oxide precipitated. The temperature of the solution was kept at about 60° during the reaction. The precipitate was washed by decantation, then filtered and washed free from permanganate and sulfate ion. The product was dried for three days at 60° under vacuum. The sample was brown and soft, and gave only a diffuse X-ray pattern. Analysis showed $MnO_{1.97}\cdot 0.33H_2O$.

Results on Oxides

Magnetic susceptibility data on the several gel-like hydrous oxides and on massive pyrolusite are shown in Table I. Results are shown also on two natural ores. The results on the natural materials are, however, less reliable because these materials always contain a trace of ferromagnetic impurity for which correction must be attempted.

TABLE I

MAGNETIC SUSCEPTIBILITIES OF MASSIVE AND DISPERSE OXIDES

(The data are given in the following order: sample, %Mn, susceptibility $\times 10^6$ at indicated temperature, and susceptibility per gram-atom of Mn at 25°)

Massive *pyrolusite*, 63.1% Mn; χ = 27 (25°), 31 (−80°), 44 (−185°); χ_M = 2360 (25°).

γ-(I), 60.7% Mn; χ = 34.8 (86°), 35.8 (61°), 37.7 (37°), 38.0 (25°), 42.6 (−26°), 46.2 (−56°), 49.0 (−87°); χ_M = 3440 (25°).

γ-(II), 55.0% Mn; χ = 45.0 (25°), 74.3 (−87°), 109 (−171°); χ_M = 4490 (25°).

Gel(I), 55.3% Mn; χ = 37.2 (25°), 46.3 (−87°), 58.2 (−171°); χ_M = 3690 (25°).

Gel II, 59.1% Mn; χ = 41.4 (25°), 62.7 (−87°), 79.1 (−171°); χ_M = 3840 (25°).

African Ore, 56.6% Mn; χ = 43 (25°); χ_M = 4160 (25°).

Brazilian Ore, 47.3% Mn; χ = 34 (25°); χ_M = 3960 (25°).

These results all show the surprising and gratifying result that natural and synthetic manganese dioxides are often magnetically dilute, and that in this respect they have the character of attenuated inorganic gels. In some cases the molal susceptibility of the manganese is almost twice what it is in the massive pyrolusite.

The sample γ-(I) is seen to follow the Curie–Weiss law, hence it is possible to calculate the magnetic moment. The moment for the manganese in this substance is 3.9, compared with a theoretical moment of 3.87. The Weiss constant has the value of 210°.

Similar calculations of Gel(II) show that the manganese has a moment of 3.7. The other hydrous oxides show small deviations from the Curie–Weiss law, hence calculations of the moment for these cases were not attempted.

All these results are in sharp contrast to data on the massive *pyrolusite* which show the typical behavior of a magnetically concentrated substance. The results on the disperse oxides show that some of these are well suited for the experiment on the dry cell. It is anticipated that this property of gel-like oxides in showing magnetic dilution will be no less useful than the corresponding property has been in structural studies of supported transition group oxides.[9]

The Dry Cell Experiment

Magnetic Measurements.—The horizontal displacement Gouy method was used. The cell was placed on a brass holder suspended by two fine copper wires. The wires were about 2 meters long and served the double purpose of suspension and electrical conduction. The cell was placed so that one end was in a region of maximum magnetic field intensity and the other end in a negligible field. The field was supplied by a large Alnico permanent magnet.[10] The field was about 9000 gauss over a 1-inch gap, with 4-inch diameter poles cut to truncated cones having 2-inch faces. This magnet gave complete satisfaction. All measurements were made at room temperature.

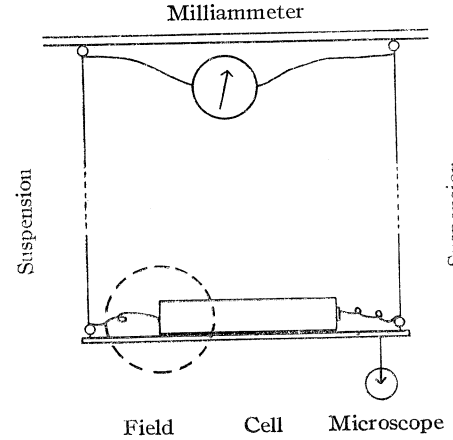

Fig. 1.—Diagram of the apparatus used in finding relative magnetic susceptibility as a function of cell discharge.

The object of the experiment was to obtain relative magnetic susceptibility measurements as a function of

(8) Weiser, "Inorganic Colloid Chemistry," Vol. II, "The Hydrous Oxides and Hydroxides," John Wiley and Sons, Inc., New York, N. Y., 1935, pp. 323–333.

(9) Eischens and Selwood, THIS JOURNAL, **69**, 1590 (1947).

(10) Obtained from the Indiana Steel Products Corporation, Valparaiso, Indiana.

time. Displacements of the cell from its initial position were observed with a micrometer microscope. These displacements may be shown to be linear with average susceptibility. The cell was connected through the copper suspension wires directly to a milliammeter. The cell, suspensions, and ammeter provided adequate resistance. For obvious reasons no measurements could be made while the current was flowing, but equilibrium was attained within a few seconds after the circuit was opened. The apparatus had excellent sensitivity.

Preparation of Cells.—Cells used in this experiment were constructed in general according to a modified standard procedure.[11] In order to have the cells of sufficient length to extend from high to negligible magnetic fields the following procedure was adopted. The zinc containers from two small commercial cells were combined to make a cell about 9 cm. long. Commercial carbon rods were used for the positive electrode, and acetylene black was used for internal conduction. It was desired to analyze the constituents of the cells before and after each run. Small muslin sacks were therefore used to hold the carbon and the depolarizer. This procedure made accurate weighing possible. The full sacks were then dipped in 10% ammonium chloride solution, and fitted into the zinc containers. Preliminary magnetic measurements on container and contents showed them to be free from ferromagnetism.

Results of Cell Experiment

A total of ten cells was prepared for this study. All gave results in general agreement. One typical set of results will be given in detail, and the remaining results will be described in more general terms.

A cell was prepared using 4.08 g. of $MnO_{1.97} \cdot 0.33H_2O$ (gel II as previously described), and 1.03 g. of acetylene black.

A plot of deflection against coulombs is shown in Fig. 2.

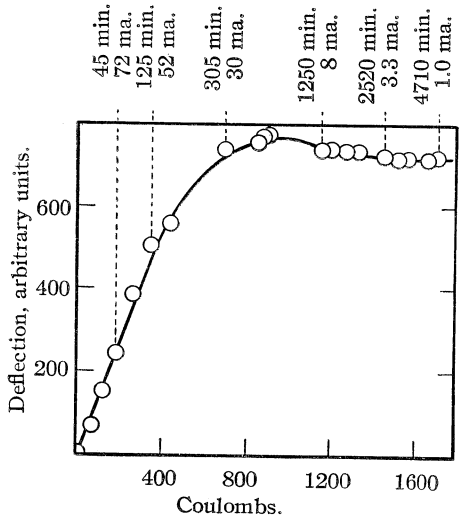

Fig. 2.—Deflection in the magnetic balance as a function of coulombs withdrawn from the cell. Time and discharge rate are given at the top.

During discharge the cell became more paramagnetic as would be expected for a decreasing oxidation state of the manganese. It is reasonable to suppose that the deflection is roughly linear with oxidation state for a cell containing gel-like manganese dioxide.

It will be noted that the deflection finally became virtually constant, although current continued to flow from the cell. The amperage fell steadily with increasing paramagnetism, but when the deflection became constant the amperage also became nearly constant. When this "steady" condition was reached the cell had already lost all its useful voltage, but nevertheless it could still yield a large number of coulombs.

Our conclusions from these observations are that the magnetic method is a very useful tool for following chemical changes in the depolarizer without in any way opening or disturbing the cell. The method gives the expected result of a linear relation between oxidation state and coulombs withdrawn over the useful life of the cell. Then, however, it is clearly indicated that there is a second depolarization mechanism. This second mechanism only comes into observation when the cell has lost its useful life, but presumably it is going on from the start of discharge. It is possible that the second depolarization mechanism may be produced by air. It is, of course, of no significance in sealed conventional cells.

A series of five cells was now made for the purpose of comparing the chemically determined oxidation state of the manganese with the magnetic data. All cells were made with 3.10 g. of a mixture prepared by adding 4.35 g. of acetylene black to 13.11 g. of Gel(II), as used in the first cell. Despite all precautions these cells differed considerably in starting amperage, total deflection, and rate of discharge. Nevertheless the deflection *vs.* coulombs curves for all cells had the same general shape.

The initial oxidation state of the manganese was, of course, 3.94, found as described above by chemical analysis. Two cells were completely discharged, and the final oxidation state was found to be 3.54 in each case. (This relatively high final oxidation state simply means that a considerable fraction of the depolarizer was not reached by continuous carbon filaments.) Three cells were run to the point where deflection stops. The final oxidation states were 3.32, 3.44 and 3.42. One cell was run to roughly two-thirds of the discharge at which deflection would have stopped. The oxidation state was then found to be 3.58.

These results support the magnetic data and serve as a rough calibration from which the oxidation state at any discharge point may be found. There is some evidence that the oxidation state of the manganese may actually increase very slightly during the period of air-depolarization, and this observation seems to be supported by the magnetic data.

One cell was discharged intermittently to answer an old question. This question is: does the oxidation state of the manganese change during discharge or during recovery? The cell had an

(11) Circular 79, U. S. Bureau of Standards, Washington, D. C.

initial discharge rate of 0.210 ampere. It was discharged for two minutes during which time the rate fell to 0.0180 ampere, and a deflection of 40 units was produced. The cell now stood for twenty minutes after which the discharge rate was 0.200 ampere, but the deflection was still exactly 40 units.

Discharge of this cell intermittently was continued with relatively long recovery periods, until discharge was virtually complete. The results were the same throughout the whole experiment, namely, that the manganese oxidation state changes during discharge and not during recovery. This view is contrary to that often expressed. The final oxidation state in this particular cell was 3.42, and the deflection *vs.* coulombs curve was similar to that already presented.

During the course of this work some cells were studied containing as depolarizers supported manganese (+4) on γ-alumina, and supported-iron (+3 and +4) on alumina and titania, respectively. The results on these cells will be described in forthcoming papers dealing with the preparation and properties of supported oxides.

Our thanks are due to Dr. T. E. Moore for invaluable assistance in some of the early phases of this work.

Summary

Preparations of manganese dioxide show widely varying magnetic dilution. This effect will be useful in studying the degree of attenuation in solid inorganic gels formed by oxides of the transition elements.

Disperse manganese dioxide showing high magnetic dilution has been used as depolarizer Leclanché cells. In this way it has been possible to make magnetic susceptibility measurements on discharging cells *in situ*.

EVANSTON, ILLINOIS RECEIVED AUGUST 4, 1948

[CONTRIBUTION NUMBER 81 FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF UTAH]

The Chromatographic Separation of Perrhenic and Molybdic Acids

BY GUY B. ALEXANDER[1]

The problem of separating rhenium from samples containing large amounts of molybdenum has been investigated in connection with the analytical determination of rhenium and in connection with the extraction of rhenium from molybdenite concentrates. Hiskey and Meloche[2] devised an analytical method, refined by Snyder[3] and Alexander,[4] for the determination of rhenium in molybdenite minerals; the procedure was based on the separation of rhenium from the other components of the mineral by distilling from sulfuric acid solution. Feit[5] utilized the slight solubility of potassium perrhenate in a process for the recovery of rhenium from molybdenite concentrates. Melaven and Bacon[6] have reported a method for extracting rhenium from molybdenite roaster flue dust by (a) a water leaching, (b) precipitation of crude potassium perrhenate, and (c) the purification of this crude product.

In the course of an experiment in which it was attempted to recover rhenium by roasting a molybdenite concentrate at a controlled temperature, Snyder[3] discovered that perrhenic acid was adsorbed by Norit. Following this discovery, Snyder studied several of the variables of the adsorption of rhenium and molybdenum compounds on Norit, including the effect of the concentration of hydrochloric and sulfuric acids on adsorption, and the effect of temperature and *p*H on desorption. Although Snyder's work was limited to the equilibrium or batch technique, his results suggest that a chromatographic process might be useful in separating compounds of rhenium and molybdenum.

The purpose of this paper is to show that a quantitative separation of rhenium and molybdenum can be made by the chromatographic method with Norit as the adsorbent. The basis of the separation is the fact that, from a sulfuric acid solution of perrhenic and molybdic acids, perrhenic acid is more strongly and more rapidly adsorbed on Norit.

Experimental

In order to provide a basis for predicting the behavior of perrhenic and molybdic acids in a chromatographic process, the adsorption of each adsorbate was studied before attempting a chromatographic separation. All adsorption studies were carried out in 1.95 *N* sulfuric acid, since it has been shown[3] that there is a difference in the adsorption of perrhenic and molybdic acids from this solvent.

Reagents.—Stock solutions of molybdic acid were prepared by dissolving reagent grade ammonium molybdate in 1.95 *N* sulfuric acid. The molybdenum content of these solutions was determined by titrating with standardized potassium permanganate after passage through a Jones reductor.

A perrhenic acid solution was prepared by dissolving a weighed amount of recrystallized potassium perrhenate in 1.95 *N* sulfuric acid. The rhenium content of this solution was checked by precipitating the perrhenate with Nitron and weighing the dried product.

Norit A, technical decolorizing carbon, from the Fisher Scientific Co. was used as the adsorbent.

(1) Present address: E. I. du Pont de Nemours and Co., 3092 Broadway, Cleveland, Ohio.

(2) Hiskey and Meloche, *Ind. Eng. Chem., Anal. Ed.*, **12**, 503 (1940).

(3) Snyder, Ph.D. Thesis, University of Wisconsin, 1945.

(4) Alexander, Ph.D. Thesis, University of Wisconsin, 1947.

(5) Feit, *Z. angew. Chem.*, **43**, 459 (1930).

(6) Melaven and Bacon, paper presented at the 105th Meeting of the ACS, Detroit, Michigan, 1943.

Molybdic Acid Adsorption.—The rate of adsorption of molybdic acid (see Table I) was determined by stirring 2.50 g. of Norit with 100 ml. of 1.95 *N* sulfuric acid containing 1.33 millimoles (based on H_2MoO_4) of molybdic acid for timed intervals, filtering, and analyzing the filtrate for molybdenum by the volumetric permanganate method.

TABLE I

RATE OF MOLYBDIC ACID ADSORPTION

Adsorbent, 2.50 g. Norit; adsorbate, 1.33 millimoles H_2MoO_4; solvent, 100 ml. of 1.95 *N* H_2SO_4

Time of contact, hours	Adsorption, %
0.13	35.7
.25	37.9
.5	39.7
1.0	41.6
3.0	43.5
10	46.0
48	46.6
72	48.0

The desorption rate (Table II) was determined by stirring 2.50 g. of Norit, on which 2.20 millimoles of molybdic acid had been adsorbed, with 100 ml. of 1.95 *N* sulfuric acid for a given time, filtering, and analyzing the filtrate. The samples

TABLE II

RATE OF MOLYBDIC ACID DESORPTION

Adsorbent, 2.50 g. Norit; adsorbed, 2.20 millimoles H_2MoO_4; solvent, 100 ml. 1.95 *N* H_2SO_4

Time of contact, hours	Remaining adsorbed, %
0.08	60.3
.33	58.2
1.0	55.5
4.0	53.2
18	50.3
72	50.0

of Norit for desorption studies were prepared by stirring 2.50 g. of Norit with 100 ml. of 1.95 *N* sulfuric acid containing 5.33 millimoles of molybdic acid for three days, then filtering. The filtrates contained 0.0314 ± 0.0003 millimole of molybdic acid per ml. The Norit "held up" approximately 6 ml. of solution containing 0.19 millimole of molybdic acid, hence the total amount of molybdic acid present in the desorption experiments was 2.39 millimoles of which 2.20 millimoles was adsorbed.

The observed slow rates of adsorption and desorption (Tables I and II) indicate that reaction rates will play a predominant role in molybdic acid chromatography. Thus in the formation of a chromatographic band, the front boundary will tend to be broad and diffuse, resulting in premature break-through. During development of the chromatogram, the band will migrate at a slower rate than might otherwise be expected, and the rear boundary will tend to become very diffuse. This condition will necessitate the use of large volumes of developing agent in order to remove the last traces of adsorbed molybdic acid from a column.

The adsorption isotherm ($\log f = 0.87 \log c - 0.45$) shown in Fig. 1 is based on data obtained by stirring 2.50 g. of Norit with various amounts of molybdic acid in 100 ml. of 1.95 *N* sulfuric acid for three days. Evidence that equilibrium is nearly complete in this time is the fact that a point almost on the isotherm is obtained by approaching equilibrium for seventy-two hours by desorption. (Note that the location of this point is unaffected when either the eighteen- or seventy-two hour reading is taken; see Table II.)

Figure 2 shows the behavior of molybdic acid in a chromatographic process. Two hundred ml. of 1.95 *N* sulfuric acid containing 1.06 millimoles of molybdic acid was passed through a column (19 mm. dia. and 100 mm. high) of 12.0 g. of Norit at a rate of 0.8 ml. per minute. The molybdate band was developed with 1.95 *N* sulfuric acid. Theory predicted[7] break-through after a total of about 450 ml. of solution had passed through the column. In actual experiment, however, 82% of the in-

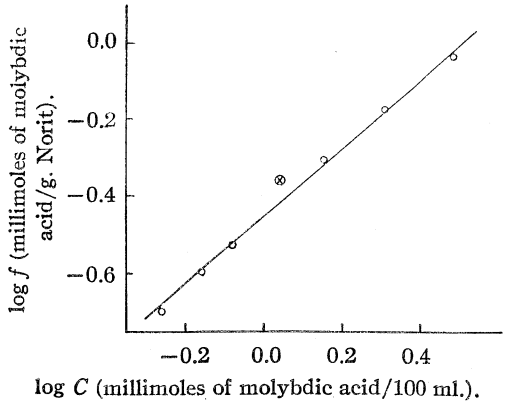

Fig. 1.—The molybdic acid isotherm: ⊗, distribution of molybdic acid after seventy-two hours of desorption (Table II).

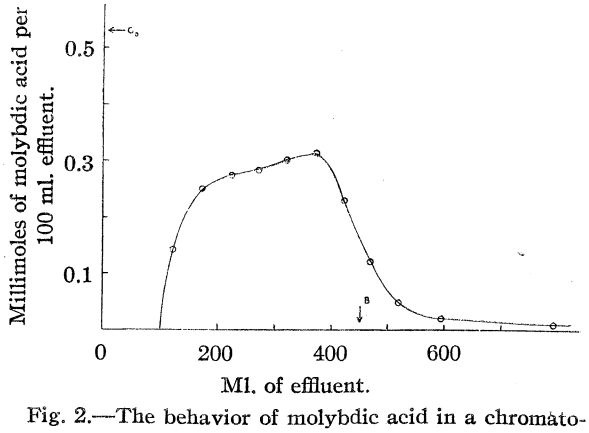

Fig. 2.—The behavior of molybdic acid in a chromatographic process: C_0, concentration of molybdic acid in the influent; B, theoretically predicted break-through.

(7) DeVault, THIS JOURNAL, **65**, 532 (1943).

fluent molybdic acid was present in the effluent at the 450-ml. stage; break-through occurred at the 100-ml. stage. Moreover, the front boundary was not sharp. This behavior is probably due to the slowness with which equilibrium is established.

Perrhenic Acid Adsorption.—The rate of adsorption of perrhenic acid is shown in Table III. After stirring the adsorbent and solution for a given time, the slurry was filtered; rhenium in the filtrate was precipitated as the sulfide and determined by the Nitron method. It is impossible to compare rigorously the reaction rates of perrhenic and molybdic acids, since the structure of the polymolybdic acid which is adsorbed is not known. However, from Tables I and III it would appear that the reaction rates are such that adsorption of perrhenic acid will be favored in the formation of a chromatogram.

TABLE III

RATE OF PERRHENIC ACID ADSORPTION

Adsorbent, 1.00 g. Norit; adsorbate, 0.349 millimole of $HReO_4$; solvent, 100 ml. 1.95 N H_2SO_4

Time of contact, hours	Adsorption, %
0.07	84.0
.25	85.4
1.0	87.1
2.0	89.8
5.0	90.9
30	91.7

Figure 3 shows the chromatographic adsorption of perrhenic acid. In this experiment a 4.0-g. Norit column (19 mm. dia. and 30 mm. high) was treated with 2.44 millimoles of perrhenic acid in 350 ml. of 1.95 N sulfuric acid at a rate of 1.6 ml. per minute. Thereafter the band was developed with 1.95 N sulfuric acid. The capacity of the column before break-through was 1.74 millimoles of perrhenic acid (*i. e.*, 109 mg. of $HReO_4$ per g. of Norit), break-through occurring after 250 ml. of solution had passed through the column. Theory[7] predicts break-through at the 425-ml. stage. (The prediction is based on the isotherm, $\log f = 0.33 \log c - 0.08$. This isotherm was determined in the usual manner; however, only three concentrations of perrhenic acid were studied.)

A comparison of the molybdic and perrhenic acid chromatographic experiments shows that despite the fact that a slower rate (0.8 compared with 1.6 ml./min.) and a longer column (100 mm. compared with 30 mm.) were used in the former case, the latter more closely approaches the theoretical behavior. Thus the ratio of experimental to theoretical capacity of the columns at break-through was 0.58 in the perrhenic acid case and was only 0.22 in the case of molybdic acid. Moreover, the maximum concentration of perrhenic acid in the effluent was 90% of that of the influent, while for molybdic acid the maximum was 60% of the original. The better agreement of theory and experiment with perrhenic acid substantiates the conclusion reached from the comparison of Tables I and III, *i. e.*, that reaction rates will favor the chromatographic separation of the two acids.

Rhenium–Molybdenum Equilibrium Adsorption.—The exchange adsorption equilibrium between perrhenic and molybdic acids was determined by stirring different amounts of these compounds in 100 ml. of 1.95 N sulfuric acid with 1.00 g. of Norit for three days. The filtrate from this slurry was analyzed; after precipitation as sulfides, molybdenum was determined by 8-hydroxyquinoline and rhenium by Nitron.[8] The results of this experiment which are found in Table IV, and Fig. 4, indicate that the adsorption of

TABLE IV

RHENIUM–MOLYBDENUM ADSORPTION EQUILIBRIUM

Adsorbent, 100 g. Norit; solvent, 100 ml. 1.95 N H_2SO_4; units, millimole

Perrhenic acid		Molybdic acid	
Taken	% Adsorbed	Taken	% Adsorbed
1.57	43	0.43	14
1.31	47	1.08	14
0.88	58	2.16	15
.43	79	3.24	19
.17	Samples lost	3.90	23

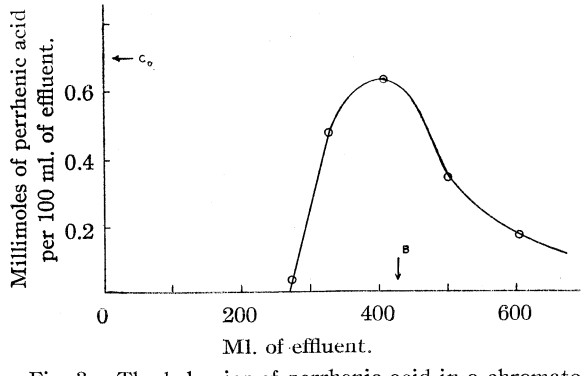

Fig. 3.—The behavior of perrhenic acid in a chromatographic process: C_0, concentration of perrhenic acid in the influent; B, theoretically predicted break-through.

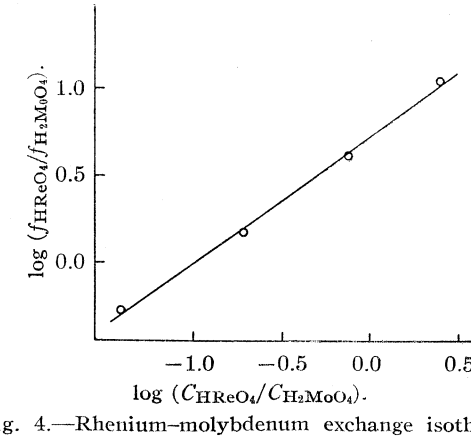

Fig. 4.—Rhenium–molybdenum exchange isotherm.

(8) Geilmann and Weibke, *Z. anorg. allgem. Chem.*, **199**, 347 (1931).

perrhenic and molybdic acids approaches the exchange isotherm[9]

$$\log (f_{HReO_4}/f_{H_2MoO_4}) = 0.72 \log (c_{HReO_4}/c_{H_2MoO_4}) + 0.73$$

over the range studied. The rhenium–molybdenum equilibrium adsorption experiments show that perrhenic acid is preferentially adsorbed.

Chromatographic Separation Run 1.—In the first experiment a solution containing 0.349 millimole of perrhenic acid (65.0 mg. of rhenium) and 0.43 millimole of molybdic acid (41 mg. of molybdenum) in 100 ml. of 1.95 *N* sulfuric acid was passed through a 19 mm. dia. and 50 mm. high column of 6.0 g. of Norit at a rate of 1.2 ml. per minute. The chromatogram was developed with 1.95 *N* sulfuric acid until the concentration of molybdenum in the effluent had dropped below 0.1 mg. per 100 ml.; this required a total of 700 ml. of developing agent. Tests for rhenium in the effluent fractions were negative. (The limit of detection of rhenium was 50 micrograms per 100 ml. of effluent.) The adsorbent was removed from the column and the remaining adsorbate was eluted by two treatments of 600 ml. of boiling 0.1 *N* sodium hydroxide solution.[3] On analysis, the combined hydroxide solutions were found to contain 63 mg. of rhenium and less than 0.2 mg. of molybdenum. The summary of Run 1, found in Table V, shows that a quantitative separation of rhenium and molybdenum was obtained in this experiment.

TABLE V

THE CHROMATOGRAPHIC SEPARATION OF RHENIUM AND MOLYBDENUM, RUN 1

Adsorbent, 6.0 g. Norit; flow rate, 1.2 ml. per minute; developing agent, 700 ml. 1.95 *N* H_2SO_4; molybdenum used, 41 mg.; rhenium used, 65 mg.

Fraction effluent, ml.	Molybdenum recovered	Rhenium recovered
100	13.5	0
100	22.7	0
100	2.0	0
100	1.4	0
100	0.8	0
100	.5	0
100	.2	0
100	.0	0
Alkaline eluate	.0	63
Total	41.1	63[a]

[a] Incomplete recovery of rhenium may have been due to incomplete elution of rhenium. In Run 2, a third treatment with sodium hydroxide eluted 1 mg. of rhenium.

(9) Rothmund and Kornfeld, *Z. anorg. allgem. Chem.*, **103**, 129 (1918).

Run 2.—In the second experiment 100 ml. of 1.95 *N* sulfuric acid solution containing 0.232 millimole of perrhenic acid and 2.90 millimoles of molybdic acid was passed through an 8.0-g. Norit column (19 mm. dia. and 65 mm. high) at a flow rate of 1.2 ml. per minute; this was followed by 2100 ml. of developing agent Analysis revealed 2.90 millimoles of molybdic acid and no perrhenic in the effluent, 0.23 ± 0.01 millimole of perrhenic acid and 0.04 millimole of molybdic in the column after development. Thus a sample which originally contained 0.080 millimole of perrhenic acid for each millimole of molybdic acid was fractionated into: one fraction containing 98.4% of the total molybdic acid recovered and no perrhenic acid; a second fraction containing 6 millimoles of perrhenic acid for each millimole of molybdic.

Conclusion.—There is sufficient difference in the adsorption characteristics of perrhenic and molybdic acids to permit a quantitative chromatographic separation of these compounds—using 1.95 *N* sulfuric acid as the solvent and developing agent and Norit as the adsorbent. It is possible that a chromatographic process similar to those described above might be applied in the separation of rhenium from samples containing molybdenum prior to analysis or for the extraction of rhenium from molybdate concentrates.

Summary

1. Equilibrium for the adsorption of molybdic or perrhenic acid from 1.95 *N* sulfuric acid on Norit requires several days. The Freundlich isotherms for the adsorption of these acids are $\log f = 0.87 \log c - 0.45$, and $\log f = 0.33 \log c - 0.08$, respectively.

2. As expected from the slow reaction rates, the chromatographic behavior of molybdic acid does not agree with the equilibrium theory. The agreement is a little better in the case of perrhenic acid.

3. The equilibrium adsorption of perrhenic and molybdic acids on Norit approaches the exchange isotherm behavior in the range studied.

4. Rhenium and molybdenum may be effectively separated chromatographically.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Rates of Water Oxidation in Ceric Perchlorate Solutions[1]

BY DON KOLP[2] AND HENRY C. THOMAS[3]

The oxidation of water by cerium(IV) in perchloric acid solutions has been observed and investigated by several workers.[4-7] In their communication Heidt and Smith[7] propose a mechanism which accounts for their results on the photochemical reduction of cerium(IV) by water. Weiss and Porret[5] as well as Heidt and Smith observed that the reaction is retarded by the presence of cerium(III). The present work was undertaken only incidental to a study of the oxidation of formic acid in perchloric acid solutions of cerium(IV) and does not constitute an exhaustive investigation of the water reaction. However, the effect of the concentration of cerium(III) has been the object of particular study. We are concerned here with the thermal reaction; excitation by ultraviolet radiation was not present.

Experimental

Eighteen solutions of mixed ceric and cerous perchlorate were used. The perchlorate solutions were near 3.6, 5.4 and 7.4 molar. Cerium(IV) concentrations varied from 0.1 to 0.4 molar in two steps; cerium(III) concentrations, from 0.1 to 0.3 molar in two steps. (All concentrations mentioned in this section and in the section on results are to be understood as analytical concentrations, in volume formal units, and will be designated by *M*.)

The solutions were prepared as follows. "Reference" grade ammonium hexanitratocerate, stated by the manufacturer (the G. Frederick Smith Chemical Co.) to be 100.0% pure, in amount 1.2 moles, was dissolved in a minimum quantity of distilled water. This solution was added slowly with vigorous stirring to twice the equivalent amount of 3% ammonia solution. After the heavy precipitate of ceric hydroxide had settled, the liquid was decanted and the precipitate transferred to a Buchner funnel fitted with a circle of hardened paper. The precipitate was washed about twenty times on the filter, the final washings giving a negative test for ammonia. The precipitate was divided into three nearly equal parts. One portion was dissolved in 670 ml. of "Baker's Analyzed" perchloric acid, another, in 500 ml., and the third, in 330 ml. of the acid. These solutions were filtered through sintered glass, and each was diluted to a volume of one liter. The three solutions were approximately 0.4 *M* in cerium(IV). Solutions approximately 0.1 and 0.2 *M* in ceric cerium were prepared by dilution with appropriate acid. Six additional solutions were thus prepared.

Solutions containing cerium(III) were prepared from the 0.2 and 0.4 *M* cerium(IV) solutions by reduction of a portion with a few drops of 30% hydrogen peroxide and subsequent addition of a similar volume of the parent solution: Of the solutions thus produced those with cerium(IV) concentrations of 0.2 *M* were further partially reduced. These operations produced nine additional solutions.

The eighteen solutions were analyzed for total cerium by the method of Willard and Young.[8] The perchloric acid was removed by evaporation with sulfuric acid to fumes of sulfur trioxide before oxidation with ammonium persulfate. Titrations were made with recently standardized ferrous ammonium sulfate solution. This solution was standardized against a ceric sulfate solution which had been standardized by weight against Bureau of Standards sodium oxalate. Duplicate determinations of total cerium agreed to 0.1%.

The perchlorate content of each of the eighteen solutions was determined by the method of V. Rothmund.[9] The excess titanous sulfate was destroyed with an equivalent amount of potassium permanganate. Chloride was determined in the resulting solutions by the Volhard titration. A blank determination was carried out on the reagents, the results of which were applied to the data. Duplicate determinations agreed to 0.2%.

If the cerium hydroxide precipitate contained no bases other than $Ce(OH)_4$ and $Ce(OH)_3$, the available hydrogen ion content of the solution resulting when the precipitate was dissolved in perchloric acid is given by $(H^+) = (ClO_4) - 3(CeIII) - 4(Ce(IV))$. This formula will continue to hold when a part of the Ce(IV) is reduced to Ce(III) because one hydrogen ion is liberated in the reduction of each Ce(IV), whether the reduction be accomplished by water or by hydrogen peroxide. Thus the hydrogen ion concentrations of the solutions may be calculated from the analytical data on perchlorate and cerium.

The rate measurements were carried out as follows. For a single series twelve 13 × 100 mm. test-tubes were cleaned by heating in dichromate–sulfuric acid solution, rinsing ten times with tap water and five times with distilled water. The tubes were dried and a 5-ml. portion of the solution to be studied was sealed into each. The tubes were placed in a thermostat and allowed two to five hours to reach temperature equilibrium. To determine the initial cerium(IV) concentration, a tube was opened and emptied into a flask, previously weighed with its contents, containing 25 ml. of cool 2 *M* sulfuric acid. The reaction was stopped by this dilution in sulfuric acid. The flask was again weighed and the cerium(IV) determined by titration with ferrous solution, using ferroin as the indicator. Because of some fading of the end-point these titrations are subject to an error of ±0.3%. The initial concentration of cerium(III) follows from the known total cerium content of the solution. The remaining samples were titrated by the same procedure at intervals of one or two days. The time at which each sample was stopped was observed with an uncertainty of no more than a minute.

The densities of the reaction mixtures were determined pycnometrically at the temperatures of the rate measurements. They were found to change less than 0.1% as the reaction proceeded.

Results

Eighteen runs were made at 60.0°. Three runs each were made at 45.0 and 30.0°. The results were much more consistent at the highest temperature. In Table I the complete data are given for a single run at 60.0°. The entries are self-explanatory with the exception of those in the fifth and sixth columns, which were arrived at as follows.

(1) This paper is based upon the dissertation presented by Don Kolp in 1948 to the Faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. The material of this paper was presented in part at the 115th National Meeting of the American Chemical Society in San Francisco, California.

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(3) At present on leave of absence from Yale University at the Brookhaven National Laboratory, Upton, L. I., N. Y.

(4) E. Bauer, *Z. physik. Chem.*, **63**, 683 (1908).

(5) J. Weiss and D. Porret, *Nature*, **139**, 1019 (1917).

(6) G. F. Smith, "Cerate Oxidimetry," G. F. Smith Co., Columbus, Ohio, pp. 93–95.

(7) L. J. Heidt and M. E. Smith, THIS JOURNAL, **70**, 2476 (1948).

(8) H. H. Willard and P. Young, THIS JOURNAL, **50**, 1379 (1928).

(9) V. Rothmund, *Z. anorg. Chem.*, **62**, 108 (1909).

An empirical differential equation has been found which correlates all of the results in a satisfactory manner. Writing C_4 and C_3 for the analytical concentrations of cerium(IV) and cerium(III), this equation is

$$\frac{dC_3}{dt} = k_e \frac{C_4^{5/3}}{C_3} \quad (1)$$

at fixed perchlorate concentration and at fixed temperature. On integration this equation gives the relation

$$f \equiv \frac{3(C_4 + C_3)}{2C_4^{2/3}} + 3C_4^{1/3} = k_e t + f_0 \quad (2)$$

where f_0 is the value of the left side of the equation at the time ($t = 0$) of the first analysis of a series. The computed values of $f - f_0$ according to (2) are given in the fifth column of Table I and the corresponding values of k_e in the sixth. The linearity with time of $f - f_0$ is evident. The results at 60° are all reasonably well represented by such straight lines. The data at the lower temperatures are much less precise. Table II gives the initial conditions for the various series and the values of k_e as graphically determined. At 30° these slopes can be considered only rough approximations.

The experimental results are summarized in the following empirical equations for the constants k_e of equation (1). Variation with total perchlorate content at fixed temperature

60°	$\log k_e = 0.116[ClO_4] - 4.29$
45°	$\log k_e = 0.238[ClO_4] - 6.19$
30°	$\log k_e = 0.218[ClO_4] - 7.08$

Variation with temperature at fixed total perchlorate content

$7.50M$ ClO_4	$\log k_e = 16.7 - 6700/T$
$5.25M$ ClO_4	$\log k_e = 20.5 - 8100/T$
$3.75M$ ClO_4	$\log k_e = 25.8 - 9900/T$

Since the total perchlorate content of the solutions does not vary during the course of the reaction, it, rather than the perchloric acid content, has been selected as the basis for the correlation of the data.[10] These equations are not to be taken as implying the independence of the reaction rate and hydrogen ion concentration. They are only summaries of the experimental results under the conditions given in Table II.

Discussion

A possible interpretation of the empirical differential equation (1) is afforded by the mechanism proposed by Heidt and Smith[7] for the photochemically excited oxidation of water by cerium (IV). For our case, in which only thermal excitation is present, their mechanism is represented by the equations

(10) In the abstract of this paper published for the 115th National Meeting of the American Chemical Society these equations were erroneously given in terms of perchloric acid content. Here also the constant for the temperature variation at 7.50 M ClO_4 was given as 17.7 instead of 16 7.

$2C_m \rightleftarrows C_p$	K
$C_p \longrightarrow C_p^*$	k_1
$C_p^* + H_2O \longrightarrow 2C_3 + 2H^+ + {}^1/_2O_2$	$k_2 = k_2'[H_2O]$
$C_p^* + C_3 \longrightarrow C_p + C_3$	k_3
$C_p^* + S \longrightarrow C_p + S$	$k_4 = k_4'[S]$

The oxidation is considered to be caused by an energetic dimer, C_p^*, of ceric cerium. The dimerization is supposed to be fast with respect to the remaining reactions. The inhibition of the water oxidation is due to the deactivation of the excited dimer by cerous cerium, C_3; further inhibition by the remainder of the environment, S, is repre-

TABLE I

OXIDATION OF WATER BY CERIC PERCHLORATE AT 60.0°

Total cerium, $0.3794M$; perchlorate, $5.24M$

Time, hours	Ce(IV), moles/liter	Ce(III), moles/liter	H, moles/liter	$f - f_0$, $M^{1/3}$	$k_e \times 10^4$ $M^{1/3}$/hours
0.0	0.1840	0.1954	3.92	0.0000	...
48.5	.1800	.1994	3.92	.0132	2.7
96.0	.1768	.2026	3.93	.0243	2.5
145.1	.1735	.2059	3.93	.0375	2.6
191.8	.1709	.2085	3.93	.0444	2.3
263.9	.1662	.2132	3.94	.0663	2.5
312.2	.1641	.2153	2.94	.0753	2.4
432.3	.1577	.2217	3.95	.1050	2.4
503.8	.1544	.2250	3.95	.1212	2.4
599.7	.1506	.2288	3.95	.1413	2.4

TABLE II

OXIDATION OF WATER BY CERIC PERCHLORATE

ClO_4, moles/liter	Total Ce, moles/liter	Initial Ce(IV), moles/liter	$k_e \times 10^4$, $M^{1/3}$/hours
	(A) 60.0°		
7.36	0.3776	0.3393	3.5
7.43	.1887	.1572	3.7
7.46	.0919	.0731	3.5
7.22	.3712	.1838	3.7
7.26	.1833	.0876	3.7
7.16	.3683	.0830	3.3
5.28	.3849	.3556	2.0
5.49	.1913	.1606	2.2
5.45	.0945	.0759	2.2
5.24	.3794	.1840	2.3
5.41	.1885	.0947	2.4
5.22	.3776	.0956	1.7
3.54	.3776	.3534	0.79
3.72	.1880	.1680	1.3
3.76	.0961	.0755	1.2
3.48	.3739	.1786	1.2
3.67	.1857	.0838	1.5
3.50	.3694	.0915	1.6
	(B) 45.0°		
			$k_e \times 10^5$
7.44	0.3817	0.3556	3.8
5.43	.3892	.3651	1.2
3.57	.3813	.3596	0.45
	(C) 30.0°		
			$k_e \times 10^7$
7.52	0.3859	0.3612	5.9
5.39	.3929	.3689	20
3.61	.3849	.3615	2.6

sented by the last equation. If we write $T = 2C_p + \sqrt{C_p/K}$ for the total Ce(IV) content of the solution, neglecting C_p* as compared to the bulk of the Ce(IV), the usual steady state approximation immediately produces the rate equation

$$-\frac{dT}{dt} = \frac{kC_p}{m + C_3} \quad (4)$$

where $k = 2k_1k_2/k_3$ and $m = (k_2 + k_4)/k_3$. For convenience we select $z = \sqrt{C_p/K}$ as the dependent variable and integrate (4) with the result

$$F \equiv \frac{M}{Kz} + \left(\frac{1}{K} - 4M\right) \ln z + 6z + 4Kz^2 = kt + F_0 \quad (5)$$

In this equation $M = m + a + b$, a and b being the initial total Ce(IV) and Ce(III) concentrations, respectively. In equation (5) we have a means of representing the rate data in terms of the equilibrium constant of the dimerization and the group of constants m. Unfortunately there are not available independent determinations of these constants, hence the application of (5) to the data of this paper can be considered only tentative. Comparison of the empirical equation (1) and equation (4) indicates that m is probably small with respect to C_3 and hence with respect to $a + b$. As a preliminary test of (5) we thus put $M \simeq a + b$. We now have an equation with one adjustable constant, K. The data on the water oxidation at 60° can be well represented by this equation with reasonable values of K. If one chooses $K = 1.0$ and applies (5) to a run with $[ClO_4] = 7.16$, $a = 0.0830$, $b = 0.2853$, the values of $F - F_0$ fall close to a straight line with slope $k = 1.15 \times 10^{-3}$. Using the same value of K in a run with nearly the same perchlorate concentration, $[ClO_4] = 7.43$, and a widely different ratio of initial concentrations, $a = 0.1572$ and $b = 0.0315$, the straight line through the points has the slope $k = 1.17 \times 10^{-3}$. Since the only criterion for the correct choice of K is the fit of the data to a straight line, considerable latitude in the choice of K is permissible. About the most that can be said is that higher values of K must be chosen for lower perchloric acid concentrations. Thus at $[ClO_4] = 3.72$, K must be chosen in the range 2.0 to 2.5. It will be necessary to test the mechanism using independent determinations of the dimerization constants. A further interesting study will be the comparison of the rate of the deactivation reaction, given by k_3, with the rate of the electron exchange reaction between ceric and cerous cerium.

Summary

1. Rate data are presented on the thermal reaction in perchloric acid solution between ceric cerium and water. Empirical equations summarizing these data are reported.

2. The results are examined in the light of the mechanism of Heidt and Smith for this reaction. The data are shown to be consistent with this mechanism.

RECEIVED MARCH 29, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY AND CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Chlorination of Bicyclo[2,2,1]heptane (Norbornylane)

BY JOHN D. ROBERTS,[1] L. URBANEK[2] AND ROSE ARMSTRONG

The nitration of bicyclo[2,2,1]heptane (norbornylane[3]) has been reported to give 1-nitrobicyclo[2,2,1]heptane.[4] In the present investigation a study was made of the peroxide-catalyzed chlorination of bicyclo[2,2,1]heptane with sulfuryl chloride[5] in an attempt to find a convenient synthesis for the 1- and 7-chlorobicyclo[2,2,1]-heptanes. Both mono- and dichloro products were isolated from the chlorination of bicyclo-[2,2,1]heptane in methylene chloride solution. The monochloride fraction had practically the same physical properties (Table I) and infrared absorption spectrum (Fig. 1) as a sample of norbornyl chloride (2-chlorobicyclo[2,2,1]heptane) made by the addition of hydrogen chloride to norbornylene (bicyclo[2,2,1]2-heptene).[6]

TABLE I

PHYSICAL PROPERTIES AND SOLVOLYTIC RATE CONSTANTS

Chloride	B. p., °C.	Mm.	M. p., °C.	$n^{25}D$	d^{25}_4	k_1,[a] hr.$^{-1}$
Product of addition of hydrogen chloride to bicyclo[2,2,1]2-heptene	97	100	−6[b]	1.4823	1.060	0.151
Product from the chlorination of bicyclo[2,2,1]-heptane	88–89	74	..	1.4824	1.061	.152
Chlorination of bicyclo-[2,2,1]heptane (after partial hydrolysis)	79	46	−4[b]	1.4825	1.059	.116
Cyclopentyl chloride	...	...	..	....	...	.017

[a] Solvolysis rate constant for aqueous alcohol (80% ethanol and 20% water by volume) at 85°. [b] Melting point of a mixture of approximately equal weights of these materials was −5°.

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(3) Bicyclo[2,2,1]heptane and its derivatives are listed by *Chemical Abstracts* as "norcamphanes." In this paper the more desirable name, norbornylane, is used for the parent hydrocarbon; *cf.* Komppa and Beckmann [*Ann.*, **512**, 172 (1934)].

(4) Blickenstaff and Hass, THIS JOURNAL, **68**, 1431 (1946).

(5) Kharasch and Brown, *ibid.*, **61**, 2142 (1939).

(6) Schmerling, *ibid.*, **68**, 195 (1946).

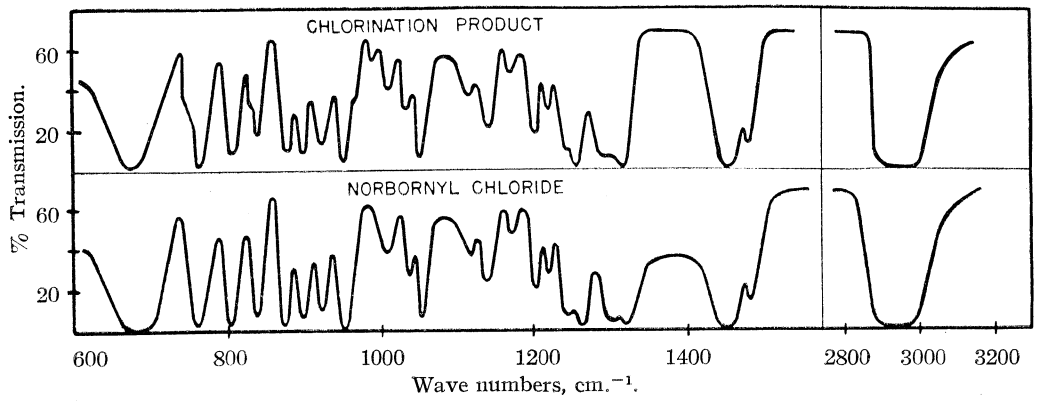
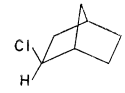


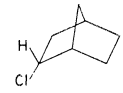
Fig. 1.—Infrared spectra.

In order to confirm the identity of the monochlorination product, the rate constant of its solvolytic reaction at 85° in aqueous alcohol (80% ethanol and 20% water by volume) was compared with that of the material prepared from norbornylene. The results are given in Table I along with the rate constant obtained for cyclopentyl chloride under the same conditions. Although the rate constant of the chlorination product was very close to that of norbornyl chloride, the presence of a small amount (5%) of less reactive chloride was indicated by the deviation from first-order kinetics in the later stages of the reaction. To concentrate any less reactive chloride, the monochlorination product was boiled for five hours with a water–acetone mixture. The physical properties of the recovered unreacted chloride were not appreciably different from those of the starting material. However, the solvolytic rate measurements (Fig. 2) showed clearly the presence of 15–25% of substances less reactive than norbornyl chloride. Since the unreacted chloride amounted to about 25% of the material taken, it is evident that only about 5% of the monochlorination product was not norbornyl chloride.[7]

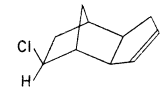


Ia

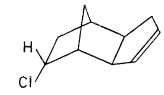
The solvolytic reactivity of norbornyl chloride is nine times greater than that of cyclopentyl chloride in 80% ethanol at 85°. The very considerable reactivity of norbornyl chloride as compared to cyclopentyl chloride is particularly interesting since cyclopentyl chloride is more reactive in solvolytic reactions than most typical secondary alkyl chlorides.[8] Furthermore, the similarly constituted chlorodihydro-*exo*-dicyclopentadiene (II) has been reported to be very unreactive.[9]



Ib



IIa



IIb

(position of double bond uncertain)

The configurations (Ia and Ib or IIa and IIb) of the chlorine atoms in I and II with respect to the methylene bridges are not certain[10] and may

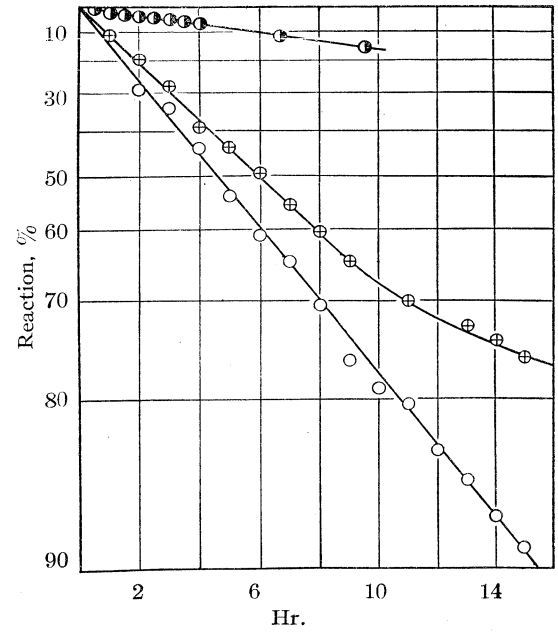


Fig. 2.—Solvolysis of chlorides at 85°: O, norbornyl chloride; ⊕, chlorination product after partial hydrolysis; ◑, cyclopentyl chloride.

(7) The high degree of specificity in this chlorination is unusual, particularly since with the possibility of *exo–endo* isomerism (*vide infra*) substitution at only four (at the most) of the ten secondary positions of norbornylane can give equivalent chlorination products.

(8) In 50% alcohol–50% water (by volume) solutions at 90°, cyclopentyl chloride solvolyses approximately five times more rapidly than diethylcarbinyl chloride. For solvolytic reaction rate constants of other secondary alkyl chlorides, see Roberts [THIS JOURNAL, **71**, 1880 (1949)].

(9) Bruson and Riener, THIS JOURNAL, **67**, 726, 1178 (1945). The compound was referred to in these papers as chloro-dihydro-*nor*-dicyclopentadiene. See Bartlett and Schneider, *ibid.*, **68**, 6 (1946) and Bruson and Riener, *ibid.*, **68**, 8 (1946). The position of the double bond is uncertain in this substance.

(10) The *exo*(*cis*)-configuration (Ia) of chlorine and bridge has been assigned by Komppa and Beckman (cited in ref. 3) to the chloride resulting from the treatment of *exo*-norborneol with phosphorus

possibly account for the difference in reactivity between I and II. However, it is noteworthy that if I is a mixture of *exo*- and *endo*-forms, these must have very similar solvolytic rate constants since the solvolysis of I follows the first-order rate law to well over 90% reaction as shown by Fig. 1.

Further experiments are in progress on the determination of the mechanisms of displacement reactions of norbornyl derivatives.

Acknowledgment.—We are indebted to Dr. R. C. Lord, Jr., and Mr. R. S. McDonald for the infrared determinations.

Experimental

Chlorination of Bicyclo[2,2,1]heptane.—A mixture of 48 g. of bicyclo[2,2,1]heptane,[11] 34 g. of sulfuryl chloride, 0.25 g. of benzoyl peroxide and 40 ml. of methylene chloride was refluxed (about five hours) until no further loss of weight was observed. The mixture was filtered and fractionally distilled through a 30-cm. Vigreux column. The yield of monochloride, b. p. 88–89° (74 mm.), was 23 g. (70% based on sulfuryl chloride). The weight of dichloride, b. p. 122–123° (75 mm.), was 4 g.

Anal. Calcd. for $C_7H_{10}Cl_2$ (dichloride): C, 50.93; H, 6.10. Found: C, 51.47; H, 6.27.

The monochloride (20 g.) was refluxed for five hours with a mixture of 50 ml. of water, 50 ml. of acetone and 50 g. of sodium carbonate. The recovered chloride amounted to 5 g., b. p. 79° (46 mm.).

Rate Determinations.—Weighed samples (0.5–1 g.) of the chlorides were made up to 50.0 ml. with aqueous alcohol (80% alcohol and 20% water by volume) at room temperature. Five-milliliter samples were sealed in soft glass test-tubes and heated in a thermostat at 85.0 ± 0.1°. The reaction rate was followed by titration of the liberated acid with standard alkali.

pentachloride. The properties b. p. 66–67° (25 mm.), m. p. −5° of the chloride prepared by Komppa and Beckman are very similar to those obtained in the present work.

(11) The bicyclo[2,2,1]heptane was prepared by low-pressure hydrogenation in acetic acid over platinum oxide of bicyclo[2,2,1]2-heptene made by the method of Joshel and Butz, THIS JOURNAL, **63**, 3350 (1941), as modified by Thomas, *Ind. Eng. Chem.*, **36**, 310 (1944). The low pressure hydrogenation process is somewhat more convenient than that described by Thomas and gives no methylcyclohexane.

Summary

The peroxide-catalyzed chlorination of bicyclo-[2,2,1]heptane with sulfuryl chloride was found to give norbornyl chloride as the principal monochlorination product.

Norbornyl chloride solvolyzes in 80% ethanol at 85° nine times faster than cyclopentyl chloride.

CAMBRIDGE 39, MASSACHUSETTS

RECEIVED OCTOBER 30, 1948

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Hydroformylation of Unsaturated Compounds with a Cobalt Carbonyl Catalyst

BY HOMER ADKINS AND GEORGE KRSEK[1]

Dicobalt octacarbonyl, $Co_2(CO)_8$, proved to be quite effective and useful[2] in catalyzing the formation of aldehydes through the addition of carbon monoxide and hydrogen (H_2CO) to alkene linkages. The present paper is concerned with improvements in the method and a survey of the usefulness and of the limitations of the hydroformylation reaction. The use of a soluble cobalt catalyst was developed from the earlier work[3–6] with a Fischer–Tropsch type of insoluble catalyst. Two publications on the use of the insoluble catalyst have appeared recently.[7,8]

The hydroformylation reaction has given good results with unsaturated compounds of quite diverse structures. Hydrocarbons of the types $RCH{=}CH_2$ and $RCH{=}CHR$, allyl ethers, α,β-unsaturated esters such as acrylates, crotonates and fumarates, and allyl and vinyl acetates and allylidene diacetate added the elements of formaldehyde in good to fair yields. A summary of the numerical results is given in Table I.

The yields of aldehydes reported in the tables are based upon distillation of the reaction mixtures, titration with hydroxylamine hydrochloride, determination of refractive indices, and the chromatographic separation of 2,4-dinitrophenylhydrazones, as described in the experimental part of this paper. Since it is difficult to isolate an aldehyde without considerable loss, the yields in Table I should be interpreted in consideration of the more detailed results given in the experimental part for representative syntheses.

The reactions were run at 120–125° in benzene, under a pressure of 100–150 atm. of hydrogen and 100–150 atm. of carbon monoxide, as measured at 23°. These conditions differ from those used earlier with dicobalt octacarbonyl, in that benzene rather than ether was the reaction medium, the total pressure was lower, and the ratio of carbon monoxide to hydrogen was 1:1 instead of 2:1. Benzene was chosen as the reaction medium after a comparison of several liquids. The hydroformylation of methyl undecylenate went twice as rapidly in benzene or methylcyclohexane as in diethyl ether and three times as rapidly as in methyl formate. The reaction went as rapidly

(1) Socony-Vacuum Oil Co. Fellow, July, 1947–November, 1948.

(2) Adkins and Krsek, THIS JOURNAL, **70**, 383 (1948).

(3) Smith, Hawk and Golden, *ibid.*, **52**, 3221 (1930).

(4) Mittasch, Winkler and Urban, German Patent 539,900, *C. A.*, **26**, 2197 (1932).

(5) Otto Roelen, U. S. Patent 2,327,066 (1943).

(6) FIAT Final Report 1000. The Oxo Process. Issued by the Office of Military Government for Germany, through the Office of Technical Services of the U. S. Department of Commerce, PB81383.

(7) Keulemans, Kwantes and Van Bavel, *Rec. trav. chim.*, **67**, 299 (1948).

(8) Gresham, Brooks and Bruner, U. S. Patent 2,437,600 (1948).

in acetone as in benzene, but the yield of aldehyde isolated was lower, presumably due to condensation. The hydroformylation reaction proceeds well in a mixture of benzene and ethanol but the acetal of the aldehyde may be the chief product, as described later in the hydroformylation of ethyl acrylate.

The catalyst for hydroformylation is apparently not poisoned by sulfur compounds, as would be true of a catalytic metal such as cobalt. The reaction of carbon monoxide and hydrogen went almost as rapidly and gave approximately the same yield of aldehyde when diphenyl sulfide was present as when it was not.

The rate of reaction and temperatures required for hydroformylation, as shown by the data in Table I, are quite dependent upon the amount and ratio of catalyst to unsaturated compound. However, the yield of aldehyde isolated was usually about the same in a rapid reaction as in a slow one.

In several cases the compounds are unsymmetrically substituted derivatives of ethylene so that, depending on the direction of addition, there was a possibility of two isomeric aldehydes being produced. In four compounds of the type $RCH{=}CH_2$ where R was $-CO_2C_2H_5$, $-CH_2O_2CCH_3$ and $-CH(O_2CCH_3)_2$, addition of —CHO went exclusively to the terminal carbon, with the production of aldehydes of the type RCH_2CH_2CHO. In the case of two alkenes $(C_2H_5)_2C{=}CH_2$ and $C_2H_5C(CH_3){=}CH_2$ addition of —CHO was also exclusively to the terminal carbon. In ethyl crotonate the addition of —CHO was apparently exclusively to the carbon carrying the methyl group rather than to the one adjacent to a carbethoxy group.

In contrast with these results four alkenes of the type $RCH{=}CH_2$, where R was phenyl, or α-naphthyl, or ethoxymethyl, or *n*-butoxy, showed addition of —CHO on the substituted carbon atom. The aldehydes isolated in good yields were of the structure $RCH(CH_3)CHO$. It is probable that the isomeric aldehydes, RCH_2CH_2CHO, were also produced, but with one exception they were not isolated. The absorption of hydrogen and carbon monoxide in the hydroformylation indicated a much higher yield of aldehyde than the 29–31% actually isolated in the four cases just mentioned.

Derivatives of ethylene of the type $RCH{=}CH_2$, where R was *n*-C_4H_9-, *n*-$C_{16}H_{33}$-, $-(CH_2)_8CO_2CH_3$, $-CH_2OC_6H_5$, $-CH_2OC_2H_5$ and $-O_2CCH_3$, all gave mixtures of aldehydes of the types RCH_2CH_2CHO and $RCH(CH_3)CHO$. The alkene $C_2H_5CH{=}CHCH_3$ also gave a mixture of $C_2H_5CH_2CH(CH_3)CHO$ and $(C_2H_5)_2CHCHO$. It is possible that the starting materials in the case of the hydrocarbons and methyl undecylenate were not homogeneous with respect to the position of the double bond, or that migration of the double bond took place during reaction.[7] However, there can be no doubt that vinyl acetate and the allyl ethers underwent simultaneous addition of —CHO at both the terminal and the secondary carbon atom.

Certain α,β-unsaturated carbonyl compounds were reduced without hydroformylation, through the action of hydrogen in the presence of cobalt carbonyls. Crotonaldehyde and acrolein were reduced to butyraldehyde and propionaldehyde, respectively, while methyl vinyl ketone and mesityl oxide gave methyl ethyl ketone and methyl isobutyl ketone. Similarly ethyl cinnamate and ethyl β-(2-furan)-acrylate gave ethyl β-phenylpropionate and ethyl β-(2-furan)-propionate. The yields with the aldehydes were 40–50% while with the ketones and esters they were in the range 70–90%. Higher yields could no doubt be obtained if the optimum conditions for the hydrogenation and isolation of the products were sought. The hydrogenation of the α,β-unsaturated carboxy compounds was apparently catalyzed by a compound soluble in benzene whose activity was not adversely affected by the addition of diphenyl sulfide (1.2 g.) to the cobalt carbonyl (1.6 g.).

Acrolein diethyl acetal, α-vinylfuran and acrylonitrile absorbed 50–75% of the amount of hydrogen and carbon monoxide required for complete hydroformylation. Apparently the desired reaction took place, but no aldehyde could be isolated from the reaction mixtures, although qualitative tests showed them to be present. It appeared that the aldehyde first formed underwent further reaction. 1,2-Dihydronaphthalene, 2-(4-methylphenyl)-propene-1,11-bromododecene-1, 5-bromo-pentene-1 and allyl chloride absorbed about 50% as much gas as required for complete hydroformylation but aldehydes were not found in the reaction mixture. In the case of the compounds containing a halogen, all of the cobalt present in the reaction mixture was converted to a cobalt halide. 1-Phenyl-butadiene-1,3, phenylacetylene, Δ^9-octalin, phenanthrene, furan and acetonylacetone did not react at an appreciable rate when exposed to carbon monoxide and hydrogen at 125° with dicobalt octacarbonyl in benzene.

Experimental Part

Attention is again called to the precautions necessary in handling carbon monoxide and metal carbonyls. The methods described in the preceding paper[2] were in general followed except that dicobalt carbonyl was prepared in benzene rather than in ether. Some of the unsaturated compounds were obtained from commercial sources, *i. e.*, butyl vinyl ether, $n^{25}D$ 1.3991, and allylidene diacetate, $n^{25}D$ 1.4172, from Carbide and Carbon Chemicals Corporation; allyl alcohol and acrolein from Shell Chemical Company; vinyl acetate, $n^{25}D$ 1.3934, from the Niacet Company; and ethyl acrylate, $n^{25}D$ 1.4037, from the Rohm and Haas Company. Several compounds were made by dehydration of alcohols over various catalysts: cyclopentanol over sulfuric acid to cyclopentene $n^{25}D$ 1.4183; 2-(1-naphthyl)-ethanol over potassium hydroxide at 165° (16 mm.) to α-vinylnaphthalene,[9] $n^{25}D$ 1.6420; and β-decalol over zinc chloride at 180° to a mixture of

(9) Cohen and Warren, *J. Chem. Soc.*, 1318 (1937).

TABLE I

HYDROFORMYLATION OF CARBON TO CARBON DOUBLE BONDS

Compounds	Time, min.	Comp. cat., g./g.		% yield of aldehyde	B. p. °C.	B. p. Mm.	M. p., °C.	$n^{25}D$
Allyl acetate	32	60	1.8	75 γ-Acetoxybutyraldehyde				
Allyl acetate	80	60	1.2	70 γ-Acetoxybutyraldehyde				
Allyl acetate	300	60	0.3	55 γ-Acetoxybutyraldehyde				
Butyl vinyl ether	105	25	0.6	31 α-Butoxypropionaldehyde	55	26	78–79[c]	1.4150
Cyclopentene	100	23	0.6	65 Cyclopentanealdehyde[16]	133–136	746	123–124[a]	1.4406
Ethyl crotonate	80	50	0.6	71 Ethyl β-formylbutyrate	58–59	0.01	67–68[c]	1.4236
Diethyl fumarate	12	35	1.6	51 Diethyl α-formylsuccinate[18]	104–105	0.04	100–101[b]	1.4486
2-Ethyl-butene-1	120	42	2.0	55 β-Ethylvaleraldehyde	50–51	20	139–140[a]	1.4135
Styrene	53	26	3.6	30 Hydratropaldehyde[19]	76–77	0.08	153–154[a]	1.5148
Allyl alcohol	60	29	2.2	18 γ-Hydroxybutyraldehyde[20]	98–99	35		1.4381
α-Vinylnaphthalene	100	31	0.6	29 α-(1Naphthyl)-propionaldehyde[21]	142–143	3	206–207[a]	1.6086
2-Methyl-butene-1	140	25	0.6	53 β-Methylvaleraldehyde[22]	35–36	28	126–127[a] 93–94[c]	
Ethylene	25	5.6	7.8	50 Propionaldehyde[23]	45–51	746	123–124[b]	1.3614
Ethylene[e]	30	5.6	21.0	62 Propionaldehyde				
Allylidene diacetate	10	51	2.7	75 Succindialdehyde-1,1-diacetate				
Allylidene diacetate	90	51	0.5	75 Succindialdehyde-1,1-diacetate	102–103	0.04		1.4030
Ethyl acrylate	16	65	1.2	74 β-Carbethoxypropionaldehyde				
Ethyl acrylate	150	65	0.3	74 β-Carbethoxypropionaldehyde				
Ethyl acrylate[d]	30	65	1.3	71 β-Carbethoxypropionaldehyde[18]	68–69	7	136.5–137.5[a]	1.4212
Vinyl acetate	15	43	4.2	30 α-Acetoxypropionaldehyde[15]	41–42	8	162–163[a]	1.4160
				22 β-Acetoxypropionaldehyde				
Hexene-1	15	20	2.4	32 *n*-Heptaldehyde				
				32 2-Methylhexaldehyde	38–39	9		1.4088–1.4100
Pentene-2	33	25	2.2	75 C_6 Aldehydes	28–29	10		1.4009
Methyl undecylenate	25	30	1.6	71 C_{13} Aldehydes	134	0.6		1.4432
Octadecene-1	15	62	2.1	54 C_{19} Aldehydes	40–65	1		
Octalins	120	26	2.4	32 C_{11} Aldehydes				
Allyl phenyl ether	50	50	0.6	50 C_{10} Aldehydes				
Allyl ethyl ether	40	15	0.6	30 β-Ethoxyisobutyraldehyde[17]	64–65	743	77–78[c]	1.3856
				6 Methylacrolein				
				4 γ-Ethoxybutyraldehyde	59–60	1	102–103[c]	1.4245

[a] Semicarbazone. [b] *p*-Nitrophenylhydrazone. [c] 2,4-Dinitrophenylhydrazone. [d] Reaction at 70° with hydrogen only. [e] 1.2 g. of diphenyl sulfide in reaction mixture.

octalins,[10] $n^{25}D$ 1.4926–1.4955. Hexene-1, $n^{25}D$ 1.3863, 2-methylbutene-1, $n^{25}D$ 1.3760, octadecane-1, $n^{25}D$ 1.4435, and 2-ethylbutene-1, $n^{25}D$ 1.3952, were made by the pyrolysis of the acetates of the corresponding primary alcohols as described by Marvel and his associates.[11] Hexene-1 was also made by the reaction of allyl chloride and *n*-propylmagnesium bromide[12] and by the dehydration of *n*-hexanol through the Tschugaev reaction. The products from all three preparations had the same refractive index. Methyl undecylenate, $n^{25}D$ 1.4381, ethyl crotonate, $n^{25}D$ 1.4230, diethyl fumarate, $n^{25}D$ 1.4395, and allyl acetate, $n^{25}D$ 1.4026, were prepared by esterification of the alcohols with the acids or acetic anhydride. Allyl phenyl ether, $n^{25}D$ 1.5181, was prepared from allyl bromide and phenol in the presence of potassium bicarbonate and allyl ethyl ether, $n^{25}D$ 1.3856, from ethyl bromide and the sodium alkoxide of allyl alcohol.[13]

The distillation of aldehydes was usually carried out in an atmosphere of hydrogen, even when distillations were made at low pressures. In most cases about 0.1 g. of hydroquinone was added to a mixture before distillation. All distillations were made at as low a pressure and as rapidly as was feasible. Some of the physical properties of the products obtained and of their derivatives are given in Tables I and II.

The estimation of aldehydes by titration[14] was made as follows. A freshly prepared 4% solution (4 ml.) of hydroxylamine hydrochloride and 3 drops of a methyl orange solution were placed in a 50-ml. Erlenmeyer and the solution made neutral with dilute sodium hydroxide. About 0.002 mole of aldehyde was added and the solution allowed to stand about fifteen minutes in a stoppered flask. The free acid was then titrated with 0.1 *N* sodium hydroxide solution. The per cent. of aldehyde in the sample is given by the expression ml. of base × *N* of base × mol. wt. of aldehyde × 100 divided by the weight of the sample. In order to secure accurate results with the hydroxylamine method it is necessary that hydroxylamine hydrochloride be in about a 20% molecular excess over the aldehyde, so that in the directions given above the size of the sample titrated is specified in terms of the amount of aldehyde added and *not* in terms of the weight of sample. Thus in order to secure good results several titrations may be necessary before the proper weight of sample is ascertained. The method has given accurate results with pure samples of propionaldehyde, butyraldehyde and acetone.

Chromatographic Separation of 2,4-Dinitrophenylhydrazones.—Sixty grams of acid-washed alumina (Merck No. 8R1605) was placed in an absorbent column containing 50 ml. of dry petroleum ether. A column 1.4 × 25 cm. with a 19/22 ground glass joint and fritted glass plate, as designed by Zechmeister and sold by Scientific Glass Apparatus Co., was used. The alumina was added slowly through a funnel and the column was tapped gently during

(10) Hückel, *Ann.*, **543**, 210 (1910).
(11) Marvel, Myers and Saunders, THIS JOURNAL, **70**, 1695 (1948).
(12) Kazanski, Lieberman, Plate, Rosengart and Tarasova, *C. A.*, **42**, 2226 (1948).
(13) "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 26.
(14) Halasz, *Ann. chim.*, **14**, 336 (1940).
(15) Nef, *Ann.*, **335**, 266 (1904).
(16) Braun, Anton, Keller and Manz, *Ber.*, **67B**, 223 (1934).
(17) Bruhl, *Ann.*, **200**, 178 (1879).
(18) Stolle and Bolle, *Helv. Chim. Acta*, **21**, 1551 (1938).
(19) Wooten, *J. Chem. Soc.*, 409 (1910).
(20) Paul and Tchelitcheff, *Bull. soc. chim.*, 201 (1948).
(21) Fieser, Joshel and Seligman, THIS JOURNAL, **61**, 2137 (1939).
(22) Levene, Rothen and Kuna, *J. Biol. Chem.*, **111**, 744 (1935).
(23) Bruhl, *Ann.*, **200**, 80 (1880).

TABLE II

ANALYSES OF ALDEHYDES AND DERIVATIVES

Mol. form.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
α-Butoxypropionaldehyde[c]				
$C_7H_{14}O_2$	64.6	64.4	10.9	10.7
$C_{13}H_{18}N_4O_5$[a]	50.3	50.5	5.9	6.0
Ethyl β-formylbutyrate[d]				
$C_7H_{12}O_3$	58.3	58.5	8.4	8.5
$C_{13}H_{16}N_4O_6$[a]	48.1	47.9	5.0	5.2
β-Ethylvaleraldehyde[e]				
$C_7H_{14}O$	73.6	73.4	12.4	12.6
$C_8H_{17}N_3O$[b]	57.4	57.2	10.0	10.0
Succindialdehyde-1,1-diacetate				
$C_8H_{12}O_5$	51.1	51.0	6.4	6.6
γ-Acetoxybutyraldehyde[f]				
$C_6H_{10}O_3$	55.4	55.4	7.8	8.0
$C_{12}H_{14}N_4O_6$[a]	46.4	46.1	4.6	4.7
γ-Acetoxybutyric acid				
$C_6H_{10}O_4$	49.3	49.3	6.7	7.1
β-Ethoxyisobutyraldehyde				
$C_{12}H_{16}N_4O_5$[a]	48.7	48.9	5.4	5.4

[a] 2,4-Dinitrophenylhydrazone. [b] Semicarbazone. [c] The aldehyde was converted by hydrogenation to 2-butoxypropanol-1, $n^{25}D$ 1.4184, b. p. 81° (24 mm.). [d] The aldehyde was converted by oxidation with air to monoethyl α-methylsuccinate. [e] The aldehyde and its derivatives were also prepared by a Grignard synthesis from 2-ethylbutanol-1 and orthoformic ester. [f] The aldehyde was converted by air oxidation to γ-acetoxybutyric acid, b. p. 113° (1 mm.), $n^{25}D$ 1.4343, and its lactone.

this addition. The hydrazone(s) (240 mg.) in petroleum ether (400 ml.) was passed into the column under a positive pressure of about 0.1 atm. The band of the absorbed hydrazone was 30–60 mm. in length depending upon the compound(s). Usually the band was developed with a solution of dry benzene in petroleum ether passed into the column under a pressure of 0.1 atm. The volume of solvent was 4–7 l. in most cases containing about 10% of benzene. However, there was considerable variation in the ratio of the solvents depending upon the solubility of the hydrazones. Petroleum ether (6 l.) without benzene was used with the hydrazone of γ-acetoxybutyraldehyde, while a solution (5 l.) containing 20% benzene was used with the hydrazone of α-butoxypropionaldehyde. The petroleum ether had a boiling range of 60–68°. The band was in most cases spread over almost all the length of the column. The column of alumina was removed from the tube and in most instances cut into five or six sections. Each section was extracted with diethyl ether and the 2,4-dinitrophenylhydrazone recovered for determination of m. p. and analysis where necessary. The weight of hydrazone recovered was usually of the order of 85–90% of that placed on the column.

Air Oxidation of Aldehydes.—Aldehydes were in several cases oxidized with air to the corresponding acids. A typical procedure was as follows: γ-acetoxybutyraldehyde (29.2 g., 94% pure) and 0.2 g. of manganese dioxide or cobalt acetate was placed above a fritted glass plate sealed in a U-tube so that air could be blown up through the plate and the sample of aldehyde. The U-tube was held in an oil-bath at 65 ± 5° and was provided with a reflux condenser. Air was passed in rapidly for a period of twenty-four hours. The crude acid (31 g.) after the removal of the manganese dioxide showed a neutral equivalent of 142. After fractionation γ-acetoxybutyric acid (25.5 g., b. p. 111–113° (1 mm.), $n^{25}D$ 1.4343) was obtained having a neutral equivalent of 144 and a saponification equivalent of 145. The calculated values for the pure acetoxy acid are 146.

Ethyl β-Formylbutyrate.—In a representative experiment 50 g. of ethyl crotonate and 0.6 g. of dicobalt octacarbonyl in 70 ml. of benzene were placed in a chrome vanadium steel reaction vessel having a void of 270 ml. Carbon monoxide was added to a pressure of 1800 p. s. i. and hydrogen to a total pressure of 3600 p. s. i. After shaking for one minute the total pressure was 3500 p. s. i. at 23°. The vessel with rocking was heated within twenty minutes to 125° and 4600 p. s. i. During eighty minutes with rocking, the pressure decreased to 2200 p. s. i. at 125°. The vessel was then allowed to cool to 23° when the pressure was 1600 p. s. i. The gases were then burned by releasing them through a Bunsen burner. The contents and washings of the reaction vessel were transferred to a 250-ml. bottle, stoppered and centrifuged. The solvent was distilled under reduced pressure and the product through a Vigreux column (1 cm. i. d., 15 cm. long). The product (50.1 g.) distilled at 96–100° (30 mm.), and was 95% pure according to titration. Upon refractionation the product had the properties given in Table I.

The 2,4-dinitrophenylhydrazone (120 mg.) was chromatographed as described above. After the alumina column was cut into six portions there was obtained six yellow crystalline portions of the derivative: 6.1 mg., no m. p.; 22.1 mg., m. p. 66–67°; 46.2 mg., m. p. 67–68°; 21.1 mg., m. p. 67–68°; 9.4 mg., m. p. 66–67°; and 5.2 mg., no m. p. These results indicate that the derivative of only one aldehyde was present.

Succindialdehyde-1,1-diacetate.—Allylidene diacetate (51 g.) and 0.5 g. of dicobalt octacarbonyl in 70 ml. of benzene, were subjected to conditions similar to those described above for ethyl crotonate. The original pressure at room temperature was 2650 p. s. i., the maximum observed pressure at 125° was 3400 p. s. i., and after reaction it was 1800 p. s. i. or 1200 p. s. i. at room temperature. The gas absorption was thus approximately 0.57 mole while 0.67 mole would be required if one mole each of hydrogen and carbon monoxide had been absorbed per mole of allylidene diacetate.

The distillation of the product was carried out in an apparatus consisting of two 250-ml. bulbs connected with a short piece of glass tubing 2.5 cm. in diameter. An opening for the insertion of a thermometer was provided in this tube. One bulb of the flask was placed in an oil-bath and the other was cooled with solid carbon dioxide. The second bulb was provided with a side-arm of glass tubing 2 mm. in diameter for connection to the oil pump and for pouring out the product after distillation. The product was distilled as rapidly as possible at 50–110° (0.8 mm.). The distillate (53.6 g.) showed 90% aldehyde by titration. Pure succinaldehyde-1,1-diacetate $n^{25}D$ 1.4030 was distilled at 102–103° (0.04) through a Vigreux column, as described above for ethyl β-formylbutyrate. If quantities as large as 50 g. are subjected to fractionation there is likely to be condensation before fractionation is complete. It was therefore necessary to carry out fractionations, intended to give pure aldehyde, upon quantities of the order of 10 g.

For purposes of characterization succindialdehyde-1,1-diacetate (0.5 g.) was hydrolyzed by shaking for five minutes in 9 ml. of a water solution containing 0.6 g. of sodium hydroxide and 3 ml. of alcohol. A solution of 1.5 g. of hydroxylamine hydrochloride in 8 ml. of water was added and the mixture warmed in a steam-bath for ten minutes. The crude dioxime of succindialdehyde was obtained by cooling the mixture in an ice-bath. After recrystallization from a mixture of water and ethanol the dioxime showed a m. p. 122–123°.[24] The 2,4-dinitrophenylhydrazone of succindialdehyde, m. p. 278–279°, was also prepared.[25]

(24) Willstätter and Heubner, *Ber.*, **40**, 3872 (1907).

(25) Keagle and Hartung, THIS JOURNAL, **68**, 1609 (1948).

β-Carbethoxypropionaldehyde.—Ethyl acrylate (65 g.) and 1.2 g. of dicobalt octacarbonyl in 50 ml. of benzene was hydroformylated as described above in sixteen minutes. The pressures at room temperature were 3500 and 1100 p. s. i. at the beginning and end of the reaction with a maximum of 4550 p. s. i. at 125°. The gas absorption was 75–80% of the theoretical amount. A product of 61.7 g., b. p. 70–80° (10 mm.), and 98% pure was obtained. Refractionation gave a product which according to titration was 99% pure. In a similar experiment with 50 g. of ethyl acrylate and 1.3 g. of dicobalt octacarbonyl 1.5 g. of diphenyl sulfide was added to the reaction mixture. The absorption of hydrogen and carbon monoxide required thirty minutes and the yield of aldehyde was 71% of the theoretical as compared with 74% for the reaction mixture not containing diphenyl sulfide.

α-(1-Naphthyl)-propionaldehyde.—The hydroformylation of α-vinylnaphthalene (31 g.) was carried out in the usual way and the drop in pressure (1050 p. s. i. at 23°) corresponded to the absorption of approximately a mole each of hydrogen and carbon monoxide per mole of unsaturated compound. Fractionation of the product gave 26 g., b. p. 110–150° (3 mm.), which by titration was 45% aldehyde. Refractionation gave a product 142–143° (3 mm.) which was by titration 96% pure.

Ethoxybutyraldehydes.—Allyl ethyl ether (15 g.) was hydroformylated in the usual way. Distillation of the products gave 21 g., b. p. 30–70° (20 mm.), which by titration was 41% aldehydes. This corresponds to a 41% yield of ethoxybutyraldehydes. Another hydroformylation on 36 g. of allyl ethyl ether gave a 40% yield of aldehydes. Refractionation of the crude product gave a mixture which titrated 97% aldehyde, b. p. 51–54° (20 mm.), $n^{25}D$ 1.4118. The mixture of 2,4-dinitrophenylhydrazones obtained from the mixture melted over the range 48–53°. Through chromatographing there was obtained, from 248 mg. of the mixture of hydrazones, 21.4 mg. (yellow) m. p. 88–89°, 28.3 mg. (red) m. p. 172–175°, 17.2 mg. (orange) m. p. 55–62°, 70 mg. (yellow) m. p. 75–76°, 87.7 mg. (yellow) m. p. 77–78° and 9.4 mg. of an oil. The derivative m. p. 88–89° corresponds to γ-ethoxybutyraldehyde,[26] while that of m. p. 77–78° is apparently that of β-ethoxyisobutyraldehyde. The α-ethoxybutyraldehyde has a much higher m. p. of 135°.[27]

α- and β-Acetoxy-propionaldehydes.—Vinyl acetate (45 g.) and 3.6 g. of dicobalt octacarbonyl in 70 ml. of benzene was hydroformylated in the usual way, the drop in pressure being from 3500 to 1700 p. s. i. as measured at 23°, corresponding to the absorption of about 0.7 mole of hydrogen and carbon monoxide for 0.5 mole of vinyl acetate. Distillation of the reaction mixture gave 31.1 g., b. p. 45–70° (8 mm.), which contained according to titration 91% of the aldehydes. Fractionation gave 15.4 g. b. p. 46–52° (8 mm.) and 9.0 g., b. p. 62–66° (8 mm.). These fractions each contain 90–94% aldehyde. Refractionation of the lower boiling sample gave α-acetoxypropionaldehyde 98% pure, b. p. 41–42° (8 mm.), $n^{25}D$ 1.4160. The aldehyde was characterized by its semicarbazone, m. p. 162–163°. The higher boiling β-acetoxypropionaldehyde could not be purified beyond 90%. The compound was characterized by hydrogenation to propanediol-1,3 and the formation of the bis-phenylurethan, m. p. 136–137°, of the glycol.

Diethylacetal of β-Carbethoxypropionaldehyde.—Ethyl acrylate (50 g.) and 1.3 g. of dicobalt octacarbonyl in 20 ml. of benzene and 50 ml. of dry ethanol was hydroformylated in the usual way and the products separated by fractionation. There was obtained 28.6 g. (98% pure) of β-carbethoxypropionaldehyde b. p. 86–92° (15 mm.), and 23.3 g. of the diethylacetal of β-carbethoxypropionaldehyde, b. p. 100–103° (10 mm.), $n^{25}D$ 1.4180.[28] Another experiment showed that β-carbethoxypropionaldehyde (46 g.) could be converted to its diethyl acetal (43.8 g.) under the conditions used for the hydroformylation. The formation of the acetal was avoided by carrying out the hydroformylation of ethyl acrylate in benzene free of alcohol.

Reduction of Ethyl 2-Furanacrylate with a Cobalt Carbonyl Catalyst.—Ethyl β-(2-furan)-acrylate (37 g.) and 0.6 g. of dicobalt octacarbonyl in 85 ml. of benzene, under a pressure of 4700 p. s. i. of equal parts hydrogen and carbon monoxide at 125° was rocked for six and one-half hours. The pressure dropped to 3700 p. s. i. during the period. After the usual procedures there was obtained 34.3 g. of ethyl β-(2-furan)-propionate b. p. 94–98° (4 mm.) $n^{25}D$ 1.4812.[29] The saponification equivalent of the product was 167 as compared with a calculated value of 168.

Summary

The hydroformylation of several unsaturated hydrocarbons, ethers and esters, through the use of dicobalt octacarbonyl in benzene at 100–300 atmospheres of carbon monoxide and hydrogen, has given good yields of aldehydes free of isomers. The reaction of substituted ethylenes of the types $RCH{=}CH_2$ and $R_2C{=}CH_2$ have given in six cases aldehydes of the type RCH_2CH_2CHO and R_2CHCH_2CHO. However, where R was phenyl, 1-naphthyl, *n*-butoxy, acetoxy and ethoxymethyl, aldehydes of the type $RCH(CH_3)CHO$ were produced. Three alkenes of the type $RCH{=}CHR'$ have given good yields of a single aldehyde.

Some of the limitations of the reaction, due to the formation of mixtures of aldehydes or the failure of the hydroformylation reaction to take place, have been illustrated. The presence of a sulfur containing compound in the reaction mixture did not significantly poison the catalytic activity of the benzene soluble cobalt carbonyl catalyst. This catalyst has proven to be effective for the hydrogenation of the carbon to carbon double bond in certain α,β-unsaturated carbonyl compounds.

MADISON, WISCONSIN RECEIVED FEBRUARY 14, 1949

(26) Paul and Tchelitcheff, *Bull. soc. chim.*, 201 (1948).

(27) Dworzak and Pierri, *Monatsh.*, **52**, 143 (1929).

(28) Carrière, *Ann. chim.*, **17**, 99 (1922).

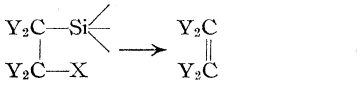
(29) Hughes and Johnson, THIS JOURNAL, **53**, 742 (1931).

[CONTRIBUTION FROM THE WHITMORE LABORATORY OF THE SCHOOL OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE COLLEGE]

γ-Eliminations Involving Silicon. A New Synthesis of the Cyclopropane Ring[1]

BY LEO H. SOMMER, RICHARD E. VAN STRIEN[2] AND FRANK C. WHITMORE[3]

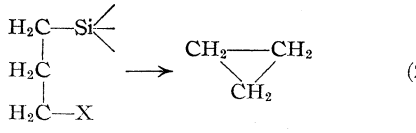
In previous work[4] we found that the remarkable reactivity of halogen bound to carbon in the beta relation to silicon (X—C—C—Si≡) is associated with cleavage of the carbon–silicon bond. Many examples of this type of reaction have been found. All take place according to the general equation



(1)

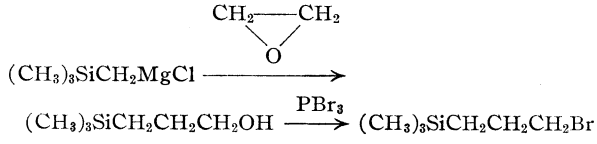
Equation (1) shows that these reactions are β-eliminations involving silicon, formally similar to the dehydrohalogenation of ordinary organic halides.

In extension of this work we have investigated the reactions of γ-haloalkyl silicon compounds and now report two γ-eliminations involving silicon which give cyclopropane.

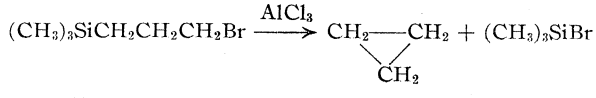


(2)

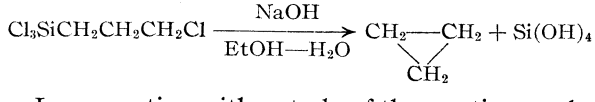
γ-Bromopropyltrimethylsilane was synthesized by the following sequence of reactions.



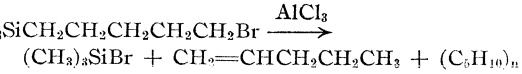
Warming with a catalytic amount of aluminum chloride gave a 92% yield of pure cyclopropane.



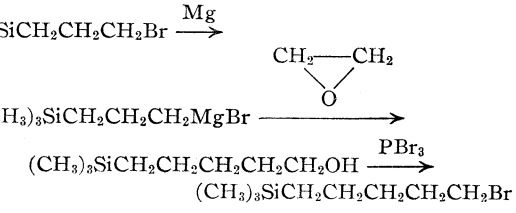
γ-Chloropropyltrichlorosilane also gave pure cyclopropane (31% yield) when heated with a solution of sodium hydroxide in aqueous ethanol.



In connection with a study of the reaction mechanisms of these γ-eliminations, it was found that when the reagents are interchanged, *i. e.*, γ-bromopropyltrimethylsilane is treated with base and γ-chloropropyltrichlorosilane is treated with aluminum chloride, no cyclopropane is formed. Furthermore, 5-bromopentyltrimethylsilane failed to give cyclopentane when treated with aluminum chloride in catalytic amounts.[5] Instead, somewhat impure 1-pentene was obtained in low yield. The other products were polymers, presumably polyamylenes, and trimethylbromosilane.



5-Bromopentyltrimethylsilane was synthesized from γ-bromopropyltrimethylsilane by the reaction sequence



Experimental

Synthesis of γ-Bromopropyltrimethylsilane.—Ethylene oxide, 10 moles, dissolved in 750 cc. of dry ether was added to the Grignard reagent prepared from 5 moles of chloromethyltrimethylsilane. The reaction mixture was stirred for three days and then 1 liter of ether was distilled and replaced by 1 liter of dry benzene. After refluxing for twenty hours, the product was treated with 500 cc. of water followed by 3 liters of 10% hydrochloric acid. The organic layer was separated and the water layer extracted once with ether. After washing the ether–benzene solution of the product with saturated salt solution and drying with sodium sulfate, the ether and most of the benzene were removed by fractionation in a column of about 15 theoretical plates and the remaining material was rapidly distilled from a 1-liter distillation flask. This distillate was then fractionated in a glass-helix packed column of about 15 theoretical plates. There was obtained 468 g., 3.57 moles, of γ-hydroxypropyltrimethylsilane, b. p. 83° at 27 mm., $n^{20}D$ 1.4290, d^{20} 0.8316, a yield of 71%.

Anal. Calcd. for $C_6H_{16}SiO$: Si, 21.2. Found: Si, 21.3.

In a 1-liter flask equipped with a stirrer, reflux condenser and dropping funnel there was placed 326 g. (2.47 moles) of γ-hydroxypropyltrimethylsilane. The flask was cooled in an ice-bath and 350 g., 1.29 moles, of phosphorus tribromide was slowly added to the alcohol. After completion of the addition, the reaction mixture was allowed to warm to room temperature. This was followed by heating (85–90°) for a period of four hours. After cooling to room temperature, the reaction product was poured on ice and the resulting layers were separated. The organic layer was washed with water and then with dilute potassium carbonate solution. Drying was effected with sodium sulfate. Fractionation gave 404 g., 2.07 moles, of γ-bromopropyltrimethylsilane, b. p. 70° (25 mm.), $n^{20}D$ 1.4541, d^{20} 1.1173, a yield of 84%.

Anal. Calcd. for $C_6H_{15}SiBr$: Si, 14.4; Br, 41.0. Found: Si, 14.6; Br, 41.3.

(1) XXIII in a series on organosilicon chemistry. For XXII see THIS JOURNAL, **71**, 2746 (1949).

(2) Taken in part from a thesis submitted by R. E. Van Strien in partial fulfillment of the requirements for the Ph.D. degree.

(3) Deceased June 24, 1947.

(4) (a) Sommer, Goldberg, Dorfman and Whitmore, THIS JOURNAL, **68**, 1083 (1946); (b) Sommer, Bailey and Whitmore, *ibid.*, **70**, 2869 (1948).

(5) When cyclopentane (10 g.) is refluxed with aluminum chloride (3 g.) for eight hours no change takes place; see Cox, *Bull. soc. chim.*, **37**, 1549 (1925).

Cyclopropane Formation from γ-Bromopropyltrimethylsilane.—The procedure used was as follows: The γ-bromopropyltrimethylsilane was placed in a 100-cc. flask equipped with a reflux condenser and a dropping bottle for introduction of aluminum chloride. The exit end of the condenser led to a 5-liter flask filled with saturated salt solution which was used to measure the volume of gas evolved.

γ-Bromopropyltrimethylsilane, 19.1 g., 0.098 mole was placed in the reaction flask and treated with a few crystals of sublimed aluminum chloride (*ca.* 0.2 g.). Reaction was spontaneous and the reaction mixture became somewhat cooler than room temperature. After most of the reaction had taken place, gentle heating was applied by means of a water-bath held at 70°. Air was then passed into the reaction flask in order to sweep all of the gaseous product into the receiving flask. The gas mixture collected comprised 2960 cc. of which 670 cc. was shown to be air by gas analysis.

A sample of the gas mixture was condensed in a trap cooled in Dry Ice acetone mixture, and was then charged to the isothermal distillation apparatus of Zook, Oakwood and Whitmore.[6] After removal of air, a series of vapor pressure–temperature measurements were made and the data were plotted for comparison with cyclopropane and propylene.[7] Figure 1 shows that the gaseous product of the reaction is pure cyclopropane. The yield was 92%.

The material remaining in the reaction flask consisted of 12.5 g., 82% yield, of trimethylbromosilane, b. p. 79° (732 mm.)[8]; Br, 52.4 (calcd., 52.3).

Formation of Cyclopropane from γ-Chloropropyltrichlorosilane.—In a 500-cc. flask equipped with a reflux condenser connected to a gas collector, and a dropping funnel, was placed a solution of 28 g., 0.50 mole, of potassium hydroxide dissolved in 100 cc. of absolute ethanol. Then 24.6 g., 0.116 mole of γ-chloropropyltrichlorosilane[9] was slowly added to this solution. An immediate reaction took place as each portion of γ-chloropropyltrichlorosilane was added, a precipitate of potassium chloride being formed. At the end of the addition, the reaction mixture was brought to reflux. However, the volume of gas collected amounted to only 70 cc. when the reaction mixture was cooled to room temperature. To the reaction flask were then added 150 cc. of water and an additional 28 g. of potassium hydroxide. The material was once more brought to reflux and the total volume of gas collected was 1320 cc. of which 410 cc. was shown to be air.

Following a procedure similar to that used above, the gaseous product of the reaction was shown to be pure cyclopropane (see Fig. 1). The yield was 31%.

Reaction of γ-Bromopropyltrimethylsilane with Potassium Hydroxide in 50% Aqueous Ethanol.—γ-Bromopropyltrimethylsilane (0.067 mole) was treated with a solution of potassium hydroxide (56 g., 1 mole) in 50% aqueous ethanol (260 cc.) at reflux temperature for five hours. No gas was evolved. Reaction was shown to be complete by treatment of the product with silver nitrate and weighing the silver bromide formed. Apparently, normal dehydrohalogenation and/or metathesis occurred. Since the major point under investigation was formation or non-formation of cyclopropane, and because of lack of material, a larger run was not made, and the organosilicon products were not identified.

Reaction of γ-Chloropropyltrichlorosilane with Aluminum Chloride.—In a 50-cc. flask was placed 9.7 g. of γ-chloropropyltrichlorosilane. Through the top of the reflux condenser was added a few crystals of aluminum chloride. No reaction was observed at room temperature. Upon heating by means of a water-bath held at 60°, the liquid turned brown. Heating was gradually increased and the reaction mixture was finally heated for two hours at 95–97°. Throughout the heating period there was no appreciable formation of a gaseous product. After cooling, the product was distilled at reduced pressure until the temperature reached 135° at 35 mm. Distillation of this material at atmospheric pressure gave only 2.7 g. of material boiling between 60° and 180°. A residue of about 3 g. of viscous material was also not identified. The complex mixture of products obtained in this reaction are characteristic of the reaction of many organic compounds with aluminum chloride at about 100° for a number of hours.

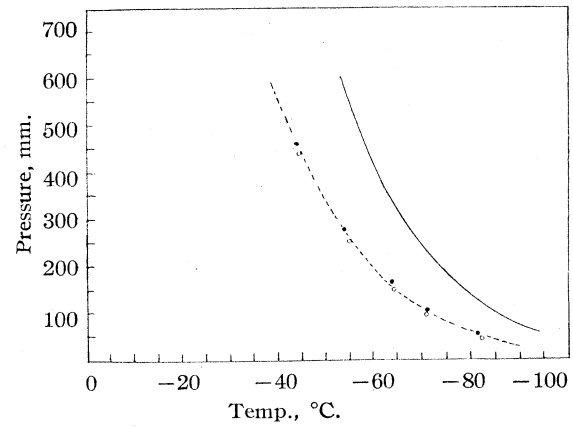


Fig. 1.—Vapor pressure curves: O, cyclopropane from γ-bromopropyltrimethylsilane; ●, cyclopropane from γ-chloropropyltrichlorosilane; ----, cyclopropane curve from the literature; —, propylene curve from the literature.

Synthesis of 5-Bromopentyltrimethylsilane.—The Grignard reagent was prepared in the usual manner from 390 g., 2 moles, of γ-bromopropyltrimethylsilane and 48 g. of magnesium turnings in 1 liter of ether. To the Grignard reagent was added 200 cc. of ethylene oxide dissolved in 150 cc. of dry ether. On standing for a period of eighteen hours at room temperature the reaction mixture solidified. This was treated with 2 liters of water followed by addition of sufficient hydrochloric acid to render the mixture acid to litmus. The water layer was extracted with pentane and the combined organic layers were washed with potassium carbonate solution and then with water. After drying with anhydrous sodium sulfate, fractionation gave 206 g., 1.3 moles, of 5-hydroxypentyltrimethylsilane, b. p. 85° at 8 mm., $n^{20}D$ 1.4371, 64% yield.

Anal. Calcd. for $C_8H_{20}SiO$: Si, 17.50. Found: Si, 17.45.

In a 100-cc. reaction flask equipped with a condenser and dropping funnel was placed 42.9 g., 0.27 mole, of 5-hydroxypentyltrimethylsilane. Phosphorus tribromide, 36 g., 0.13 mole, was then slowly added with frequent shaking of the flask. After standing at room temperature for eighteen hours, followed by heating at 95–99° for one hour, the layers were separated. Ether was added to the organic layer which was then washed twice with water and once with ammonium hydroxide. The product was dried over calcium chloride and fractionated under reduced pressure. There was obtained 47.1 g., 0.21 mole, of 5-bromopentyltrimethylsilane, b. p. 113° at 23 mm., $n^{20}D$ 1.4570, 78% yield.

Anal. Calcd. for $C_8H_{19}SiBr$: Si, 12.57; Br, 35.81. Found: Si, 12.72; Br, 35.66.

Reaction of 5-Bromopentyltrimethylsilane with Aluminum Chloride.—A 200-cc. flask was equipped with a condenser arranged for distillation. 5-Bromopentyltrimethylsilane was placed in the flask and a few small crystals of aluminum chloride were added. Reaction was spontaneous, but heat was applied to distill any volatile

(6) Design of the apparatus will be submitted for publication.

(7) (a) Ruehrwein and Powell, THIS JOURNAL, **68**, 1063 (1946); (b) Burrel and Robertson, *ibid.*, **37**, 2188 (1945).

(8) Gilliam, Meals and Sauer, THIS JOURNAL, **68**, 1161 (1946); Pray, Sommer, Goldberg, Kerr, DiGiorgio and Whitmore, *ibid.*, **70**, 433 (1948).

(9) Sommer, Dorfman, Goldberg and Whitmore, THIS JOURNAL, **68**, 488 (1946).

material which formed. Two runs, utilizing a total of 108 g., 0.485 mole, of the bromide were made.

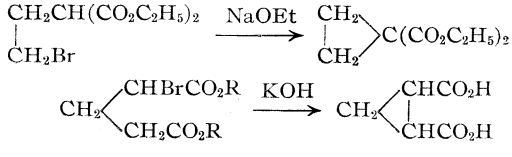
The combined distillate, 54 g., which contained trimethylbromosilane, was carefully washed with ice-water and then with potassium carbonate solution. All washings were made in capped bottles to prevent loss by volatilization. Drying was effected with sodium sulfate to give 34 g. of product. Fractionation in a column of 40 theoretical plates gave 6.0 g. of somewhat impure pentene-1, b. p. 28.6–29.5° at 732 mm., $n^{20}D$ 1.3702–1.3722, d^{20} 0.644,[10] which was identified by characterization of its ozonolysis products as formaldehyde (dimedone deriv., m. p., 189–190°) and butyraldehyde (2,4-dinitrophenylhydrazone deriv. m. p. 120–121°). The yield of impure pentene-1 was 17%. No evidence was found for formation of cyclopentane, b. p. 49.3° at 760 mm., $n^{20}D$ 1.40645, or ethylcyclopropane, b. p. 32.5°, $n^{20}D$ 1.379.[11]

In addition to pentene-1, there was also obtained from the fractionation 15.0 g., 0.098 mole, of hexamethyldisiloxane, b. p. 98°, $n^{20}D$ 1.3770, and a higher-boiling residue of 3.8 g.

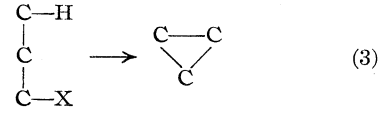
Fractionation of the material originally remaining in the reaction flask gave 20.1 g., 0.131 mole, of trimethylbromosilane, b. p. 77° at 725 mm., Br 52.6 (calcd. 52.3), and a residue of black tarry material, likely consisting of polymerized pentene. The yield of recovered material containing the trimethylsilyl group was 67%.

Discussion

Some Common Aspects of γ-Eliminations Involving Silicon and Other Syntheses of Cyclopropyl Compounds.—One of the methods for closing the cyclopropane ring involves γ-elimination of hydrogen halides from organic compounds. The following equations provide two examples of this type of synthesis.[12]

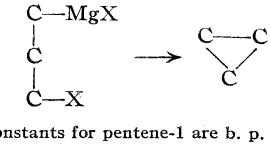


A large number of cyclopropane derivatives (but not cyclopropane itself) have been prepared by these reactions which take the general form



(3)

For the preparation of cyclopropane, reaction of an active metal such as magnesium or sodium with a 1,3-dihalopropane in an organic solvent may be used. In these reactions it seems probable that cyclopropane is formed from an organometallic intermediate.[13]



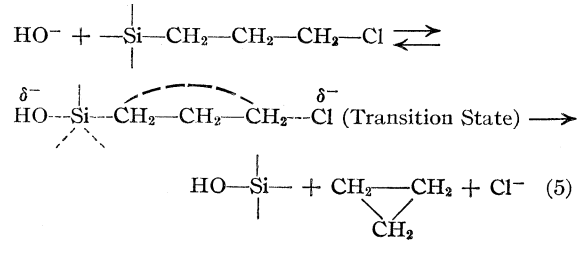
(4)

Comparison of equations (2), (3) and (4) indicates that the formation of cyclopropyl compounds from γ-haloalkyl silicon compounds and from purely organic halides are similar in three general ways: (1) Both give cyclopropyl compounds by 1:3 elimination reactions. (2) Both involve removal of an element more electropositive than carbon (silicon, hydrogen, or an active metal)[14] together with an element more electronegative than carbon (halogen). (3) Both types involve electron-release to carbon from an element more electropositive than carbon.

Similar considerations apply to a comparison of β-eliminations involving silicon with the dehydrohalogenation of purely organic halides to give olefins.[4b]

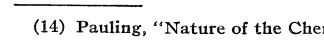
Mechanism.—β-Eliminations involving silicon are greatly accelerated by bases and take place by a one-stage mechanism involving initial nucleophilic attack on silicon. A study of the effect of structural variations in the β-haloalkylsilane on reaction velocity has shown that substitution of a single halogen on silicon by alkyl results in a tenfold decrease in rate. This relationship of structure to reactivity is the expected one for a mechanism involving nucleophilic attack on silicon since the presence of electronegative substituents should make the silicon a more effective center for nucleophilic attack.[4b]

If the mechanism of cyclopropane formation from compound II and alkali involves nucleophilic attack on silicon as the major driving force, it should follow that a decrease in the electrophilic activity of the silicon, *i. e.*, by replacement of halogen on silicon by alkyl, would result in a decrease of reaction velocity or in complete prevention of the reaction. The effect on γ-elimination should far exceed that on β-elimination because of the lesser ease of formation of cyclopropane as compared to olefin formation. The observed facts and the nucleophilic character of aqueous base are therefore in complete harmony with the following mechanism



(5)

The above mechanism is closely similar to the mechanism of γ-eliminations of purely organic compounds with bases which consist of 1:3 elimination of HX.[14a]



(10) Physical constants for pentene-1 are b. p. 30.1° at 760 mm., $n^{20}D$ 1.3714, d^{20} 0.630. See Egloff, "Physical Constants of Hydrocarbons," Vol. I, Reinhold Publishing Corporation, New York, N. Y., 1940.

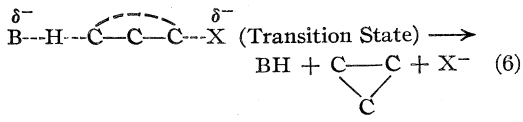
(11) See ref. 10, Vol. II.

(12) See Fuson in Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 65–67.

(13) Hass, *Ind. Eng. Chem.*, **28**, 1178 (1936).

(14) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 60.

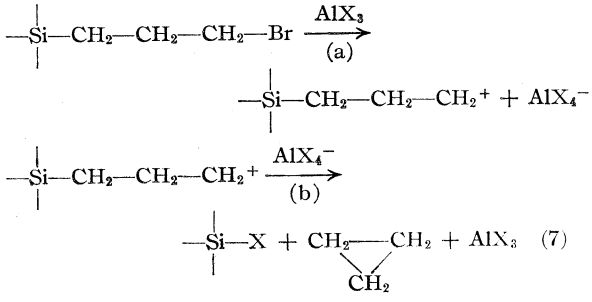
(14a) Hauser, THIS JOURNAL, **62**, 933 (1940).



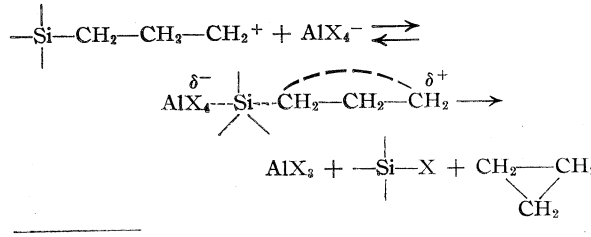
In these latter syntheses of cyclopropyl compounds nucleophilic attack on γ-hydrogen is facilitated by the activating effect of a carbonyl group adjacent to the hydrogen atom.

The only difference between the mechanisms is that in (5) the base attacks electropositive silicon instead of the protonic part of an activated hydrogen atom.

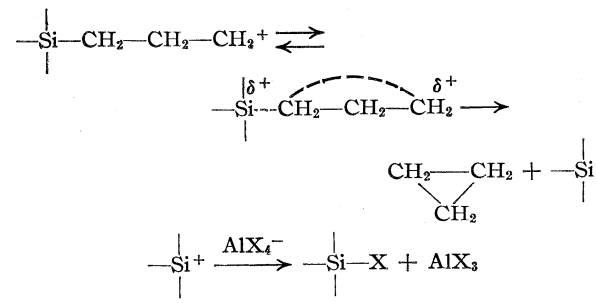
Previous work has shown that electron-release from silicon to electronically deficient carbon in the beta relation to silicon constitutes a general mechanism whereby cleavage of the carbon–silicon bond can occur in a variety of organosilicon structures.[4b] β-Eliminations involving silicon which take place with electrophilic reagents such as aluminum chloride are examples of reactions proceeding by this mechanism. The electropositive nature of silicon and the ability of aluminum chloride to cause ionization of the carbon–halogen bond make a similar mechanism seem probable for the reaction of γ-bromopropyltrimethylsilane with aluminum chloride.[15]



There are two reaction paths for the silicon in (7b) which comprise possible extremes of mechanism: (1) A transition state in which the siliconium ion is transferred to the new linkage with halogen without being set free. (2) A reaction process



in which a siliconium ion is actually set free prior to combination with halogen from AlX_4^-.



The question as to whether a siliconium ion is set free for a period of time sufficient for the designation of such an ion as an actual reaction intermediate, or is transferred to the new linkage without acquiring the full status of an ion, is an interesting one. However, we wish to make it clear that the important general aspects of the mechanism given in equation (7) in no way depend upon the degree of freedom of the siliconium ion involved. These aspects are adequately summarized by the concept that the major driving force for these reactions derives from the ability of electropositive silicon to release an electron-pair to electronically deficient carbon within the molecule, regardless of whether the silicon has started to combine with an anion at substantially the same time. Similar considerations apply to β-eliminations involving silicon which result from reaction with electrophilic reagents.[16]

The failure of 5-bromopentyltrimethylsilane to give cyclopentane when treated with aluminum chloride is in accord with the mechanism for cyclopropane formation given in (7). In 5-bromopentyltrimethylsilane the deficiency on carbon is created at a distance from silicon which is great enough to prevent an intramolecular transmission of charge sufficient for cyclization, despite the lesser strain involved in a 5-membered ring.

Summary

1. A synthesis of pure cyclopropane has been found which results from γ-elimination of silicon and halogen from two organosilicon compounds.

2. Proposed mechanisms for these γ-eliminations involve as major driving forces (1) nucleophilic attack on silicon, and (2) electrophilic attack on halogen in the group being cleaved from silicon.

3. The latter type of γ-elimination extends the applicability of the concept of electron-release from silicon to electronicallydeficient carbon as constituting *one* major factor in eliminations involving silicon. Formation of free siliconium ions

(15) The failure of γ-chloropropyltrichlorosilane to give cyclopropane with aluminum chloride is very likely due to the inhibiting effect of chlorine substituents on silicon (relative to alkyl) toward electron-release from silicon to electronically deficient carbon. For example, work on intramolecular rearrangements has shown that the replacement of only one alkyl group on silicon by a chlorine substituent completely prevents intramolecular rearrangement with aluminum chloride of $(CH_2)(CH_3)_2SiCl$ as compared to $(CH_2Cl)(CH_3)_3Si$: paper presented before the Organic Division in Chicago, April 22, 1948. These effects are readily explained on an inductive effect basis.

(16) Swain, Esteve and Jones, THIS JOURNAL, **71**, 965 (1949), have recently shown that a siliconium ion intermediate is unlikely in the reaction of triphenylfluorosilane with the relative weak electrophilic reagent, 50% water–50% acetone solution. These authors further point out, however, that their work does not preclude the possibility of siliconium ion intermediates with more powerful electrophilic reagents such as aluminum chloride.

as reaction intermediates is not a necessary condition for reactions proceeding by this mechanism. The greater or lesser degree of freedom of such ions must depend upon the organosilicon compound undergoing reaction, the attacking reagent, and the reaction medium, whereas the only essential requirement for reactions proceeding by the above mechanism is the creation of electron-deficiency at a carbon atom which is sufficiently close to the silicon so as to cause release of an electron-pair from silicon to carbon.

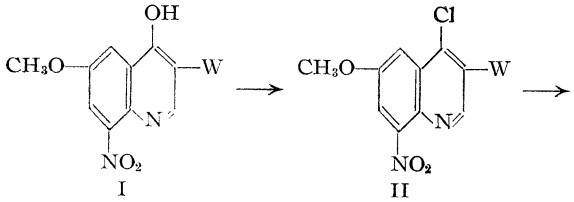
STATE COLLEGE, PA. RECEIVED FEBRUARY 25, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

6-Methoxy-8-nitroquinolines with Substituents in the 3- and 4-Positions[1]

BY ROBERT H. BAKER, J. G. VAN OOT, SAMUEL W. TINSLEY, JR., DOROTHY BUTLER AND BYRON RIEGEL

A common procedure for the replacement of hydroxyl by hydrogen in 4-quinolinols is conversion to the halide followed by reduction. Although this sequence of reactions had not been studied when other groups were in the 3-position, it appeared to be an attractive route to the 3-substituted-6-methoxy-8-aminoquinolines, III.

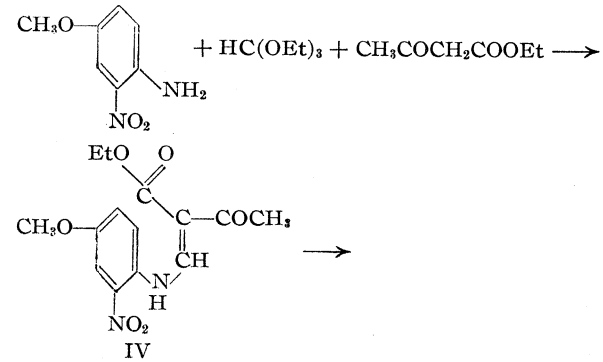


I II III

(W = CN, COOEt, C_6H_5 or CH_3CO)

The conversion to the halide, II, was difficult but could be accomplished with a mixture of phosphorus oxychloride and pentachloride.[2] However, none of a variety of conditions of hydrogenation over palladium, platinum or Raney nickel catalysts would effect reductive dehalogenation of II to III.

The preparation of 3-acetyl-6-methoxy-8-nitro-4-quinolinol (V) was accomplished by cyclization of the "anil" (IV) which in turn could be made by three methods. Direct combination of the nitroanisidine, ortho ester and keto ester is simpler but gives poorer yields than the reaction of the anisidine with ethoxymethyleneacetoacetic ester (formed by prior reaction of the latter two reagents). The third method involves reaction of the ortho ester and anisidine to give the substituted diphenylformamidine which in turn reacts with the keto ester.[3] Attempts were also made to produce ethoxymethylene-*m*-nitroanisidine which would be expected to be a useful intermediate but generally the diarylformamidine was the product.



IV V

Considerable difficulty has been encountered during "anil" formation in the use of α-formyl esters for quinolinol syntheses.[4] With formylphenylacetic ester and *m*-nitroanisidine, this difficulty is overcome by the use of zinc chloride to catalyze the reaction.

Successful attempts to prepare plasmochin-type drugs with blocking groups in the 3-position will be described in forthcoming publications.

Experimental[5]

3-Acetyl-6-methoxy-8-nitro-4-quinolinol.—Equimolar quantities of *m*-nitroanisidine and ethyl ethoxymethyleneacetoacetate were heated at 150° for fifteen minutes, cooled and the "anil" crystallized from ethanol in quantitative yield, m. p. 153–154°. This material was added to fifteen times its weight of boiling Dowtherm (a mixture of biphenyl and diphenyl ether). Eighteen minutes of

(1) This work was supported by a grant from the National Institute of Health, U. S. Public Health Service.

(2) C. C. Price, N. J. Leonard and H. F. Herbrandson, THIS JOURNAL, **68**, 1251 (1946), used thionyl chloride for this conversion on simpler compounds but we were unable to use it in this work.

(3) These combinations of reactants were previously studied by H. R. Snyder and R. E. Jones, *ibid.*, **68**, 1253 (1946).

(4) Because of this, we have previously used the α-oxalyl esters and subsequent decarboxylation, R. H. Baker and R. M. Dodson, *ibid.*, **68**, 1283 (1946); B. Riegel, C. J. Albisetti, Jr., G. R. Lappin and R. H. Baker, *ibid.*, **68**, 2685 (1946).

(5) Microanalyses by Jane Gibbs, Rosalind Guy and Virginia Hobbs.

heating was found to be the optimum time for 5 g. of "anil." The quinolinol was precipitated from the cooled reaction mixture by addition of Skellysolve "C" (petroleum ether, b. p. 85–100°). Crystallized from methanol the maximum yield was 40% of yellow plates. These change to needles at 180°, m. p. 232.5–235°.

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: N, 10.68. Found: N, 10.72.

3-Acetyl-4-chloro-6-methoxy-8-nitroquinoline.—The corresponding 4-quinolinol was covered with a large excess of freshly distilled phosphorus oxychloride and heated on the steam-bath for an hour. Fresh oxychloride was added and the solution refluxed for another hour. The excess phosphorus oxychloride was distilled at reduced pressure and the residue cooled in an ice-bath. This was slowly poured with vigorous stirring into a slurry of shaved ice. The acid was partially neutralized at 0° with sodium hydroxide. The precipitate was removed by filtration and crystallized from isopropyl alcohol (decolorized by Norit) to give fibrous white crystals, m. p. 118–119°. The yield varies greatly from run to run and has never exceeded 15%.

Anal. Calcd. for $C_{12}H_9ClN_2O_4$: N, 10.0. Found: N, 9.94.

2,2′-Dinitro-4,4′-dimethoxydiphenylformamidine.—A solution of 4.2 g. (0.025 mole) of *m*-nitroanisidine and 3.7 g. (0.025 mole) of ethyl orthoformate in 50 ml. of xylene was distilled slowly through a short distilling column until 3 ml. of alcohol and xylene had been collected. On cooling, 3 g. (69%) of red needles was obtained, m. p. 165–166°. Occasionally the product was long yellow needles, m. p. 41–42°, which appeared to be **ethoxymethylene-*m*-nitroanisidine,** but the preparation of this compound was unreliable.[6]

The formamidine was also prepared by the method of Lander.[7] 2-Nitro-4-methoxyformanilide, m. p. 142–143°, was prepared in 88% yield by refluxing 16.8 g. (0.10 mole) of the amine in 50 ml. of 50% formic acid for twelve hours and cooling to produce crystals. To a solution of 3.3 g. (0.027 mole) of the formanilide in 12.5 g. (0.08 mole) of ethyl iodide was added portionwise 10 g. of freshly prepared dry silver oxide. During the addition the mixture was diluted with 50 ml. of dry ether, and when it had all been added, the mixture was refluxed for two hours. After filtration, the solvent was evaporated and the residue crystallized from acetone, 1 g. (22%), m. p. 163–164°. Mixed with the material from the ortho ester preparation there was no depression in m. p.

Anal. Calcd. for $C_{15}H_{14}N_4O_6$: N, 16.2. Found: N, 16.1.

3-Carbethoxy-4-chloro-6-methoxy-8-nitroquinoline.—The corresponding 4-quinolinol[8] was covered with phosphorus oxychloride and heated at 100° for six hours. After cooling and pouring into a slurry of ice, the product was crystallized from Skellysolve "C" to give yellow needles, m. p. 108–109°, in 20% yield.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_5$: N, 9.34. Found: N, 9.11.

(6) Compare the preparation of ethoxymethyleneaniline, H. W. Post, "The Chemistry of the Aliphatic Ortho Esters," Reinhold Publishing Corp., New York, N. Y., 1943, pp. 87–88.

(7) H. Lander, *J. Chem. Soc.*, **83**, 414 (1903).

(8) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson and R. H. Baker, THIS JOURNAL, **68**, 1264 (1946).

Ethyl α-Phenyl-β-(2-nitro-4-methoxyanilino)-acrylate.—An equimolar mixture of *m*-nitroanisidine and ethyl formylphenylacetate[9] was heated in an oil-bath to 165–170° and then freshly fused and powdered zinc chloride (one part per ten parts of mixture) was carefully added.[10] After maintaining the temperature for twenty-five minutes, the solution was cooled, diluted with chloroform and filtered. The filtrate was evaporated and the residue crystallized from ethanol to give two crystalline modifications of red needles. The higher melting, 138–139°, was the one most readily purified.

Anal. Calcd. for $C_{18}H_{18}N_2O_5$: N, 8.19. Found: N, 8.15.

The lower melting isomer, 114–115°, was obtained by repeated crystallization from ethanol. A mixture of the two forms melted at 100°, but both forms gave the same cyclization products described below.

3-Phenyl-6-methoxy-8-nitro-4-quinolinol.—The "anil," 3.5 g., was added to 50 ml. of refluxing Dowtherm and heated for twenty-five minutes. Addition of Skellysolve "C" to the cooled solution precipitated an amorphous product which was very difficult to crystallize due to gel formation. Brown prisms, m. p. 178–180°, were produced by slow evaporation of a dilute methanol solution.

Anal. Calcd. for $C_{16}H_{12}N_2O_4$: N, 9.46. Found: N, 9.58.

3-Phenyl-4-chloro-6-methoxy-8-nitroquinoline.—The procedure described for the 3-acetyl derivative was used on the amorphous 4-quinolinol. The product was crystallized from isopropyl alcohol in white fibrous needles, m. p. 166–167°. The yield based on "anil" was 56%.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_3$: N, 8.91. Found: N, 8.33.

3-Cyano-4-chloro-6-methoxy-8-nitroquinoline.—According to the method of Snyder and Jones[3] 0.25 mole each of *m*-nitroanisidine, 42 g., ethyl orthoformate, 37 g., and ethyl cyanoacetate, 28 g., were mixed and heated at 160–165° until no more ethanol distilled. The "anil," m. p. 160–164°, was cyclized by refluxing for four hours in ten times its weight of Dowtherm. The product obtained by dilution with Skellysolve "C" was crystallized from acetic acid to give 8 g., 13%, of yellow needles, m. p. about 320°. This crude quinolinol was covered with an excess of a 3:1 mixture of phosphorus oxychloride and pentachloride and refluxed for five hours. The product worked up as previously described and crystallized from ethanol gave yellow needles, m. p. 194–195°, in 80% yield.

Anal. Calcd. for $C_{11}H_6ClN_3O_3$: N, 15.9. Found: N, 15.6.

Summary

6-Methoxy-8-nitro-4-quinolinols with cyano, carbethoxy, acetyl and phenyl groups in the 3-position have been described. These have been converted into the corresponding 4-chloro derivatives. Reductive dehalogenation of the chloro derivatives was unsuccessful.

EVANSTON, ILLINOIS RECEIVED APRIL 13, 1949

(9) Prepared by the method of W. Wislicenus, *Ber.*, **20**, 2930 (1887), in 76% yield, b. p. 96–97° at 3 mm.

(10) This is the method of G. Reddelien, *ibid.*, **43**, 2476 (1910); **47**, 1364 (1914).

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

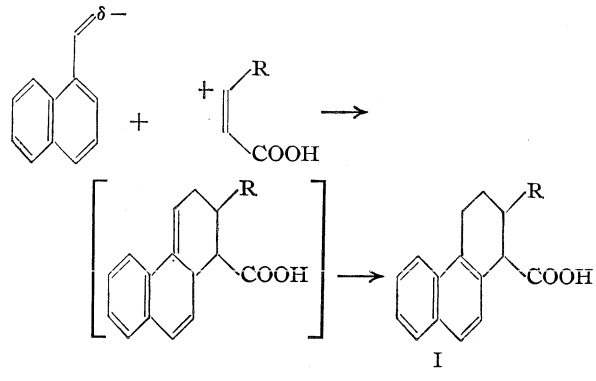
The Diels–Alder Reaction of 1-Vinylnaphthalene with α,β- and $\alpha,\beta,\gamma,\delta$-Unsaturated Acids and Derivatives

BY W. E. BACHMANN AND N. C. DENO[1]

The reaction of 1-vinylnaphthalene as a diene in the Diels–Alder reaction[2] was extended recently to the addition of fumaric acid, citraconic anhydride, and mesaconic acid.[3] We have now studied the addition of a number of α,β- and $\alpha,\beta,\gamma,\delta$-unsaturated acids and derivatives. In general, the yields of adducts were low on account of two competing reactions: homopolymerization of the 1-vinylnaphthalene and copolymerization with the dienophile. In most of the reactions two structural isomers were possible of formation, since the diene and the dienophile were unsymmetrically substituted. The structural isomer which was formed in each reaction was that expected from an application of the general principle of the English school that the most nucleophilic carbon atom will bond to the most electrophilic carbon atom.[4] In applying this principle to 1-vinylnaphthalene, the terminal carbon atom of the vinyl group was assumed to be the most potentially nucleophilic carbon atom by analogy with styrene.[5]

In the usual type of Diels–Alder reaction which involves a hydrocarbon diene and an α,β-unsaturated carbonyl compound as the dienophile, we prefer to consider that the attack is initiated by the strongly electrophilic β-carbon atom of the dienophile upon the easily polarizable diene. A second type of reaction suggests itself in which the polarities are reversed. A strongly electrophilic diene (such as sorbic acid) could attack an easily polarizable nucleophilic olefin. Apparently no unequivocal examples of this type involving unsymmetrical reactants have been mentioned; the closest approach appears to be the reaction of cyclones with unsaturated hydrocarbons. Three examples are reported in this paper. The cyclic dimerization of dienes does not fall cleanly into either category, but represents an intermediate type where both the diene and the dienophile are easily polarizable.

1-Vinylnaphthalene as the Diene. Formation of Hydrophenanthrene Derivatives.—1-Vinylnaphthalene reacted with α,β-unsaturated acids in acetic acid or propionic acid to yield 1,2,3,4-tetrahydrophenanthrene-1-carboxylic acids (I).



I

The initial adducts (shown in brackets) were isomerized to the compounds with a naphthalene nucleus by the action of the acidic medium in accordance with previous experience.[3]

Acrylic acid yielded 1,2,3,4-tetrahydrophenanthrene-1-carboxylic acid (I, R = H) whose structure was proved by the ultraviolet absorption spectrum (Fig. 1), which showed the presence of a naphthalene ring, by the failure of the compound to decolorize neutral permanganate, and by sulfur dehydrogenation to the known phenanthrene-1-carboxylic acid. Acrylic acid was the only dienophile of those studied which polymerized extensively with itself.

Crotonic acid (*trans*-β-methylacrylic acid) and β-ethylacrylic acid gave 2-methyl and 2-ethyl-1,2,3,4-tetrahydrophenanthrene-1-carboxylic acids (I, R = CH_3; I, R = CH_3CH_2), respectively. Both stereoisomers (*cis* and *trans*) of I (R = CH_3) were isolated in a 1:4 ratio, but the configurations were not established. This result is not considered to be an exception to the rule of *cis* addition, but is attributed to partial isomerization of the crotonic acid to isocrotonic acid under the conditions of the reaction. The structures were proved by decarboxylation and dehydrogenation of I (R = CH_3) to 2-methylphenanthrene and of I (R = CH_3CH_2) to 2-ethylphenanthrene. Neither dienophile showed much tendency to copolymerize with 1-vinylnaphthalene.

A study of the factors affecting the yields of adduct was made with crotonic acid. When the reaction was carried out in air, total polymerization of the 1-vinylnaphthalene resulted. For this reason all of the reactions were conducted in an inert atmosphere of nitrogen or carbon dioxide. Strong acids such as *p*-toluenesulfonic acid promoted complete polymerization of the 1-vinylnaphthalene. The addition of small amounts of picric acid or *sym*-trinitrobenzene, which have been found to act as inhibitors of

(1) From the Ph.D. dissertation of N. C. Deno (present address: Department of Chemistry, The Ohio State University). The dissertation, which is available on microfilm, contains more detailed directions for some of the experiments.

(2) Cohen, *Nature*, **136**, 869 (1935); Cohen and Warren, *J. Chem. Soc.*, 1315 (1937).

(3) Bachmann and Scott, THIS JOURNAL, **70**, 1458 (1948).

(4) See Hudson and Robinson, *J. Chem. Soc.*, 715 (1941), for a discussion of this principle in the Diels–Alder reaction.

(5) Wheland, "The Theory of Resonance and Its Application to Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 246.

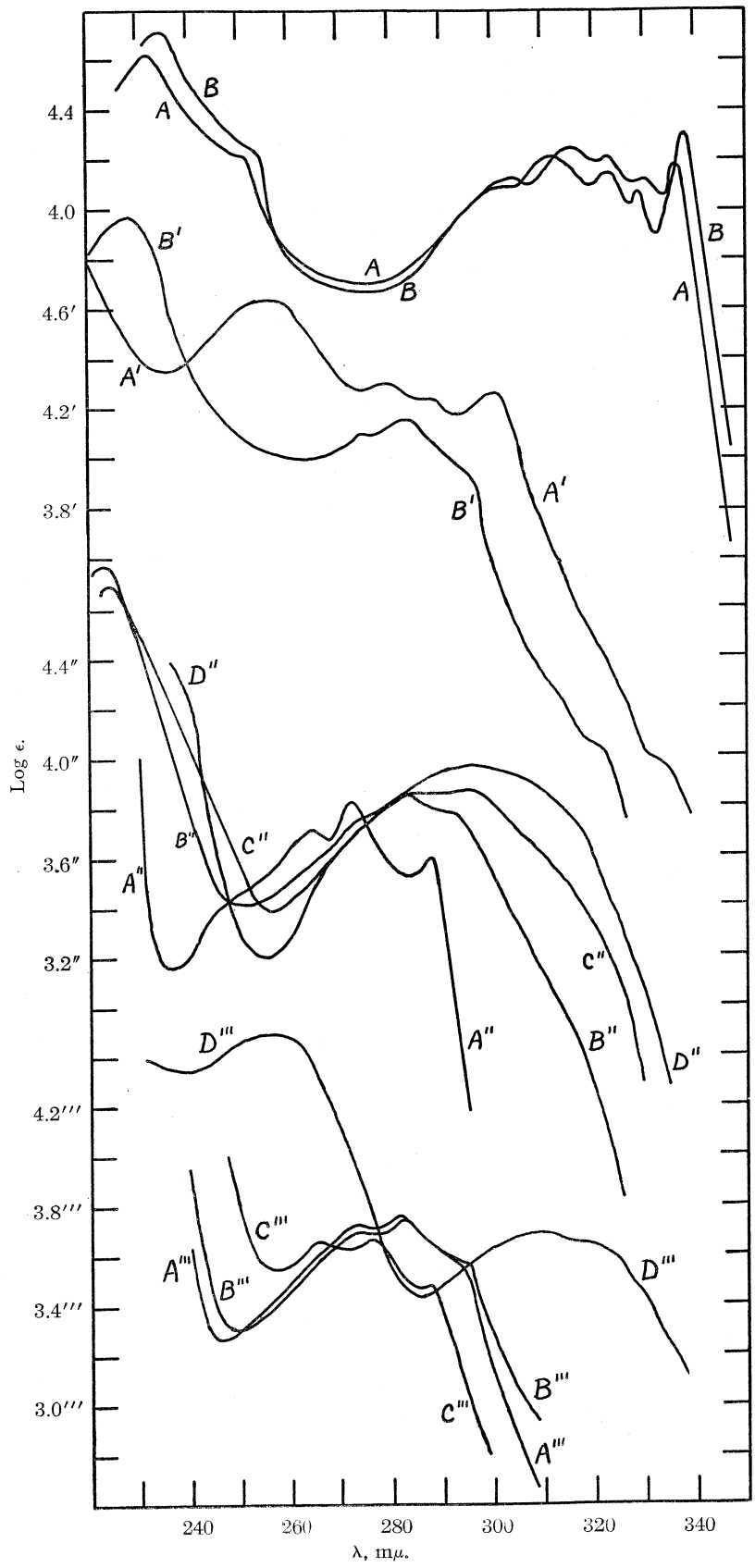
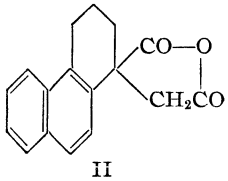


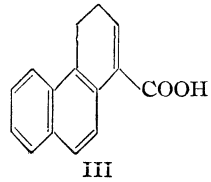
Fig. 1.—A, 3,4-Benzfluorene (XIII, R = H); B, 6-methyl-3,4-benzfluorene (XIII, R = CH_3); A′, 1-(1′-naphthyl)-phenanthrene; B′, 1-(1′-naphthyl)-1,2,3,4-tetrahydrophenanthrene (XVI); A″, naphthalene (Askew, *J. Chem. Soc.*, 512 (1935); B″, 1-(1′-cyclohexenyl)-naphthalene; C″, 1-(1′-cyclopentenyl)-naphthalene; D″, 1-propenylnaphthalene [Pestemer and Manchen, *Monatsh.*, **68**, 97 (1936)]. A‴, 1,2,3,4-Tetrahydrophenanthrene-1-carboxylic acid (I, R = H); B‴, 1-carboxymethyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (IV); C‴, *trans*-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid; [3] D‴, 3,4-dihydrophenanthrene-1-carboxylic acid (III).

certain polymerizations,[6] resulted in very low yields of adduct. Hydroquinone was employed in many runs as a precautionary measure, although it had no effect on the yield of the adduct from crotonic acid.

Itaconic acid yielded the anhydride of 1-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (II) in addition to copolymer. The structure of the adduct was proved by decarboxylation and dehydrogenation to 1-methylphenanthrene.



II



III

The adduct from α-bromoacrylic acid split out hydrogen bromide during the reaction and formed 3,4-dihydrophenanthrene-1-carboxylic acid (III). The acid rapidly decolorized permanganate in aqueous acetone, and the ultraviolet absorption spectrum (Fig. 1) clearly showed the double bond conjugated with the naphthalene ring. Addition of a mole of hydrogen to the unsaturated acid yielded 1,2,3,4-tetrahydrophenanthrene-1-carboxylic acid (I, R = H), which confirmed the structures of both acids.

Aconitic acid yielded the anhydride of 1-carboxymethyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid to which the structure IV has been assigned. The degradation of the compound with various reagents is of interest. Sulfur dehydrogenation eliminated the acetic acid group with the formation of phenanthrene-1,2-dicarboxylic anhydride (V), while treatment with palladium at 310° yielded 1-methylphenanthrene. Unexpectedly, the acetic acid moiety was removed also by dry distillation of a mixture of the sodium salt of the acid and calcium hydroxide, and phenanthrene was the sole volatile product. The monomethyl ester anhydride, the free triacid, and the trimethyl ester were prepared from the adduct.

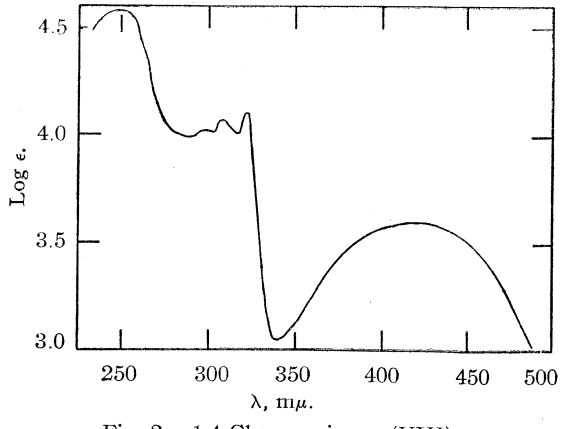
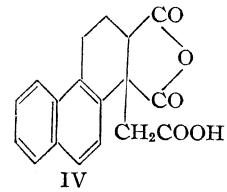
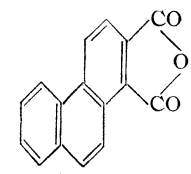


Fig. 2.—1,4-Chrysoquinone (VIII).

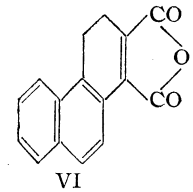
(6) Frank and Adams, THIS JOURNAL, 63, 908 (1946).



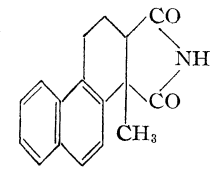
IV



V



VI

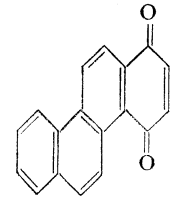


VII

Chloromaleic anhydride reacted with 1-vinylnaphthalene with elimination of hydrogen chloride, for the product was 3,4-dihydrophenanthrene-1,2-dicarboxylic anhydride (VI). Mesacon-β-amidic acid, $CH_3(COOH)C{=}CHCONH_2$, gave 1-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic imide (VII), whose structure was established by independent synthesis of the imide from the corresponding acid of Bachmann and Scott.[3] The same imide was obtained from 1-vinylnaphthalene and *cis*- and *trans*-ethyl β-cyanocrotonate after the reaction mixture had been submitted to hydrolytic conditions. The major product from 1-vinylnaphthalene and fumaronitrile was copolymer.

Under the usual conditions acetylenedicarboxylic acid gave only copolymer. In dibutyl ether, however, phenanthrene-1,2-dicarboxylic anhydride was produced in low yield, the intermediate adduct having been dehydrogenated apparently by the excess dienophile.

1,2-Chrysoquinone (VIII, absorption spectrum in Fig. 2) was formed in high yield from *p*-benzoquinone. The intermediate adduct was dehydrogenated by the excess quinone. Methyl



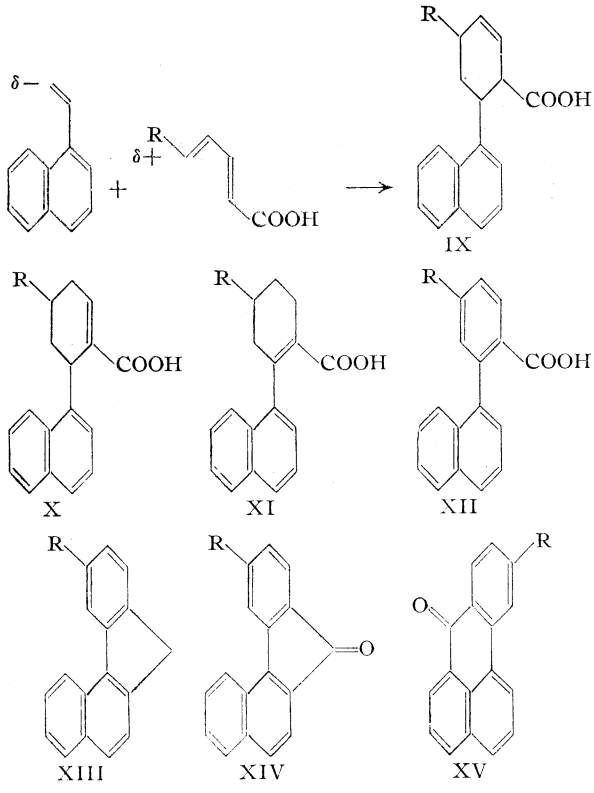
VIII

vinyl ketone gave an adduct which from theoretical considerations is probably 1-acetyl-1,2,3,4-tetrahydrophenanthrene, although its structure has not been established.

Under the conditions that were successful with crotonic acid, aconic acid, β-angelica lactone, and β-acetylacrylic acid gave low yields of products that were not investigated further; 1,2-diacetylethylene and mucobromic acid gave chiefly copolymer; and β,β-dimethylacrylic acid, β-furylacrylic acid, 5-methylcyclohexene-1,5-dicarboxylic acid, and butadiene monoxide failed to react.

1-Vinylnaphthalene as the Dienophile. Formation of 1-Cyclohexenylnaphthalene Deriva-

tives.—1-Vinylnaphthalene reacted as the dienophile with butadiene-1-carboxylic acid, sorbic acid, and muconic acid and formed 1-cyclohexenylnaphthalene derivatives. This represents a new synthesis of hydrobiaryl acids. We found no evidence for the formation of tetrahydrophenanthrene derivatives.



Each of the three diene acids yielded a mixture of adducts from which crystalline isomeric (called α and β) 1-cyclohexenylnaphthalene-2′-carboxylic acids were isolated, in which the location of the double bond has not been established with certainty. The six adducts behaved toward bromine in carbon tetrachloride more like α,β-(slow decolorization) than β,γ-unsaturated acids (IX); this implied that the double bond had shifted toward the carboxyl group (as in X and XI) during the reaction. The β adducts were isomerized to the α adducts by alkali; with R = H or CH_3, the conversion was quantitative. In agreement with the interpretation that this might represent a further shift of the double bond from its position in the β adduct (X) to a position in conjugation with the aromatic ring in the α adduct (XI)[7] was the greater reactivity of the α adducts to 3% sodium amalgam and water. On the basis of the available information, these structures seem more likely than IX for the β adducts and X or an epimer of IX for the α adducts. The ultraviolet absorption spectra (Fig. 3) do not distinguish between the various possibilities, because the absorption due to the conjugation of the double bond with the carboxyl group is masked by the strong absorption of the naphthalene ring, and the conjugation with the naphthalene ring is not manifested apparently on account of steric inhibition of resonance.[8]

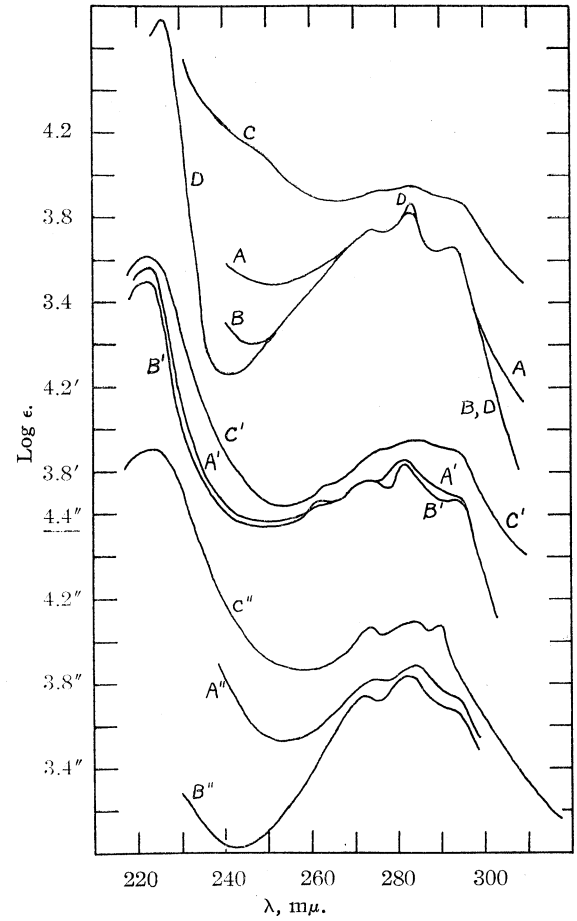


Fig. 3.—A, α-1-Cyclohexenylnaphthalene-2′,5′-di-carboxylic acid (probably XI, R = COOH); B, β-1-cyclohexenylnaphthalene-2′,5′-dicarboxylic acid (probably X, R = COOH); C, 1-phenylnaphthalene-2′,5′-dicarboxylic acid (XII, R = COOH); D, presumably 1-cyclohexylnaphthalene-2′,5′-dicarboxylic acid. A′, α-1,1-Cyclohexenylnaphthalene-2′-carboxylic acid (probably XI, R = H); B′, β-1-cyclohexenylnaphthalene-2′-carboxylic acid (probably X, R = H); C′, 1-phenylnaphthalene-2′-carboxylic acid (XII, R = H). A″, α-5′-Methyl-1-cyclohexenylnaphthalene-2′-carboxylic acid (probably XI, R = CH_3); B″, β-5′-methyl-1-cyclohexenylnaphthalene-2′-carboxylic acid (probably X, R = CH_3); C″, 5′-methyl-1-phenylnaphthalene-2′-carboxylic acid (XII, R = CH_3).

The cyclohexenylnaphthalene structure of the adducts from butadiene-1-carboxylic acid was proved by sulfur dehydrogenation to the known 1-phenylnaphthalene-2′-carboxylic acid (XII, R

(7) Linstead, *J. Chem. Soc.*, 2498 (1929).

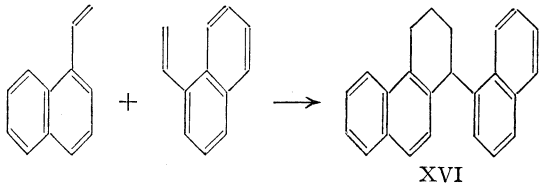
(8) Compare the spectrum of 1-(1′-cyclohexyl)-naphthalene in Fig. 8 with that of 1-phenylnaphthalene [Jones, *Chem. Rev.*, **32**, 34 (1942)].

= H; absorption spectrum in Fig. 3). Dry distillation of a mixture of the sodium salt of the adduct and calcium hydroxide followed by palladium treatment of the distillate at 300° gave the known 3,4-benzfluorene (XIII, R = H). This unexpected result apparently involved cyclization in the alkaline medium to tetrahydrobenzfluorenone followed by internal dehydrogenation–reduction to the hydrocarbon. After the structure of the product had been elucidated, it was learned that *o*-phenylbenzoic acid yields fluorenone when heated with soda–lime.[9]

In a similar manner sulfur dehydrogenation of the adducts from sorbic acid yielded 5′-methyl-1-phenylnaphthalene-2′-carboxylic acid (XII, R = CH_3), which was cyclized to the known 10-methyl-7-oxo-7-benz(de)anthracene (XV, R = CH_3). Likewise, 6-methyl-3,4-benzfluorene (XIII, R = CH_3) was obtained by the procedure which gave 3,4-benzfluorene; the similarity in absorption spectra of these two hydrocarbons (Fig. 1) was evidence for the structure of the methyl derivative.[10]

The adducts from muconic acid were dehydrogenated to 1-phenylnaphthalene-2′,5′-dicarboxylic acid (XII, R = COOH) with palladium. Apparently some disproportionation took place, for a compound was isolated whose analysis and absorption spectra (Fig. 3) corresponded to those of 1-cyclohexylnaphthalene-2′,5′-dicarboxylic acid.[11] The best method of preparation of 1-phenylnaphthalene-2′,5′-dicarboxylic acid (36% yield from 1-vinylnaphthalene) was dehydrogenation of the dimethyl ester of the crude adduct with sulfur followed by hydrolysis. The ring system was established by decarboxylation of the diacid to 1-phenylnaphthalene and by cyclization to the known 7-oxo-7-benz(de) anthracene-10-carboxylic acid (XV, R = COOH).

1-Vinylnaphthalene as the Diene and Dienophile. Dimerization.—When 1-vinylnaphthalene alone was refluxed in propionic acid, polymerization occurred; from the product 1-(1′-naphthyl)-1,2,3,4-tetrahydrophenanthrene (XVI) was isolated. The absorption curve (Fig. 1) showed the presence of two naphthalene rings and the complete structure was proved by sulfur dehydrogenation to 1-(1′-naphthyl)-phenanthrene.



XVI

(9) Fittig and Schmitz, *Ann.*, **193**, 115 (1878); Fittig and Ostermayer, *ibid.*, **166**, 372 (1873).

(10) These spectra differed from the spectrum of 7-benz(de)-anthracene [Clar and Furnari, *Ber.*, **65**, 1420 (1932)], which had been a ring system under consideration.

(11) Cook and Lawrence, *J. Chem. Soc.*, 1431 (1936), observed disproportionation of 1-cyclohexenylnaphthalene under similar conditions.

The resemblance of the spectrum of the latter hydrocarbon with that calculated for a mole of naphthalene and one of phenanthrene may be interpreted in terms of steric inhibition of conjugation between the two ring systems in the molecule.

Observations on the Reactions.—Our results are in agreement with the view that a strongly electrophilic carbon atom of an olefin or diene attacks the potentially nucleophilic terminal carbon atom of 1-vinylnaphthalene. They also demonstrate a close correlation between the reaction of an electrophilic olefin or diene in the Diels–Alder reaction and the reaction of the olefin or diene with strongly nucleophilic anions. For example, the anion of malonic ester attacks diethyl citraconate at the β-position[12] and the ester of sorbic acid and of butadiene-1-carboxylic acid at the δ-carbon atom.[13] Analogously, it is the β-carbon atom of citraconic anhydride[3] and the δ-carbon atom of the two diene acids that bond to the terminal carbon atom of 1-vinylnaphthalene.

In connection with the study of the derivatives of phenylnaphthalenes, the absorption curves of 1-(1′-cyclohexenyl)-naphthalene and of 1-(1′-cyclopentyl)-naphthalene were recorded (Fig. 1). Calvin[14] had noticed a correlation between nonplanarity (as evidenced by steric inhibition of resonance in the ultraviolet spectra) and decreased reactivity of certain dienes in the Diels–Alder reaction. This effect may explain the low reactivity of 1-(1′-cyclohexenyl)-naphthalene[15] compared to the reactivity of 1-(1′-cyclopentenyl)-naphthalene,[16] for the absorption curves seem to indicate a lesser tendency for the cyclohexenyl derivative to be planar.

Experimental

1-Vinylnaphthalene and Acrylic Acid.—A mixture of 20 cc. of an 85% aqueous solution of acrylic acid,[17] 0.4 g. of hydroquinone and 3 cc. of 1-vinylnaphthalene (prepared by dehydration of β-1-naphthylethyl alcohol[2]) was refluxed for one hundred hours in an atmosphere of carbon dioxide. The clear brown gum was dissolved in aqueous potassium hydroxide, the solution was extracted with benzene, and the aqueous layer was acidified. The precipitated gum was evaporatively distilled up to 250° at 0.1 mm., and the distillate (2.68 g.) was again evaporatively distilled at 200° and 0.1 mm. Crystallization of the distillate from ethyl acetate gave 0.53 g. (12%) of **1,2,3,4-tetrahydrophenanthrene-1-carboxylic acid (I, R = H)**; m. p. 155–159°, which was raised to 159–161° by several recrystallizations.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.48; H, 6.34.

Only 1.5% of the 1-vinylnaphthalene was accounted for as neutral homopolymer. A 6% yield of the acid (I, R =

(12) Hope, *J. Chem. Soc.*, 892 (1912); Ingold, Shoppee and Thorp, *ibid.*, 1477 (1926).

(13) Kohler and Butler, THIS JOURNAL, **48**, 1036 (1926).

(14) Calvin, *J. Org. Chem.*, **4**, 256 (1939).

(15) Bergmann and Bergmann, THIS JOURNAL, **59**, 1443 (1937); Bergmann and Szmuszkovicz, *ibid.*, **69**, 1367 (1947); Henri and Bergmann, *Nature*, **143**, 278 (1939).

(16) Bachmann and Kloetzel, THIS JOURNAL, **60**, 2204 (1938).

(17) Kaszuba, *ibid.*, **67**, 1227 (1945).

H) was obtained from a solution of methyl acrylate in acetic acid that had been refluxed for six hours with 0.5 g. of *p*-toluenesulfonic acid. After the addition of 0.5 g. of sodium acetate, 1-vinylnaphthalene was added and the mixture was refluxed for two hundred hours.

Dehydrogenation of the Adduct.—A mixture of 55 mg. of I (R = H) and 30 mg. of sulfur was heated at 235–245° under nitrogen for fifteen minutes, and the product was separated into neutral and acidic fractions with alkali and benzene. The resulting phenanthrene-1-carboxylic acid (40 mg., m. p. 217–225°), after two recrystallizations from ethanol, had the m. p. 229–230° (reported, 232–233°,[18] 228°[19]); the m. p. of its methyl ester was not depressed when mixed with an authentic sample.

1-Vinylnaphthalene and Crotonic Acid.—A mixture of 1.5 cc. (0.01 mole) of 1-vinylnaphthalene, 4.3 g. (0.05 mole) of crotonic acid, and 0.2 g. of hydroquinone in 10 cc. of propionic acid was refluxed for two hundred hours under carbon dioxide. By means of alkali the product was separated into 1-vinylnaphthalene homopolymer (1.14 g. or 74%) and acidic material; the latter on evaporative distillation at 200° and 0.1 mm. yielded a colorless solid (0.63 g. or 26%; m. p. 151–158°), which was separated into the *cis* and *trans* forms of **2-methyl-1,2,3,4-tetrahydrophenanthrene-1-carboxylic acid (I, R = CH_3)** by numerous fractional recrystallizations from benzene. Both isomers formed colorless prisms; one (21% yield) with m. p. 156–157°, the other (5%) with m. p. 211–212°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.97; neut. equiv., 240. Found: (lower melting isomer) C, 79.91; H, 6.97; neut. equiv., 241; (higher melting isomer) C, 79.91; H, 6.78; neut. equiv., 241.

When the reaction was carried out in the presence of air, 5% of *p*-toluenesulfonic acid, 5% of *sym*-trinitrobenzene, or in pyridine as the solvent, only the homopolymer of 1-vinylnaphthalene was formed. The presence of 5% of picric acid or of water lowered the yield; the addition of hydroquinone had no effect.

The **methyl ester** of the 156–157° acid, formed in quantitative yield with diazomethane, crystallized from methanol in colorless prisms; m. p. 57–57.5°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.29; H, 7.14. Found: C, 80.50; H, 7.38.

The ester yielded the original acid when refluxed with 20% aqueous-methanolic sodium hydroxide for twenty-four hours.

Degradation of the Adducts to 2-Methylphenanthrene.—To a solution of 240 mg. of the 156–157° acid in 5 cc. of 0.5 *N* sodium hydroxide was added 0.5 g. of calcium oxide. After thorough mixing, the mixture was evaporated and the residue was ground with 0.5 g. of calcium oxide. Dry distillation in a nitrogen atmosphere gave a liquid distillate, which was heated with 50 mg. of 5% palladium on charcoal catalyst under nitrogen. Evaporative distillation of the product at 150° and 0.01 mm. yielded 170 mg. of a colorless liquid which gave the picrate of 2-methylphenanthrene (56% yield based on the original acid); m. p. 115.5–116.5° (reported,[20] 118–119°). The hydrocarbon generated from the picrate had the m. p. 54.5–55.5° (reported,[20] 55–56°). In a similar manner, 42 mg. of the 211–212° acid yielded 22 mg. (66%) of 2-methylphenanthrene. When the methyl ester of the lower melting acid was heated with 5% palladium on charcoal under nitrogen at 310–320° for fifteen minutes, 2-methylphenanthrene was formed in 70% yield.

1-Vinylnaphthalene and β-Ethylacrylic Acid.—The unsaturated acid was prepared by the method of Auwers.[21] When the malonic acid was completely dissolved in the pyridine before the addition of the propionaldehyde, the yield of β-ethylacrylic acid was 59%; the yield was much lower when a small amount of piperidine[22] was added.

The reaction with 1-vinylnaphthalene, carried out in the manner described for crotonic acid, gave 28% of adduct and 68% of neutral homopolymer. After several recrystallizations from ethyl acetate, the **2-ethyl-1,2,3,4-tetrahydrophenanthrene-1-carboxylic acid (I, R = CH_3-CH_2)** had the m. p. 129.5–131°; yield, 18%.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.22; H, 7.11.

By the procedure described for the methyl homolog, 2-ethylphenanthrene (52%; m. p. 52–55°) was obtained; after several recrystallizations from ethanol the hydrocarbon melted at 65–65.5° (reported,[23] 64–65°); m. p. of the picrate, 92–93.5° (reported,[23] 92–93°).

1-Vinylnaphthalene and Itaconic Acid.—The procedure was similar to that with crotonic acid except that 2.6 g. (0.02 mole) of itaconic acid[24] was used. After being poured into excess dilute potassium hydroxide, the mixture was heated for thirty minutes at 100° in order to hydrolyze anhydrides. Evaporative distillation of the acidic portion up to 200° at 0.1 mm. gave 1.41 g. of distillate, a solution of which in acetone–petroleum ether deposited 1.26 g. (47%) of **the anhydride of 1-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (II)**; m. p. 145.5–148°, raised by further recrystallization to 147.5–148°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.94; H, 5.40.

The diacid obtained by alkaline hydrolysis did not have a sharp melting point; at about 190° it changed to the anhydride. The **dimethyl ester of 1-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid**, formed in nearly quantitative yield with diazomethane, crystallized from methanol–petroleum ether in large, glistening prisms; m. p. 60–62°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.84; H, 6.33.

The picrate of the dimethyl ester crystallized from methanol in yellow needles; m. p. 90.5–91.5°.

Degradation of the Adduct to 1-Methylphenanthrene.—A mixture of 100 mg. of II and 400 mg. of 5% palladium–charcoal catalyst was heated at 310–320° under nitrogen for fifteen minutes. The 1-methylphenanthrene obtained on distillation at 15 mm. crystallized from ethanol in glistening flakes (16 mg.); m. p. 119–119.5° alone and when mixed with an authentic sample. Of interest is the observation that the melting point (135–136°) of the picrate of 1-methylphenanthrene is not depressed by the picrate (m. p. 142–143°) of phenanthrene.

When less catalyst was used or when II was dry-distilled with soda-lime, the m. p. of the 1-methylphenanthrene could not be raised above 110°, although its picrate melted sharply at 135–136°.

1-Vinylnaphthalene and α-Bromoacrylic Acid.—The acidic adduct (from 2 g. of α-bromoacrylic acid, 1.5 cc. of 1-vinylnaphthalene, 10 cc. of acetic acid, fifty hours refluxing under nitrogen), after separation from the neutral homopolymer (1.14 g.), was evaporatively distilled up to 210° at 0.1 mm., and the solid distillate (0.4 g. or 18%, m. p. 194–204°) after several recrystallizations from ethanol gave colorless, glistening prisms of 3,4-dihydro-1-phenanthrenecarboxylic acid (III); m. p. 211–212° (reported,[25] 213–214°). The product immediately decolorized a solution of potassium permanganate in aqueous acetone.

Hydrogenation of the Unsaturated Acid.—A mixture of 95 mg. of 3,4-dihydrophenanthrene-1-carboxylic acid and 20 mg. of Adams catalyst in 15 cc. of ethanol was shaken for two hours under two atmospheres of hydrogen. The colorless needles of 1,2,3,4-tetrahydrophenanthrene-1-carboxylic acid (80 mg.) after recrystallization from aqueous ethanol melted at 157–159.5°, alone and when mixed with the adduct from acrylic acid.

1-Vinylnaphthalene and Aconitic Acid.—The reaction mixture (3 cc. 1-vinylnaphthalene, 7 g. aconitic acid, 20

(18) Fieser, THIS JOURNAL, **54**, 4110 (1932).
(19) Bachmann, *ibid.*, **57**, 555 (1935).
(20) Haworth, *J. Chem. Soc.*, 1133 (1932).
(21) Auwers, *Ann.*, **432**, 63 (1923).
(22) Goldberg and Linstead, *J. Chem. Soc.*, 2351 (1928).
(23) Haworth and Mavin, *ibid.*, 1015 (1933).
(24) Kindly supplied by Chas. Pfizer and Co.
(25) Bachmann and Fujimoto, unpublished results.

cc. acetic acid, one hundred hours refluxing under nitrogen) was concentrated at 100° in a current of air and the acidic adduct was separated from the neutral homopolymer (2 g.) with alkali. The adduct was evaporatively distilled up to 270° at 0.1 mm.; addition of benzene to a solution of the distillate (1.07 g.) in hot ethyl acetate gave 0.86 g. (14%) of colorless prisms of the **anhydride of 1-carboxymethyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (IV)**; m. p. 215–219°, which was raised to 218–219° by recrystallization.

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.91; H, 4.08. Found: C, 68.92; H, 4.48.

The **monomethyl ester** of the anhydride acid, formed with diazomethane in ether, crystallized from benzene–petroleum ether in colorless prisms; m. p. 178.5–179.5°.

Anal. Calcd. for $C_{19}H_{16}O_5$: C, 70.36; H, 5.00. Found: C, 70.61; H, 5.11.

The **trimethyl ester of 1-carboxymethyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid,** formed from the triacid (obtained by alkaline hydrolysis of IV) and diazomethane in ether–methanol, crystallized from methanol in colorless prisms; m. p. 95–97°.

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 68.09; H, 5.98. Found: C, 67.73; H, 5.97.

When a mixture of acetic acid (15 cc.) and acetic anhydride (5 cc.) was used as the solvent, the distilled product contained phenanthrene-1,2-dicarboxylic anhydride (V), isolated as yellow needles (1%, m. p. 304–306°) on recrystallization from acetone. This surprising result was checked repeatedly. When propionic acid was employed, the higher temperature caused decarboxylation of some of the aconitic acid to itaconic acid with the resultant formation of the itaconic acid adduct (II) in 14% yield in addition to the aconitic acid adduct (IV) in 8% yield.

Degradation of the Adduct from Aconitic Acid.—Palladium–charcoal treatment of the adduct in the manner described for II gave 1-methylphenanthrene (m. p. 115–116°) in 18% yield. After recrystallization from ethanol the hydrocarbon melted at 118–119°, alone and when mixed with an authentic specimen.

A mixture of 74 mg. of IV and 17.6 mg. of sulfur was heated at 310–320° under nitrogen for fifteen minutes and then sublimed under reduced pressure. Two recrystallizations from acetic anhydride gave 10 mg. (16%) of phenanthrene-1,2-dicarboxylic anhydride (V); m. p. 305–308°, alone and when mixed with an authentic specimen.

A solution of 0.1 g. of the anhydride acid (IV) and 0.3 g. of sodium hydroxide in 5 cc. of water was treated with calcium oxide and worked up as described for the itaconic acid adduct; yield of phenanthrene, 20 mg. (32%). The product obtained from the soda-lime pyrolysis before the treatment with palladium was chiefly phenanthrene.

1-Vinylnaphthalene and Chloromaleic Anhydride.—The cooled mixture (1.5 cc. of 1-vinylnaphthalene, 2.64 g. of chloromaleic anhydride, 10 cc. acetic acid, twenty-five hours refluxing under nitrogen) deposited 3,4-dihydrophenanthrene-1,2-dicarboxylic anhydride (VI, 1.12, g., m. p. 270–272°), which was separated mechanically from adhering brown powder and recrystallized from 40 cc. of acetic anhydride; yield, 1.01 g. (40%); m. p. 270–271°, alone and when mixed with an authentic sample.[26]

1-Vinylnaphthalene and Mesacon-β-amidic Acid.—From 1.55 g. of mesacon-β-amidic acid[27] 37% of evaporatively distilled adduct was obtained by the procedure used with crotonic acid. Recrystallization of the adduct from ethyl acetate gave 0.49 g. (19%) of colorless prisms of **1-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic imide (VI)**; m. p. 209–212° which was raised to 211.5–212.5° by recrystallization.

Anal. Calcd. for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.06; H, 5.63; N, 5.26.

The same imide was formed by shaking 50 mg. of *cis*-1-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride[3] with 20 cc. of concentrated aqueous ammonia for five hours, acidifying the concentrated solution, and subliming the precipitate at 170° and 0.1 mm. Recrystallization of the sublimate from ethyl acetate gave the imide; m. p. 210–212°, alone and when mixed with the adduct described previously.

1-Vinylnaphthalene and *cis* and *trans* Ethyl β-Cyanocrotonate.—To the propionic acid solution of the adduct from 1.8 cc. of *cis*-ethyl β-cyanocrotonate[28] obtained by the procedure used with crotonic acid was added 5 cc. of concentrated hydrochloric acid and 5 cc. of acetic acid, and the mixture was refluxed for forty-eight hours. Evaporative distillation of the acidic fraction at 0.1 mm. and fractional crystallization of the distillate from ethyl acetate–petroleum ether and from benzene yielded 1-methyl-1,2,3,4-tetrahydrophenanthrene dicarboxylic anhydride (4.5%) and its imide (VI, 9.5%). Under similar conditions *trans*-ethyl β-cyanocrotonate[28] gave 10% of the anhydride and 7.5% of the corresponding imide (VI).

1-Vinylnaphthalene and Fumaronitrile.—By the procedure used in the preceding experiment, 0.41 g. of crystalline sublimate (m. p. 187–226°) was obtained from 1.56 g. of fumaronitrile; the chief product was copolymer (1.74 g.). Two recrystallizations of the sublimate from ethyl acetate gave 40 mg. (1.5%) of phenanthrene-1,2-dicarboxylic anhydride (V); m. p. 305–307°.

1-Vinylnaphthalene and Acetylenedicarboxylic Acid.—A solution of 1.55 cc. of 1-vinylnaphthalene, 2.28 g. of acetylenedicarboxylic acid, and 0.2 g. of hydroquinone in 20 cc. of dibutyl ether was kept at 100° under carbon dioxide for one hundred and fifty hours. The yellow precipitate was isolated and sublimed at 220° and 0.1 mm. and the sublimate (0.31 g.) was recrystallized from acetic anhydride; yield of phenanthrene-1,2-dicarboxylic anhydride (V), 0.2 g. (8%); m. p. 307.5–310°.

When the reaction was run in boiling acetic acid only copolymer was formed. The product obtained at room temperature in acetic acid was the phenanthrene derivative in low yield.

1-Vinylnaphthalene and Methyl Vinyl Ketone.—The ketone which separated on addition of excess potassium carbonate to 15 cc. of the 85% azeotrope[29] at 0° was decanted into a solution of 3 cc. of 1-vinylnaphthalene in 50 cc. of acetic acid, and the solution was refluxed under nitrogen for seventy hours. The viscous liquid (2 g., b. p. 112–185° at 0.1 mm.) obtained by fractional distillation formed yellow needles, presumably the **picrate of 1-acetyl-1,2,3,4-tetrahydrophenanthrene,** when treated with 1 g. of picric acid in 10 cc. of methanol; yield, 0.48 g. (5%); m. p. 90–91°.

Anal. Calcd. for $C_{16}H_{16}O \cdot C_6H_3N_3O_7$: C, 58.22; H, 4.22. Found: C, 58.12; H, 4.10.

1-Vinylnaphthalene and *p*-Benzoquinone.—The precipitate in the cooled mixture (6 cc. of 1-vinylnaphthalene, 24 g. of *p*-benzoquinone, 100 cc. of acetic acid, five hours at 100°) was collected and washed with three 10-cc. portions of acetic acid and two of ether; yield, 8.23 g. (78%); m. p. 200–207°. After several recrystallizations from acetic acid the glistening golden-bronze flakes of **1,4-chrysoquinone (VIII)** melted at 206.5–207.5°.

Anal. Calcd. for $C_{18}H_{10}O_2$: C, 83.71; H, 3.90. Found: C, 83.47; H, 4.15.

In an attempt to isolate the intermediate in the formation of 1,4-chrysoquinone, several solvents were tried; only in diethyl ether did the solution remain bright yellow. When the isolated yellow solid was heated in acetic acid, the solution became red and the golden flakes of 1,4-chrysoquinone crystallized.

1-Vinylnaphthalene and Butadiene-1-carboxylic Acid.—A solution of 3 g. of butadiene-1-carboxylic acid (prepared from acrolein and malonic acid[30]), 3 cc. of 1-vinylnaphthalene and 0.5 g. of hydroquinone in 20 cc. of acetic acid was

(26) Fieser and Hershberg, THIS JOURNAL, **57**, 1853 (1935).
(27) Anschütz, *Ann.*, **353**, 139 (1907).
(28) Mowry and Rossow, THIS JOURNAL, **67**, 926 (1945).
(29) Kindly furnished by E. I. du Pont de Nemours and Co.
(30) Doebner, *Ber.*, **35**, 1137 (1902).

heated at 100° under nitrogen for two hundred hours, and then added with good stirring to 100 cc. of benzene. The clear solution which was decanted from the precipitated gum was washed well with dilute sodium sulfate solution and then extracted with 50 cc. of 5% aqueous potassium hydroxide. The acid obtained on acidification of the alkaline extract with acetic acid was evaporatively distilled up to 230° at 0.1 mm., and the distillate (1.6 g.) was crystallized from aqueous methanol. Repeated recrystallization of the prisms (1 g., m. p. 143–182°) from aqueous methanol gave 0.23 g. (5%) of the α adduct, probably **1-(1′-cyclohexenyl)-naphthalene-2′-carboxylic acid (XI, R = H)**; m. p. 180–185°. The highest m. p. obtained was 184–185°. This acid and most of the others were dried at 100° and 0.1 mm. for analysis.

Anal. Calcd. for $C_{17}H_{16}O_2 \cdot CH_3OH$: C, 75.53; H, 6.67. Found: C, 75.97; H, 6.24.

The β adduct was obtained by refluxing a solution of 9.5 g. of butadiene-1-carboxylic acid, 15 cc. of 1-vinylnaphthalene and 0.1 g. of hydroquinone in 100 cc. of propionic acid for two hundred hours under nitrogen. After removal of the solvent at 100° and 15 mm. the residue was stirred with 50 cc. of benzene, 150 cc. of water and 20 g. of sodium bicarbonate. The benzene layer was separated and extracted twice with 50 cc. of saturated sodium bicarbonate solution. Extraction with dilute aqueous potassium hydroxide followed by acidification of the extract gave an acid which was evaporatively distilled up to 210° at 0.1 mm.; crystallization of the distillate (3.58 g.) from ethanol gave massive prisms of the β adduct, probably **1-(3′-cyclohexenyl)-naphthalene-2′-carboxylic acid (X, R = H)**; yield, 1.35 g. with m. p. 135.5–136° and 0.11 g. with m. p. 133–134°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.62; H, 6.44.

Isomerization of the β-Adduct to the α-Adduct.—A solution of the β-adduct in 10% aqueous potassium hydroxide was kept at 100° for four days. Acidification and ether extraction gave the α adduct (m. p. 178–184°) in quantitative yield.

Dehydrogenation of the Adducts.—A mixture of 111 mg. of the α-adduct from butadiene-1-carboxylic acid and 30 mg. of sulfur was heated at 250–260° under nitrogen for twenty minutes, and then evaporatively distilled up to 220° at 0.1 mm. The acidic fraction, after purification through its salt, was dissolved in benzene–petroleum ether; slow evaporation of the solution gave 20 mg. (18%, m. p. 147–150°) of 1-phenylnaphthalene-2′-carboxylic acid. After two recrystallizations from methanol the acid melted at 154–155°, alone and when mixed with an authentic specimen prepared from diazotized methyl anthranilate and naphthalene.[31]

Formation of 3,4-Benzofluorene.—A solution of 370 mg. of the β-adduct from butadiene-1-carboxylic acid and 60 mg. of sodium hydroxide in 10 cc. of water was stirred at 100° with 1.8 g. of calcium oxide for five minutes and evaporated. The residue was ground with 1.8 g. of calcium oxide and heated under nitrogen with a free flame. The yellow distillate was heated with 30 mg. of 5% palladium–charcoal catalyst at 310–320° under nitrogen for ten minutes and evaporatively distilled up to 145° at 0.1 mm. The nearly colorless distillate (170 mg.) when treated with an equal weight of picric acid in ethanol gave 80 mg. of the picrate of 3,4-benzfluorene as red needles; m. p. 113–116°. Further recrystallization raised the m. p. to 120–123°, not depressed when mixed with an authentic specimen.[32] The hydrocarbon, generated from the picrate, after two recrystallizations from aqueous ethanol formed glistening flakes; m. p. 120–122° alone and when mixed with 3,4-benzfluorene.[32] There was excellent agreement in the ultraviolet absorption spectra of the two samples.

Anal. Calcd. for $C_{17}H_{12}$: C, 94.40; H, 5.60. Found: C, 94.42; H, 5.50.

(31) Grieve and Hey, *J. Chem. Soc.*, 108 (1938).

(32) Cook, Dansi, Hewett, Iball, Mayneord and Roe, *ibid.*, 1319 (1935).

1-Vinylnaphthalene and Sorbic Acid.—A solution of 10.5 g. of sorbic acid (prepared from crotonaldehyde and malonic acid[30]) and 11.3 cc. of 1-vinylnaphthalene in 50 cc. of propionic acid was refluxed under carbon dioxide for two hundred hours, and then worked up as described for X (R = H). The crystalline distillate (6.41 g.) obtained by evaporative distillation up to 240° at 0.1 mm. of the potassium hydroxide extracted material was triturated with benzene and with 30–60° alkanes, and the fine, colorless needles of the α adduct, probably **5′-methyl-1-(1′-cyclohexenyl)-naphthalene-2′-carboxylic acid (XI, R = CH_3)**, were collected; m. p. 175–178°. The acid was recrystallized from ethyl acetate or aqueous ethanol; m. p. 180–181°. Usually another crystalline modification crystallized in colorless prisms with m. p. 168–168.5°; when this was mixed with the 180–181° form, the mixture sintered at 168°, resolidified and melted at 181°. A similar result was obtained with a third modification which was obtained as long colorless needles with m. p. 160–161°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.8; neut. equiv., 266. Found: C, 80.82, 80.94; H, 6.83, 6.91; neut. equiv., 265.

The colorless crystals (0.73 g., m. p. 145–151°) recovered from the benzene and alkanes digestion appeared to be a mixture of the α- and β-adducts.

The β-adduct was obtained by refluxing a solution of 22.4 g. of sorbic acid and 15 cc. of 1-vinylnaphthalene in 100 cc. of acetic acid under nitrogen for one hundred and twenty hours. The solution was diluted with 200 cc. of benzene and 100 cc. of ether and extracted with three 200-cc. portions of dilute aqueous sodium sulfate, then with 130 cc. of saturated sodium bicarbonate solution (to remove sorbic acid), and finally with 200 cc. of 5% aqueous potassium hydroxide. Acidification of the last extract gave a gum which was rinsed well with water and heated with 200 cc. of ethanol. The cooled solution, after being filtered to remove some copolymer, yielded 5.81 g. of crystals (m. p. above 140°) which crystallized from ethanol–water in colorless prisms; yield 3.83 g.; m. p. 149.5–152° (which was depressed to 134–148° by the α adduct). The β adduct, probably **5′-methyl-1-(3′-cyclohexenyl)-naphthalene-2′-carboxylic acid (X, R = CH_3)**, crystallized from benzene–alkanes in colorless needle-like blades; m. p. 152.5–153.5°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.27; H, 6.86.

Additional β-adduct was isolated from the aqueous alcoholic filtrate; it was purified by evaporative distillation up to 210° at 0.1 mm. followed by recrystallization. The total yield of β-adduct was 14%. Both the α- and β-adducts showed typical naphthalenic absorption in the ultraviolet (Fig. 3). They decolorized permanganate rapidly at *p*H 10; neither showed any evidence of decomposition when heated to 250°.

Isomerization of the β-Adduct to the α-Adduct.—After a solution of the β-sorbic acid adduct in 10% aqueous potassium hydroxide had been kept at 100° for six days, acidification and ether extraction gave the α adduct in quantitative yield; m. p. 179–181°. After a single day's treatment a mixture of acids (m. p. 78–92°) was obtained.

Dehydrogenation of the Adducts to 5′-Methyl-1-phenylnaphthalene-2′-carboxylic Acid (XII, R = CH_3).—A mixture of 250 mg. of the adduct (α or β) and 70 mg. of sulfur was kept at 260–270° under nitrogen for forty-five minutes, and then evaporatively distilled up to 190° at 0.1 mm. After a separation from neutral material with alkali, the acidic portion was dissolved in ethanol–water; slow spontaneous evaporation to dryness gave yellowish granules (110 mg. or 44%, m. p. 164–169°), which were separated mechanically from a brittle gum. By recrystallization from benzene–alkanes and then from methanol the dehydrogenated acid was obtained as colorless needles; m. p. 174–174.5°.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.84; H, 5.38. Found: C, 82.80; H, 5.85.

Cyclization to 10-Methyl-7-oxo-7-benz(de)anthracene (XIV, R = CH_3).—A mixture of 60 mg. of 5′-methyl-1-

phenylnaphthalene-2′-carboxylic acid and 60 mg. of phosphorus pentachloride in 4 cc. of benzene was kept at 60° for thirty minutes; 300 mg. of aluminum chloride was added and the mixture kept at 60° for eight hours. The product was extracted from the hydrolyzed mixture with ether, the ether solution was washed with water and dilute alkali, the solvent was removed and a solution of the residue in 10 cc. of benzene was passed through a $^3/_8'' \times 12''$ alumina column. Development into a dark brown upper band, an orange-red middle band, and a yellow lower band was accomplished with benzene (100 cc.). Elution of the yellow band with hot ethanol yielded 10 mg. (18%) of yellow needles of 10-methyl-7-oxo-7-benz(de)anthracene; m. p. 155–157°. After one recrystallization the cyclic ketone melted at 157–158°, alone and when mixed with a sample prepared by the Scholl reaction from 1-naphthyl *p*-tolyl ketone,[33] but purified more efficiently by chromatographic adsorption than by recrystallization from ethanol alone.

Elution of the orange-red band with hot ethanol gave 3 mg. (5%) of orange-red blades (m. p. 155–156°), which may be the isomeric 6-methyl-3,4-benzfluorenone.

6-Methyl-3,4-benzfluorene (XIII, R = CH_3).—The reaction with 230 mg. of the adduct (α or β) from sorbic acid was carried out as described for 3,4-benzfluorene. The liquid (90 mg.) obtained by evaporative distillation gave 30 mg. of deep red needles of the **picrate of 6-methyl-3,4-benzfluorene** in alcohol; m. p. 116–116.5°, raised to 119–120.5° by recrystallization.

Anal. Calcd. for $C_{18}H_{14}\cdot C_6H_3N_3O_7$: N, 9.17. Found: N, 9.14.

The hydrocarbon, generated from the picrate, crystallized from ethanol in glistening colorless flakes; m. p. 72–72.5°. Its absorption curve (Fig. 1) agrees with that of 3,4-benzfluorene. The *sym*-**trinitrobenzene complex** crystallized from ethanol in fine, yellow needles; m. p. 147.5–148.5°.

Anal. Calcd. for $C_{18}H_{14}\cdot C_6H_3N_3O_6$: C, 65.16; H, 3.87; N, 9.50. Found: C, 65.52; H, 3.50; N, 9.48.

Hydrogenation, Oxidation, and Bromination of the α-Adduct.—A solution of 110 mg. of the adduct in 15 cc. of ethanol and 1 cc. of acetic acid (necessary for reaction) with 30 mg. of platinum oxide catalyst absorbed a mole of hydrogen in one hour. Crystallization of the product from ethyl acetate gave 20 mg. of colorless needles; m. p. 201–202.5°, raised to 202–202.5° by recrystallization from ethanol–water. The analysis corresponds to a **tetrahydro derivative** of the adduct.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.15. Found: C, 79.58; H, 8.02.

The ultraviolet absorption curve corresponded to a benzenoid system without conjugation with a double bond. The acid slowly decolorized permanganate in aqueous acetone.

A solution of 130 mg. of the α adduct and 1.3 g. of potassium permanganate in 50 cc. of water was kept at 100° for six hours. The manganese dioxide was removed by filtration and washed with water, and the filtrate was acidified and evaporated to dryness. Sublimation at 200° in a slow current of air gave 30 mg. of sublimate which after trituration with water yielded 15 mg. (20%) of phthalic anhydride (m. p. 127.5–128.5°), identified by mixed m. p. and through its imide and anilide. Oxidation with potassium dichromate in acetic acid likewise gave phthalic acid.

A crystalline bromo derivative was obtained in one experiment. A solution of 266 mg. of α adduct, 1 cc. of thionyl chloride and a drop of pyridine was allowed to stand for six hours. After removal of the excess thionyl chloride at 15 mm., bromine (0.2 g.) was added. After six hours the mixture was heated with aqueous alkali and the acidic product was sublimed at 0.1 mm., and recrystallized several times from aqueous ethanol; yield of colorless needles, 190 mg. (55%); m. p. 201°, raised to 208–209° by further recrystallization. The compound is considered to be **4-bromo-5′-methyl-1-(1′-cyclohexenyl)-naphthalene-2′-carboxylic acid,** for the absorption curve indicated the presence of the bromine on the naphthalene ring.

Anal. Calcd. for $C_{18}H_{17}O_2Br$: C, 62.62; H, 4.96. Found: C, 62.20; H, 4.90.

1-Vinylnaphthalene and Muconic Acid.—A mixture of 8.5 g. of muconic acid (prepared from α,α'-dibromoadipic acid and alkali[34]), 7.5 cc. of 1-vinylnaphthalene and 0.2 g. of hydroquinone in 300 cc. of propionic acid was refluxed under carbon dioxide for two hundred hours. The chilled solution was filtered from unchanged muconic acid and evaporated at 100° and 25 mm. The residue was warmed with 100 cc. each of benzene and water and an excess of sodium bicarbonate, the layers were separated and the benzene solution extracted again with 50 cc. of saturated sodium bicarbonate solution. The gum obtained on acidification of the aqueous extracts was heated with 150 cc. of methanol containing 1 g. of benzenesulfonic acid hydrate for eighteen hours. After the addition of sodium acetate and the removal of the methanol, acidic material was removed with alkali, and the dimethyl ester of the adduct was evaporatively distilled up to 205° at 0.1 mm.; yield, 9.73 g. Treatment of the acidic fraction with diazomethane, followed by evaporative distillation yielded an additional 0.42 g. of the ester; total yield, 10.15 g.

A solution of the ester in 50 cc. of benzene was added to an alumina column, $^1/_2'' \times 24''$; the first 10 cc. of eluate contained practically no product; the next 30 cc. contained 6.38 g. of colorless oil, which was hydrolyzed by heating with 30 cc. of acetic acid and 15 cc. of concentrated hydrochloric acid at 100° for twenty-four hours. After several recrystallizations of the product from acetic acid, 3.13 g. (19%) of the β-adduct, probably **1-(3′-cyclohexenyl)-naphthalene-2′,5′-dicarboxylic acid (X, R =** COOH), containing one-half mole of acetic acid of crystallization was obtained as colorless, granular crystals; m. p. 271–274°, raised to 274–275° by further recrystallization. The acetic acid is not removed at 65° and 0.1 mm.

Anal. Calcd. for $2(C_{18}H_{16}O_4)\cdot CH_3COOH$: C, 69.92; H, 5.56; neut. equiv., 130. Found: C, 70.06; H, 5.68; neut. equiv., 126.

When the compound is heated to 150° the acetic acid is eliminated.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44; neut. equiv., 148. Found: C, 72.75; H, 5.56; neut. equiv., 147, 149.

When the residues from the β-adduct were recrystallized from acetone–ethyl acetate, 0.27 g. of the α adduct, probably **1-(1′-cyclohexenyl)-naphthalene-2′,5′-dicarboxylic acid (XI,** R = COOH) was obtained; m. p. 275–275.5° (depressed to 248–256° by the β adduct). The α adduct crystallized from acetic acid with one mole of acetic acid that was not lost at 65° and 0.1 mm.

Anal. Calcd. for $C_{18}H_{16}O_4\cdot CH_3COOH$: C, 67.40; H, 5.65. Found: C, 67.77; H, 5.65.

Both adducts are little soluble in most solvents except hot ethanol and acetic acid. They sublime unchanged at 180–210° and 0.1 mm. and show no evidence of decomposition even at 300°. Decolorization of permanganate is slow in aqueous acetone but is rapid in aqueous solution at *p*H 10. The absorption curves (Fig. 3) are nearly identical with the curve for naphthalene.

In addition to the adducts described above 0.01 g. of 1-phenylnaphthalene-2′,5′-dicarboxylic acid (XII, R = COOH; m. p. 299–301°) was isolated. This result showed that some dehydrogenation took place.

Isomerization of the β-Adduct to the α-Adduct.—The dimethyl ester, prepared from 1 g. of the β adduct and diazomethane in methanol–ether followed by removal of the solvents, was added to a suspension of sodium methoxide (prepared from 0.3 g. of sodium) in 15 cc. of dry benzene, and the mixture was refluxed for five hours. After the addition of acetic acid to the cooled mixture, the benzene solution was washed with bicarbonate solution

(33) Fieser and Martin, THIS JOURNAL, **58**, 1443 (1936).

(34) Ingold, *J. Chem. Soc.*, 952 (1921).

and evaporated. Hydrolysis of the ester by refluxing with 10 cc. of acetic acid and 5 cc. of concentrated hydrochloric acid for twelve hours gave the acid from which 0.29 g. of the α adduct (m. p. 274–275°) was obtained by recrystallization from acetic acid.

Dehydrogenation of the Adducts to 1-Phenylnaphthalene-2′,5′-dicarboxylic Acid (XII, R = COOH).—The dimethyl ester (from 0.45 g. of the β-adduct) and 50 mg. of 5% palladium–charcoal catalyst was heated under nitrogen at 310–320° for thirty minutes. The product obtained by evaporative distillation up to 190° at 0.1 mm. was heated with 8 cc. of acetic acid and 4 cc. of concentrated hydrochloric acid at 100° for twenty-four hours. Crystallization of the isolated diacid from 3 cc. of acetic acid gave 0.1 g. (22%) of cream-colored granules of XII (R = COOH); m. p. 304–304.5°, raised to 304.5–305° by further recrystallization.

Anal. Calcd. for $C_{18}H_{12}O_4$: C, 73.97; H, 4.13. Found: C, 73.43; H, 4.04.

The diacid failed to decolorize permanganate even at a *p*H of 10.

A mixture of 0.45 g. of sulfur and 2.07 g. of the dimethyl ester of the crude adducts (part of the 10.15 g.) was heated at 250–260° under nitrogen for fifty minutes and evaporatively distilled up to 220° at 0.1 mm. A solution of the distillate in 40 cc. of acetic acid and 20 cc. of concentrated hydrochloric acid was refluxed for fifty hours, concentrated to 20 cc. and cooled, whereupon 1.1 g. (58%, or 36% based on 1-vinylnaphthalene) of 1-phenylnaphthalene-2′,5′-dicarboxylic acid (m. p. 299–301°) precipitated.

When the crude dimethyl ester was heated with palladium, a 16% yield of XII (R = COOH) was obtained; in addition, 9% of a new diacid (colorless needles from ethyl acetate–benzene) was isolated; m. p. 242–244.5°, raised to 247.5–248° by further recrystallization. The diacid does not decolorize permanganate even at *p*H 10; its analysis corresponds to that of **1-cyclohexylnaphthalene-2,5′-dicarboxylic acid.**

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.42; H, 6.34.

Decarboxylation of 1-Phenylnaphthalene-2′,5′-dicarboxylic Acid.—A mixture of 0.2 g. of the acid, 0.2 g. of copper bronze, and 0.6 g. of barium hydroxide octahydrate was thoroughly mixed and dry-distilled. After the removal of water in the distillate by reduced pressure, the nearly colorless liquid (100 mg.) was dissolved in 0.5 cc. of acetic acid and treated with 0.2 cc. of 100% nitric acid in 0.5 cc. of acetic acid. After two hours, seeding induced immediate crystallization of 4-nitro-1-phenylnaphthalene (23 mg., m. p. 121–124°); after one recrystallization from ethanol it melted at 124–125°, alone and when mixed with a sample (m. p. 124–126°) prepared by the method of Weiss and Woidlich,[35] who report a m. p. of 132°.

10-Carbomethoxy-7-oxo-7-benz(de)anthracene (XV, R = $COOCH_3$).—A solution of 100 mg. of 1-phenylnaphthalene-2′,5′-dicarboxylic acid in 3 cc. of acetic anhydride was refluxed for one hour. The acetic anhydride was removed slowly by distillation, the temperature was raised to 300°, and the pressure was lowered to 0.1 mm. After two hours at 320°, sublimation was complete. The yellow-orange crystals (60 mg. or 64%, m. p. 285–298°) were converted to the methyl ester by diazomethane and a solution of the ester in benzene was passed through an alumina column, where it was developed with benzene (400 cc.). Elution of the yellow band with hot methanol gave 7 mg. of bright yellow needles of XV (R = $COOCH_3$); m. p. 168–169° (reported,[36] 167–168°). Cyclization of 100 mg. of the acid with 10 cc. of anhydrous hydrogen fluoride at 25° gave similar results.

Dimerization of 1-Vinylnaphthalene.—A solution of 10 cc. of 1-vinylnaphthalene in 67 cc. of propionic acid was refluxed under nitrogen for two hundred hours. The chilled solution was filtered from precipitated gum, the propionic acid was removed under reduced pressure, and a solution of the residue in 50 cc. of benzene was passed through a 30″ × ½″ column of alumina and followed with more benzene. The first 50 cc. was collected and evaporated, and the residue was evaporatively distilled at 160–240° and 0.1 mm. The colorless crystalline distillate (2.16 g. or 21%; m. p. 140–145°) of **1-(1′-naphthyl)-1,2,3,4-tetrahydrophenanthrene (XVI)** was recrystallized from benzene–ethanol; m. p. 147–148°.

Anal. Calcd. for $C_{24}H_{20}$: C, 93.46; H, 6.54; mol. wt., 308. Found: C, 93.34; H, 6.44; mol. wt. (Rast method), 325.

1-(1′-Naphthyl)-phenanthrene.—A mixture of 100 mg. of the tetrahydro compound and 25 mg. of sulfur was heated in a narrow tube at 240–250° for fifteen minutes; the sides of the tube were washed down with a few drops of acetone and the process repeated. The product obtained by evaporative distillation up to 250° at 15 mm. was dissolved in acetone and heated with 0.5 g. of zinc dust. After removal of the zinc, a little ethanol was added and the solution was concentrated by boiling on a steam-bath. On cooling 25 mg. of 1-(1′-naphthyl)-phenanthrene crystallized in glistening, colorless blades; m. p. 113–115°, raised to 115–116.5° by further recrystallization. The second crop (60 mg., m. p. 112–115°) was converted to the picrate, which was recrystallized from ethanol; m. p. 135–136°.

The hydrocarbon and its picrate were identical with those prepared from 2 g. of 1-keto-1,2,3,4-tetrahydrophenanthrene and 1-naphthylmagnesium bromide.[37] The carbinol, which was not obtained crystalline, was dehydrated when heated at 200° and above under reduced pressure and evaporatively distilled. The resulting **1-(1′-naphthyl)-3,4-dihydrophenanthrene** crystallized from alcohol–acetone in colorless plates or hexagonal prisms, yield, 0.6 g.; m. p. 134–134.5°. The hydrocarbon gives a blue color with concentrated sulfuric acid.

Anal. Calcd. for $C_{24}H_{18}$: C, 94.1; H, 5.9. Found: C, 94.4; H, 5.9.

The 1-(1′-naphthyl)-phenanthrene, obtained in 80% yield by treatment of the dihydro derivative with palladium-charcoal at 320° for one-half hour, crystallized from alcohol–acetone in colorless plates; m. p. 117.5–118°.

Anal. Calcd. for $C_{24}H_{16}$: C, 94.7; H, 5.3. Found: C, 94.5; H, 5.2.

The picrate crystallized from absolute ethanol in light orange plates; m. p. 135.5–136°.

Anal. Calcd. for $C_{24}H_{16}\cdot C_6H_3N_3O_7$: N, 7.9. Found: N, 7.9.

Summary

1-Vinylnaphthalene reacted as the diene component in the Diels–Alder reaction with twelve olefinic dienophiles. The adducts were derivatives of 1,2,3,4-tetrahydrophenanthrene except in two examples in which the adduct was dehydrogenated to the phenanthrene derivative during the reaction.

With two olefinic dienophiles containing an α-halogen atom, the halogen acid was eliminated during the reaction with the formation of a dihydrophenanthrene derivative. The single acetylenic dienophile that was tried gave a phenanthrene derivative.

1-Vinylnaphthalene acted as the dienophile component with three diene acids and gave 1-cyclohexenylnaphthalene compounds, representing a new synthesis of partially hydrogenated biaryl acids as well as the first unequivocal examples of the combination of an electrophilic diene and a nucleophilic dienophile.

(35) Weiss and Woidlich, *Monatsh.*, **46**, 453 (1925).

(36) Copp and Simonson, *J. Chem. Soc.*, 209 (1942).

(37) Bachmann and Wilds, unpublished results (dissertation of Wilds, 1939).

1-Vinylnaphthalene acted both as diene and dienophile in undergoing a Diels–Alder type of dimerization to 1-(1′-naphthyl)-1,2,3,4-tetrahydrophenanthrene.

The results of the reactions have added support to current electronic interpretations of the Diels–Alder reaction.

ANN ARBOR, MICHIGAN RECEIVED MARCH 11, 1949

[CONTRIBUTION FROM THE SUGAR RESEARCH FOUNDATION LABORATORY, DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Preparation and Proof of Structure of 1,2:5,6-Dicyclohexylidene-D-glucofuranose[1]

BY ROBERT C. HOCKETT,[2] ROBERT ELLSWORTH MILLER[3] AND ALLEN SCATTERGOOD

Acetone is the only ketone whose reaction products with D-glucose have been fully characterized and determined structurally.[4] The products of the reaction, the water-soluble and non-reducing "monoacetoneglucose" and "diacetoneglucose" have been unequivocally shown to be 1,2-isopropylidene-D-glucofuranose and 1,2:5,6-diisopropylidene-D-glucofuranose, respectively.[5]

We have now found that the acid-catalyzed condensation of D-glucose with cyclohexanone forms a crystalline non-reducing dicyclohexylidene-glucose (I) which, in contrast to "diacetoneglucose," is water-insoluble. A 14-experiment yield study in which the variables were mole ratio of cyclohexanone to glucose, sulfuric acid concentration, and time, indicated that the best crude yield that could be secured under anhydrous conditions at room temperature was about 40%.

Structure

One hydroxyl group was shown to be present in I by the preparation in crystalline form of a monobenzoate (IIa), a benzenesulfonate (IIb) and a *p*-toluenesulfonate (tosylate, IIc). We were unable to secure the acetylation product or the methylation product of I in the crystalline condition. The preparation of these monoesters of non-reducing I showed that four of the five hydroxyl groups of a hemiacetal form of the D-glucose were blocked, probably by the formation of two heterocyclic rings. When compound IIb was heated under reflux with sodium iodide in acetic anhydride, practically no insoluble sodium benzenesulfonate was formed. This indicated that the benzenesulfonate group of IIb would undergo a displacement reaction only with considerable difficulty. In the absence of a neighboring hydroxyl group, an arylsulfonate group reluctant to undergo a displacement reaction is usually considered to be attached to a secondary carbon atom[6] or to have the back side approach of the replacing group blocked.[7] Thus it seemed probable that the hydroxyl group of I was on a ring which was blocked by other attached groups so that the approach of a replacing group was made difficult.

The location of the hydroxyl group of I was ascertained by an acid-catalyzed methanolysis of tosylate IIc followed by an acetylation of the sirupy product (III). Crystalline methyl 3-tosyl-2,4,6-triacetyl-β-D-glucopyranoside (IV) resulted, and demonstrated that carbon atom number three of I was the site of the hydroxyl group. Compound IV had previously been obtained by Peat and Wiggins[8] through a similar series of reactions starting with 1,2:5,6-diisopropylidene-D-glucofuranose (diacetoneglucose).

The location and size of the acetal rings of I was determined by the discovery that one of the two cyclohexylidene groups of I could be removed selectively. Controlled acid-catalyzed methanolysis of I gave a non-reducing crystalline monocyclohexylidene-D-glucose (V). Product V, obtained in good yield, could readily be recrystallized from water in contrast to 1,2-isopropylidene-D-glucofuranose ("monoacetone-glucose") which is very soluble in water.

The benzoylation of V gave a crystalline tribenzoate (VI) demonstrating the presence of three hydroxyl groups in V. The acid-catalyzed hydrolysis of VI gave 3,5,6-tribenzoyl-D-glucofuranose (VII) previously obtained by Fischer and Rund[9] from 1,2-isopropylidene-D-glucofuranose ("monoacetoneglucose"). Compound VII was isolated as its carbon tetrachloride addition product first observed by Fischer.

(1) A portion of the material in this paper was presented before the Division of Sugar Chemistry and Technology at the 115th meeting of the American Chemical Society, San Francisco, California, March 27, 1949.

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(3) The material presented in this paper is taken from a thesis submitted to the Department of Chemistry of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy by Robert Ellsworth Miller whose present address is: The American Sugar Refining Company, Research and Development Division, Philadelphia 48, Pennsylvania.

(4) Kranslein, Dickhauser and Voss, U. S. Patent 1,902,866 (March 28, 1933) reported a "dicyclohexanoneglucose of m. p. 134°" which they formulated as a 1,2:5,6-dicyclohexylidene-D-glucofuranose in the patent. No analytical results, specific rotation, yield, or proof of structure were given.

(5) (a) K. Freundenberg and A. Doser, *Ber.*, **56**, 1243 (1923); (b) Anderson, Charlton and Haworth, *J. Chem. Soc.*, 1329 (1929).

(6) (a) Bell, Friedmann and Williamson, *ibid.*, 252 (1937); (b) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

(7) Bartlett and Knox, *ibid.*, **61**, 3184 (1939).

(8) Peat and Wiggins, *J. Chem. Soc.*, 1092 (1938).

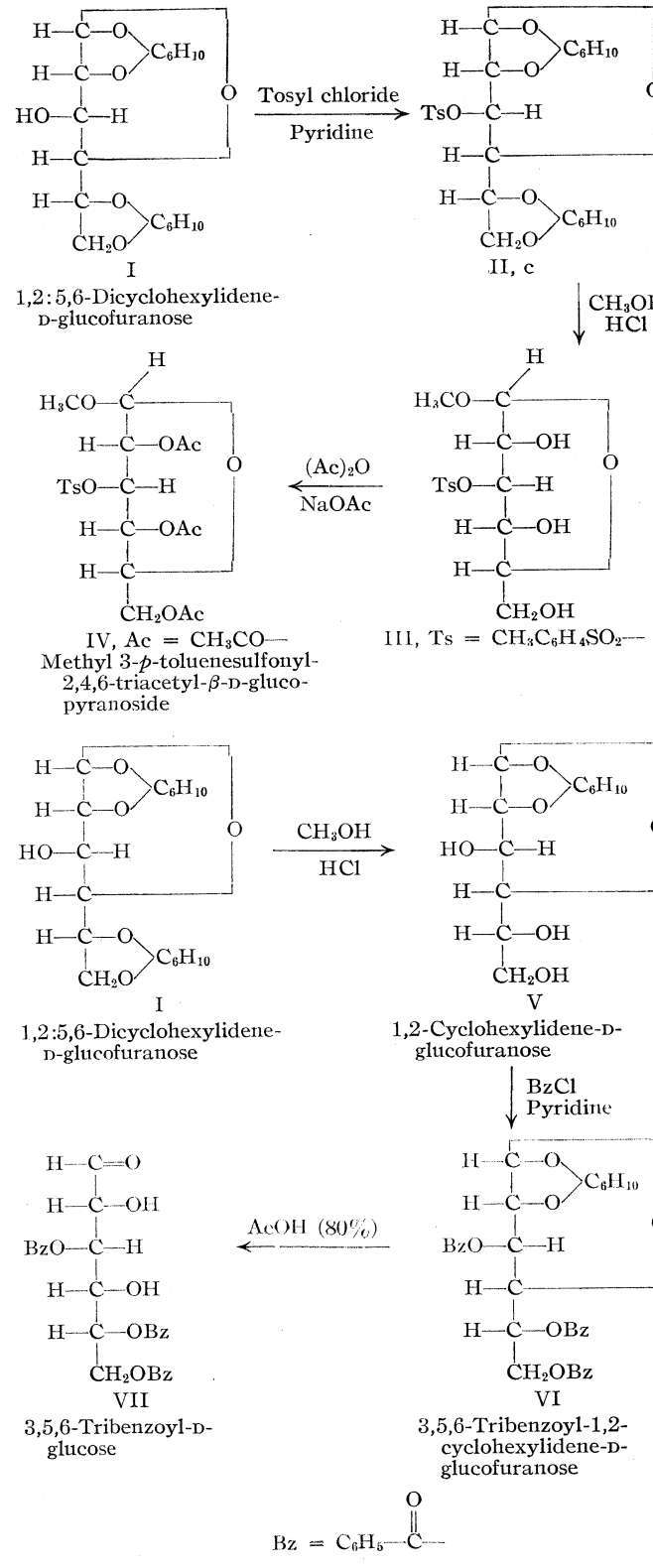
(9) Fischer and Rund, *Ber.*, **49**, 88 (1916).

The isolation of VII from VI indicated that the three benzoyl groups in VI and thus the three hydroxyl groups in V are in the 3, 5 and 6 positions. Since V was obtained by the removal of one cyclohexylidene residue from I (which had previously been shown to contain one hydroxyl group in position 3) the two hydroxyl groups thus liberated (positions 5 and 6) must be the site of one of the cyclohexylidene residues.

Since V is non-reducing the aldehyde group originally present at carbon atom number one in the glucose molecule must be blocked in some manner. Positions 2 and 4 must also be blocked since it has been demonstrated above that V has only three hydroxyl groups which are located on carbon atoms 3, 5 and 6. The most probable explanation for the blocking of positions 1, 2 and 4 in V is the presence of two heterocyclic rings involving these three positions. Of the structures that can be written for such a monocyclohexylideneglucose the one most probable is 1,2-cyclohexylidene-D-glucofuranose, V. Thus I becomes 1,2:5,6-dicyclohexylidene-D-glucofuranose.

Two other possibilities remain to be considered. They are (1) the inversion of the configuration of one or more of the asymmetric carbon atoms of the glucose molecule and (2) the wandering of a tosyl group or acetal ring during one or more of the reactions carried out. Results of parallel experiments under similar conditions conducted by many other workers on reactions of 1,2:5,6-diisopropylidene-D-glucofuranose make both of these possibilities unlikely.

Determination of the position of the hydroxyl group in 1,2:5,6-dicyclohexylidene-D-glucofuranose is shown in I, IIc, III, IV; preparation and structure determination of 1,2-cyclohexylidene-D-glucofuranose in I, V, VI, VII.



Experimental

1,2:5,6-Dicyclohexylidene-D-glucofuranose, I.—Anhydrous D-glucose (45 g., 0.25 mole, Merck reagent grade) was added to a mixture of cyclohexanone (100 ml., 1 mole, du Pont commercial grade) and concentrated sulfuric acid (6.5 ml., d. 1.84) and the reaction mixture was shaken at room temperature for twelve hours. Commercial *n*-heptane (250 ml.) was then added and the mixture was heated until the solids had dissolved and two liquid layers had formed. The *n*-heptane layer was decanted from the dark oily layer, allowed to cool and then refrigerated. The product (36.8 g., 43.2%) crystallized overnight. It softened at 105° (uncor.) and melted at 109–113° (uncor.). The compound was recrystallized from methylcyclohexane (6 ml./g.) and then from *n*-heptane (20 ml./g.) to give a product which melted at 131.4–132.4° (cor.) and showed a rotation in alcohol $[\alpha]^{31}D$ −2.20° (*c*, 2.27) (0.5683 g. in 25 ml. solution gave α −0.10° in a 2-dcm. tube). The rotation in chloroform was $[\alpha]^{31}D$ + 1.65° (*c*, 2.10) (1.0509 g. in 50 ml. of solution gave α + 0.14° in a 4-dm. tube). The compound is soluble in acetone, alcohol, chloroform, benzene and methyl "cellosolve." It is soluble in warm isobutanol, hot *n*-heptane and hot methylcyclohexane but is insoluble in water. It does not reduce hot Fehling solution.

Anal. Calcd. for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.36; H, 8.13.

3-Benzoyl-1,2:5,6-dicyclohexylidene-D-glucofuranose, IIa.—1,2:5,6-Dicyclohexylidene-D-glucofuranose (6.8 g., 0.02 mole) was added to a mixture of benzoyl chloride (3.7 g., 0.026 mole, Hooker Chemical Company) in anhydrous pyridine (10 ml., 0.124 mole). The reaction mixture was chilled until the initial heat evolution had dissipated. After standing at room temperature for three days the mixture was chilled, cold water (10 ml.) was added with chilling and shaking and the turbid solution was refrigerated. An oil separated which did not crystallize. The oil was extracted with chloroform (100 ml.) and water was bubbled through the chloroform solution overnight. The chloroform layer was removed, dried over granular calcium chloride and then concentrated under reduced pressure at 45–50° to a thick, yellow sirup. This sirup was dissolved in hot methanol (50 ml.) and the solution was allowed to cool to room temperature. An oil formed which upon standing and scratching with a glass rod crystallized. This product (5.20 g., 58.5%) melted at 109–110.3° (uncor.). The compound was recrystallized from *n*-heptane (5 ml./g.) and then from methanol (8 ml./g.) to a product which melted at 111.2–112.2° (cor.) and showed a rotation in chloroform $[\alpha]^{26}D$ −37.0° (*c*, 1.2) (0.6210 g. in 50 ml. of solution gave α −0.92° in a 2-dm. tube). The substance is soluble in acetone and chloroform, slightly soluble in methanol, methyl "cellosolve" and alcohol. It is soluble in warm *n*-heptane and warm isobutanol but is insoluble in water.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.54; H, 7.26. Found: C, 67.14; H, 7.59.

3-Benzenesulfonyl-1,2:5,6-dicyclohexylidene-D-glucofuranose, IIb.—Benzenesulfonyl chloride (14 ml., 0.109 mole, Eastman Kodak Company, "Eastman" grade) was added in one portion to a solution of 1,2:5,6-dicyclohexylidene-D-glucofuranose (34.0 g., 0.1 mole) in anhydrous pyridine (50 ml., 0.62 mole). A heat evolution was not observed. After being shaken at room temperature overnight the reaction mixture was chilled; cold water (50 ml.) was added slowly with shaking and the turbid solution was refrigerated. A sirup formed which did not crystallize. The liquid layer was decanted and discarded. The sirup was triturated with six portions (25 ml. each) of cold water and these water washings were discarded. The residue was dissolved in warm absolute alcohol (100 ml.), decolorized with charcoal and filtered. The clear filtrate upon refrigeration gave a product (24 g., 50%) melting at 90–92° (uncor.). Concentration of the mother liquor gave a second crop of 7.14 g. (total yield 65%). The product after recrystallization from *n*-heptane (2.5 ml./g.) and then from absolute alcohol (5 ml./g.) melted at 94.6–95.4° (cor.) and showed a rotation in chloroform $[\alpha]^{28}D$ −61.4° (*c*, 1.71) (0.8585 g. in 50 ml. of solution gave α −2.11° in a 2-dm. tube). The compound is soluble in acetone and chloroform. It is soluble in warm alcohol, warm isobutanol, warm methyl "cellosolve" and hot *n*-heptane but is insoluble in water.

Anal. Calcd. for $C_{24}H_{32}O_8S$: C, 59.98; H, 6.71; S, 6.67. Found: C, 59.80; H, 6.79; S, 6.63.

Attempted Replacement of the Benzenesulfonate Group in 3-Benzenesulfonyl-1,2:5,6-dicyclohexylidene-D-glucofuranose, IIb.—A solution of 3-benzenesulfonyl-1,2:5,6-dicyclohexylidene-D-glucofuranose (1.20 g., 0.0025 mole) and sodium iodide (0.5 g., 0.0034 mole, Merck reagent grade) in acetone (25 ml.) was boiled under reflux for three days. No precipitate was formed.

A solution of 3-benzenesulfonyl-1,2:5,6-dicyclohexylidene-D-glucofuranose (1.20 g.) and sodium iodide (0.5 g.) in acetic anhydride (25 ml.) was heated under reflux for twenty-four hours. The reaction mixture became very black but only a negligible amount of a precipitate formed.

3-*p*-Toluenesulfonyl-1,2:5,6-dicyclohexylidene-D-glucofuranose, IIC.—1,2:5,6-Dicyclohexylidene-D-glucofuranose (6.80 g., 0.02 mole) was added to a solution of *p*-toluenesulfonyl chloride (4.8 g., 0.025 mole, Eastman Kodak Company, "Eastman" grade) in anhydrous pyridine (10 ml., 0.124 mole). The solid immediately dissolved without any heat evolution. After being shaken at room temperature for ten days the reaction mixture was chilled; cold water (10 ml.) was added slowly with chilling and shaking and the resultant turbid solution was refrigerated. A white sirup formed which did not crystallize. The liquid layer was decanted and discarded. The sirup was triturated with three portions (20 ml. each) of cold water and these washings were discarded. The residue was dissolved in chloroform (150 ml.) and water was bubbled through the chloroform solution overnight. The chloroform layer was dried over granular calcium chloride and then concentrated under reduced pressure to a sirup. This residue was dissolved in warm methanol (50 ml.) and the methanol solution was allowed to stand in an open beaker overnight. A crystalline product (7.5 g., 75.8%) of m. p. 88.5–90° (uncor.) was thus obtained. The compound was alternately recrystallized from isobutanol (4 ml./g.) and from *n*-heptane (7 ml./g.) to a constant m. p. of 89.7–91.1° (cor.) and then showed a rotation in chloroform $[\alpha]^{26}D$ −67.6° (*c*, 0.18) (0.0924 g. in 50 ml. of solution gave α −0.50° in a 4-dm. tube). The compound is soluble in acetone and chloroform; slightly soluble in ethyl acetate and methyl "cellosolve." It is soluble in hot alcohol, hot *n*-heptane and hot 80% alcohol but is insoluble in water.

Anal. Calcd. for $C_{25}H_{34}O_8S$: C, 60.71; H, 6.93; S, 6.48. Found: C, 60.41; H, 7.20; S, 6.48.

Conversion of 3-*p*-Toluenesulfonyl-1,2:5,6-dicyclohexylidene-D-glucofuranose, IIc, to Methyl 3-*p*-Toluenesulfonyl-2,4,6-triacetyl-D-glucopyranoside, IV.—3-*p*-Toluenesulfonyl-1,2:5,6-dicyclohexylidene-D-glucofuranose (19 g., 0.038 mole) was dissolved in warm, anhydrous methanol containing hydrogen chloride (500 ml., 1.97 g. hydrogen chloride/100 ml. solution). The reaction mixture was refluxed under a water-cooled condenser, protected from the atmosphere by a calcium chloride drying tube, until a constant angular rotation was observed (approximately twenty-seven hours). The light yellow solution was then neutralized with excess silver carbonate and filtered. The residue was washed with four portions of methanol (50 ml. each) and discarded. The filtrate and washings were combined and concentrated under reduced pressure to a sirup. The sirup was dissolved in chloroform and some residual silver *p*-toluenesulfonate was removed by filtration. The chloroform filtrate was then concentrated under reduced pressure at 45° to a thick sirup. The sirup was dissolved in a hot mixture of acetic anhydride (200 ml.) and anhydrous sodium acetate (15 g.) The reaction mixture was heated at 85–90° on a steam-bath for three hours and was then poured into a vigorously stirred mixture of ice and water (1 liter). An oil separated which did not crystallize. The mixture was extracted with four portions of chloroform (50 ml. each) and the combined chloroform extracts were concentrated to a thin sirup under reduced pressure at 50°. The sirup was dissolved in anhydrous benzene (50 ml.) and the resulting solution was concentrated under reduced pressure to a thick sirup. Ether was added (50 ml.); the sirup slowly dissolved and a crystalline material soon began to appear. Refrigeration gave 4.7 g. (26.2%) of product melting at 131–132° (uncor.). After several recrystallizations from methanol the product melted at 135.5–137° (cor.) and showed a rotation in chloroform $[\alpha]^{25}D$ −18.6° (*c*, 0.6), (0.1513 g. in 25 ml. of solution gave α −0.45° in a 4-dm. tube).

Anal. Calcd. for $C_{20}H_{26}O_{11}S$: C, 50.62; H, 5.52; S, 6.76. Found: C, 50.49; H, 5.57; S, 6.77.

An authentic sample of methyl 3-*p*-toluenesulfonyl-2,4,6-triacetyl-D-glycopyranoside, IV, was obtained from Dr. L. F. Wiggins. His sample melted at 135–135.5° (cor.). A mixture of his sample and our product melted at 135–136° (cor.).

Acid-catalyzed Methanolysis of 1,2:5,6-Dicyclohexylidene-D-glucofuranose, I.—1,2:5,6-Dicyclohexylidene-D-glucofuranose (3.4034 g., 0.01 mole) was dissolved in commercial methanol (45 ml.) in a 50-ml. volumetric flask.

Methanolic hydrogen chloride (1.12 *N*, 0.45 ml.) was added and the reaction mixture was immediately diluted to the mark with commercial methanol. (The reaction mixture was 0.20 molar in 1,2:5,6-dicyclohexylidene-D-glucofuranose and 0.01 *N* in hydrogen chloride.) The reaction mixture was thoroughly mixed; transferred to a 2-dm. polarimeter tube and the reaction was followed polarimetrically. The curve (angular rotation *versus* time) is plotted on Fig. 1.

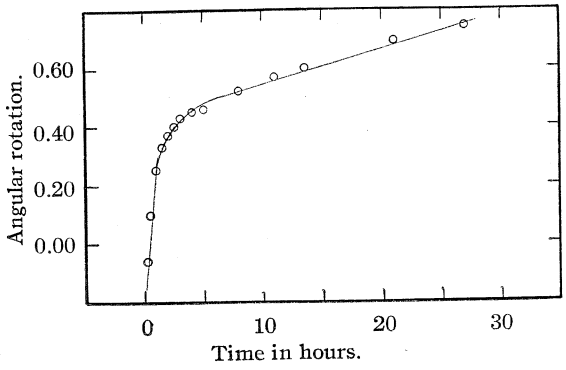


Fig. 1.—Acid-catalyzed methanolysis of 1,2:5,6-dicyclohexylidene-D-glucofuranose: 0.2 molar in dicyclohexylidene-D-glucose, 0.01 molar in hydrogen chloride.

1,2-Cyclohexylidene-D-glucofuranose, V.—1,2:5,6-Dicyclohexylidene-D-glucofuranose (68 g., 0.2 mole) was dissolved in commercial methanol (980 ml.) in a one-liter volumetric flask and methanolic hydrogen chloride (1.12 *N*, 9.0 ml.) was then added. The reaction mixture was diluted to the mark with methanol and allowed to stand at room temperature for four hours. (The reaction mixture was 0.2 molar in 1,2:5,6-dicyclohexylidene-D-glucofuranose and 0.01 *N* in hydrogen chloride. These are the same concentrations as those used in following the reaction polarimetrically.) Excess solid sodium bicarbonate was added and then 10% aqueous sodium hydroxide until the mixture became alkaline to litmus. The solution was filtered and the filtrate was concentrated under reduced pressure at 45–50° to a thick, sirupy-solid mass. Water (100 ml.) and *n*-heptane (200 ml.) were added and the mixture was heated until two clear liquid layers were obtained. The two layers were separated, allowed to cool to room temperature and then refrigerated. From the *n*-heptane layer, starting material (16.2 g.) was recovered, while the aqueous solution yielded crystalline 1,2-cyclohexylidene-D-glucofuranose (29.5 g., 74.5% based on 1,2:5,6-dicyclohexylidene-D-glucofuranose consumed) of m. p. 145–148° (uncor.). Concentration of the aqueous filtrate gave a second crop of product, 4.85 g. (total yield 87%). The compound after recrystallization from isobutanol (7 ml./g.) and from water (3 ml./g.) melted at 151.7–153.1° (cor.) and showed a rotation in acetone $[\alpha]^{29}D$ +4.00° (*c*, 1.4), (0.1376 g. in 10 ml. of solution gave α +0.11° in a 2-dm. tube). The compound is soluble in acetone and only slightly soluble in water. It is soluble in hot alcohol, hot isobutanol and hot methyl "cellosolve." The compound does not reduce hot Fehling solution.

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.01; H, 7.71.

3,5,6-Tribenzoyl-1,2-cyclohexylidene-D-glucofuranose, VI.—Benzoyl chloride (4 ml., 0.034 mole, Hooker Chemical Company) was added in one portion with vigorous stirring to a chilled mixture of 1,2-cyclohexylidene-D-glucofuranose (2.60 g., 0.01 mole) in anhydrous pyridine (10 ml., 0.12 mole). The reaction mixture was kept overnight in a 50° bath and the mixture was then poured into a vigorously stirred mixture of ice and water (400 ml.). An oil formed which slowly solidified. The solid was removed by filtration, washed several times with water and dried. The product (5.34 g., 93%) melted at 123.5–125° (uncor.). The compound after recrystallization from isobutanol (10 ml./g.) and then from *n*-heptane (20 ml./g.) melted at 124.6–125.6° (cor.) and showed a rotation in chloroform $[\alpha]^{26}D$ −90.4° (*c*, 0.62), (0.3139 g. in 50 ml. of solution gave α −2.27° in a 4-dm. tube). The compound is soluble in acetone, benzene, chloroform and ethyl acetate. It is soluble in hot isobutanol, hot *n*-heptane and hot methyl "cellosolve" but is insoluble in water.

Anal. Calcd. for $C_{33}H_{22}O_9$: C, 69.21; H, 5.63. Found: C, 68.80; H, 5.64.

3,5,6-Tribenzoyl-D-glucofuranose–Carbon Tetrachloride, VII.—3,5,6-Tribenzoyl-1,2-cyclohexylidene-D-glucofuranose (26.3 g., 0.046 mole) was dissolved in hot 80% acetic acid (600 ml.) and the reaction mixture was refluxed for five and one-third hours. The solution was allowed to cool to room temperature and was then seeded with starting material but nothing crystallized from the reaction mixture while standing overnight. (Previous experimentation had shown that the starting material while soluble in hot 80% acetic acid crystallized readily from the cool solution.) The reaction mixture was concentrated under reduced pressure at 45–50° to a light yellow, thick sirup. The sirup was taken up in room temperature carbon tetrachloride (200 ml.); the solution was seeded with 3,5,6-tribenzoyl-D-glucofuranose–carbon tetrachloride[10] and refrigerated. The product (20.8 g., 70%) crystallized overnight. The compound after several recrystallizations from carbon tetrachloride (15 ml./g.) softened at 65° (cor.) and melted at 69–78° (cor.).

Anal. Calcd. for $C_{28}H_{24}O_9Cl_4$: C, 52.03; H, 3.74; Cl, 21.94. Found: C, 51.88; H, 3.85; Cl, 20.81.

Mutarotation of 3,5,6-Tribenzoyl-D-glucofuranose–Carbon Tetrachloride.—A solution of 0.5030 g. of 3,5,6-tribenzoyl-D-glucofuranose–carbon tetrachloride which had been prepared from 1,2-cyclohexylidene-D-glucofuranose and recrystallized five times from carbon tetrachloride was made in absolute alcohol in a 25-ml. volumetric flask. The alcohol was added at zero time and the solution was made up to 25 ml. and transferred to a jacketed 2-dm. polarimeter tube. In Fig. 2 the specific rotation observed during the mutarotation is plotted against the time for two different temperatures.

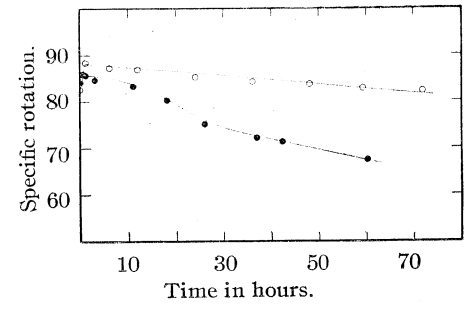


Fig. 2.—Mutarotation of 3,5,6-tribenzoyl-D-glucose in alcohol: ● at 30°; ○ at 20°.

Not all the mutarotation values which have been reported for this compound by Fischer and Rund[9] could be checked. The temperature at which these workers made their observations was not stated, but if it was 20° or lower the final part of the curve may have been so slow that the change was not detected.

Summary

1. Condensation of D-glucose with cyclohexanone has been found to form crystalline 1,2:5,6-dicyclohexylidene-D-glucofuranose (I). Three crystalline esters of this substance have also been prepared.

(10) Prepared by Dr. Franklin E. Morris, M. I. T. Chemistry Department Thesis, 1945, from 1,2-isopropylidene-D-glucofuranose.

2. Preferential hydrolysis of I has been found to yield crystalline 1,2-cyclohexylidene-D-glucofuranose. A crystalline tribenzoate of this substance has also been secured.

3. Proof of structure of all these substances is offered.

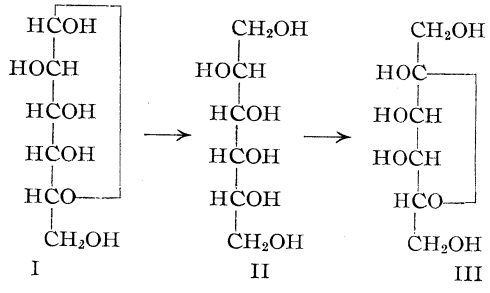
CAMBRIDGE 39, MASSACHUSETTS
RECEIVED APRIL 23, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

The Synthesis of D-Tagatose by Biochemical Oxidation and by an Improved Chemical Method[1]

BY EZRA L. TOTTON AND HENRY A. LARDY

In connection with work being carried out in this Laboratory on the intermediary metabolism of galactose, it became necessary to prepare D-tagatose (III). Since a wide variety of polyalcohols containing *cis*-hydroxyl groups at one end of the carbon chain had been oxidized to ketoses by *Acetobacter* species,[2] it was decided to test the action of *Acetobacter suboxydans* on D-talitol (II) as a means of preparing D-tagatose (III).



D-Talitol (II) was prepared for this purpose by the catalytic reduction of D-altrose (I). The latter was synthesized by methods developed by Robertson and Griffith[3] and Richtmyer and Hudson.[4]

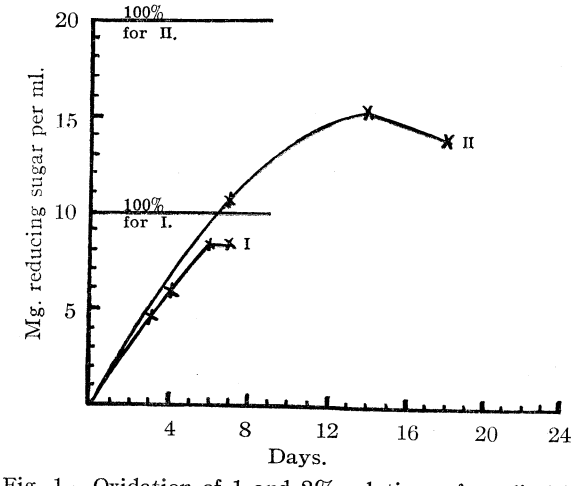


Fig. 1.—Oxidation of 1 and 2% solutions of D-talitol by *A. suboxydans*.

The D-talitol was rapidly oxidized by growing cultures of *A. suboxydans*. At concentrations of talitol below 5%, D-tagatose (III) was produced in yields of 75 to 84%. The rate of oxidation at 30° is shown in Fig. 1. When more concentrated solutions (5 to 16%) of talitol were employed, about 50% of the talitol was converted to tagatose. The yields quoted were based on a copper reduction method[5] standardized against pure D-tagatose. The bacterial oxidation product from D-talitol was demonstrated to be D-tagatose, since it gave a strongly positive test with Selivanov's reagent, was only very slightly oxidized by alkaline iodine, and gave a *p*-bromophenylosazone and a phenylosazone which were identical with those prepared from galactose.

The oxidation of D-talitol (II) to D-tagatose (III) by *A. suboxydans* offers a synthesis of D-tagatose which might be of preparative value should D-talitol become more readily available.

Since the synthesis of sufficient D-talitol to meet our needs for preparing tagatose would have been too laborious, we used the chemical procedure of Reichstein and Bosshard[6] for the preparation of larger quantities of tagatose. However, when using their procedure considerable difficulty was experienced in isolating, consistently, the tagatose from the mixture of isomerized galactose. The method was therefore modified by the use of lead acetate rather than absolute ethanol[6] to precipitate proteins and gums following the fermentation of the remaining galactose. The excess lead ions were then removed with an IR-100 ion exchange resin.[7] This modification eliminated many of the difficulties involved in the isolation of the product, and insured reproducible results.

It was also found that the rate of removal of galactose from the isomerized mixture may be increased by the use of a strain of yeast which rapidly adapts to galactose fermentation. The baker's yeast used by Reichstein and Bosshard required four days to ferment the excess galactose.

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. This work was supported in part by a grant from the U. S. Public Health Service (RG: 313).

(2) Bertrand, *Compt. rend.*, **126**, 762 (1898); Hann, Tilden and Hudson, THIS JOURNAL, **60**, 1201 (1938); Anderson and Lardy, *ibid.*, **70**, 594 (1948).

(3) Robertson and Griffith, *J. Chem. Soc.*, 1193 (1935).

(4) Richtmyer and Hudson, THIS JOURNAL, **65**, 740 (1943).

(5) Schaffer and Somogyi, *J. Biol. Chem.*, **100**, 695 (1933).

(6) Reichstein and Bosshard, *Helv. Chim. Acta*, **17**, 753 (1934).

(7) From Resinous Products Co., Philadelphia, Pennsylvania.

In this work a culture of *S. cerevisiae* (Y-30)[8] fermented the galactose in fourteen to twenty-four hours.

The D-tagatose obtained by this modification of Reichstein and Bosshard's procedure agreed in m. p. with that reported by them for a product recrystallized several times. It gave the same characteristic tests and derivatives as the D-tagatose produced by the action of *A. suboxydans* on D-talitol. Since the bacterial oxidation product has a higher negative rotation, $[\alpha]^{25}D$ − 5°, than any previously described specimen of D-tagatose, it probably represents a purer compound.

Experimental[9]

D-Talitol (II) was prepared by the catalytic reduction of 18 g. of D-altrose in a 14% aqueous solution with 18 g. Raney nickel[10] under 1500 lb. hydrogen pressure at 100° for five hours.

D-Tagatose (III).—In a typical experiment, a solution of 1 g. of talitol, 0.5 g. of Difco yeast extract and 0.1 g. of glycerol in 100 ml. of water were placed in a cotton-stoppered 2-liter erlenmeyer flask. After autoclaving for fifteen minutes at 15 lb. pressure the cooled solution was inoculated with 1 ml. of a growing culture of *A. suboxydans*.[8] A test for reducing sugar was negative. After incubation at 30° for four days the medium was well covered with pellicle and an aliquot showed a reducing sugar value of 5.8 mg. per ml. calculated as tagatose. Two days later the substrate was 84% oxidized. The value was unchanged on the following day. The bacterial culture was then filtered to remove the cells, decolorized with norite and the proteins were removed from the solution by adding 6 ml. of saturated lead acetate solution. The clear filtrate was passed through a bed (30 cm. × 2.5 cm. diameter) of IR-100 ion exchange resin in the acid phase to remove the lead ions. The solution was concentrated under reduced pressure to a dry sirup. This was then taken up in 6 ml. of hot absolute methanol and 25 ml. of hot absolute ethanol was added with shaking. After 75 ml. of cold absolute ethanol was added, the mixture was allowed to stand one hour before filtering. The filtrate was again evaporated to a dry sirup under reduced pressure. The product was taken up in the smallest possible amount of absolute methanol and hot absolute ethanol was added until the first signs of turbidity appeared. Scratching the flask initiated crystallization. The product was collected after crystallization had proceeded at 5° for twenty-four hours. The dry crystals weighed 0.76 g. and melted at 120°. Recrystallization from 0.5 part water and 3 parts absolute alcohol gave a product which melted at 131–132°; $[\alpha]^{25}D$ − 5° (*c* 1 in water).[10a] Repeated recrystallizations raised the m. p. to 133–134° but did not alter the rotation. Reichstein and Bosshard[6] reported m. p. 134–135° and $[\alpha]^{20}D$ −2.3° (*c* 2.19 in water) for recrystallized tagatose prepared by treating galactose with pyridine.

Reaction with Hypoiodite (Willstätter-Schudel titration).—This reaction was run under conditions described by Hinton and Macara.[11] In a standardizing run 0.080 g. of glucose was quantitatively oxidized by iodine, giving a value of 1.40 g. iodine per g. of glucose. Under these conditions, galactose gave an iodine value of 1.17 g. per g. of galactose; the bacterial oxidation product of D-talitol gave an iodine value of 0.018 g. of iodine per gram of product.

D-Tagatose, reacting for twenty-five minutes with the reagent of Shaffer and Somogyi,[5] gave a copper reduction value 79% as great as an equivalent amount of glucose reacting for fifteen minutes.

The Selivanov Test.—The procedure of Roe[12] was followed in carrying out this test. A quantitative comparison (Evelyn colorimeter, filter 490) of the color formed by Selivanov's reagent and the bacterial oxidation product with the color formed by the reagent and D-fructose showed that the intensity of the colors were practically identical.

D-*lyxo*-Hexose *p*-Bromophenylosazone.—The method of Neuberg[13] was used to prepare this compound from a sample of the bacterial oxidation product. Two recrystallizations from 70% ethanol gave crystals which melted at 180–182° (slow heating). A mixed m. p. with an authentic sample prepared from galactose showed no depression. Neuberg reported a m. p. of 182–183° for D-*lyxo*-hexose *p*-bromophenylosazone prepared from galactose.

Anal. Calcd. for $C_{18}H_{20}O_4N_4Br_2$ (516.2): N, 10.85. Found: N, 10.73.

D-*lyxo*-Hexose Phenylosazone.—The procedure of Fischer[14] was followed for the synthesis of the phenylosazone from a sample of the bacterial oxidation product. Three recrystallizations from ethanol and water gave crystals which melted at 186° (slow heating). A mixed m. p. with a sample prepared from galactose showed no depression.

Anal. Calcd. for $C_{18}H_{22}O_4N_4$ (358.39): N, 15.64. Found: N, 15.55.

The Synthesis of D-Tagatose by an Improved Chemical Method.—One hundred grams of dry galactose in 1 liter of dry pyridine[15] was refluxed for five hours; the reaction mixture was protected from moisture with a calcium chloride tube. The pyridine was removed under reduced pressure. Remaining traces of pyridine were removed by evaporating, successively, two 0.5-liter portions of water under reduced pressure. The solution was concentrated to 125 ml. and 200 ml. of warm absolute ethanol was added in small portions. After twenty-four hours at 5°, the galactose was collected on a filter and washed with methanol. About 75% of the original galactose was recovered. The mother liquor was concentrated under reduced pressure to a thick sirup (30 ml.). A small amount of galactose was removed by filtration. The combined sirup and rinsings (50 ml.) were divided into two equal parts and each portion was added to a 2-liter erlenmeyer flask containing 500 ml. of a 0.5% Difco yeast extract solution. After sterilizing, each solution was inoculated with 25 ml. of a growing culture of *S. cerevisiae* (Y-30) and incubated with shaking at 30° for twenty-four hours. The combined medium was filtered, decolorized with norite, and concentrated under reduced pressure to 70 ml. Five ml. of saturated lead acetate solution was added. After filtering, the solution was passed through an IR-100 exchange resin in the acid phase. Three hundred ml. of warm absolute alcohol was added to the solution. After three hours the mixture was filtered and the mother liquor concentrated to a thin, free flowing sirup. Scratching the flask initiated crystallization, and the flask was allowed to remain at 5° for twenty-four hours. The product weighed 6 g. (6% of theoretical), and melted at 124–125°, $[\alpha]^{25}D$ −0.8° (*c* 5 in water). When recrystallized from ½ part water and 3 parts absolute alcohol, m. p. 131–132°, $[\alpha]^{25}D$ −0.8° (*c* 5 in water). This m. p. agrees with that reported for D-tagatose by Reichstein and Bosshard.[6] The product gave the same characteristic tests and derivatives as the compound produced by the bacterial oxidation of D-talitol.

(8) Thanks are due Professor Elizabeth McCoy, who kindly supplied the cultures of *S. cerevisiae* and *A. suboxydans*.

(9) All melting points were determined in capillaries. Anschütz, NBS calibrated thermometers were used.

(10) Pavlic and Adkins, THIS JOURNAL, **56**, 2463 (1934).

(10a) Final equilibrium value. The compound showed a slight downward mutarotation.

(11) Hinton and Macara, *Analyst*, 1 (1920).

(12) Roe, *J. Biol. Chem.*, **107**, 15 (1934).

(13) Neuberg, *Ber.*, **32**, 3384–3388 (1899).

(14) Fischer, *ibid.*, **17**, 579 (1884).

(15) Dried by refluxing and distilling in the presence of barium oxide

Summary

Acetobacter suboxydans oxidized D-talitol to D-tagatose, m. p. 133–134°, $[\alpha]^{25}D - 5°$, in yields of 75 to 84%.

The isomerization method by which Reichstein and Bosshard prepared tagatose from galactose has been modified to obtain more consistent yields by the use of an ion exchange resin in the purification procedure.

MADISON 6, WISCONSIN RECEIVED MAY 9, 1949

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

An Improved Synthesis of Esters of Nitroacetic Acid[1]

BY H. FEUER, H. B. HASS[2] AND K. S. WARREN[3]

Esters of nitroacetic acid have recently come into prominence as intermediates in the preparation of amino acids.[4] These esters have been prepared by W. Steinkopf[5] who employed two methods. The one which gave a 37% yield of the ethyl ester consisted of suspending dipotassium nitroacetate in absolute ethanol and introducing dry hydrogen chloride.

The second method, which gave a 71% yield based on nitroacetic acid, involved the following three steps

$$2CH_3NO_2 + 2KOH \longrightarrow KO_2N{=}CHCOOK + NH_3 + 2H_2O \quad (1)$$

$$KO_2N{=}CHCOOK + 2HCl \longrightarrow O_2NCH_2COOH + 2KCl \quad (2)$$

$$O_2NCH_2COOH + ROH \xrightarrow{H^+} O_2NCH_2COOR + H_2O \quad (3)$$

The disadvantage of this procedure lies in the second step because it requires the preparation and isolation of nitroacetic acid from the dipotassium salt and this can only be accomplished with a 60–70% yield. Furthermore, nitroacetic acid is very unstable. It decomposes into nitromethane and carbon dioxide, and this further decreases the yield in the esterification step. Steinkopf[5] stated that he was unable to prepare esters directly from the dipotassium salt with concd. sulfuric acid and the desired alcohol. He claimed that the rate of decomposition of the nitroacetic acid liberated from its dipotassium salt was faster than the rate of esterification. This statement seemed, however, contradictory to the fact that he was able to prepare esters by working with the free nitroacetic acid and using an equimolar amount of concd. sulfuric acid at −15 to +3° as indicated in step 3 above.

It seemed therefore advisable to attempt the synthesis of esters of nitroacetic acid directly from the dipotassium salt by acidification with concd. sulfuric acid and by working at low temperatures. As a result, the methyl and ethyl esters have been prepared in a 60% yield.

The results of several experiments are given in the following three tables to illustrate the influence of reaction temperature, reaction time, and amount of sulfuric acid upon the ester formation.

TABLE I

EFFECT OF REACTION TEMPERATURE ON THE YIELD OF METHYL NITROACETATE

In run No. 6 anhydrous sodium sulfate was omitted.

Run	Temp. during first 24 hours, °C.	Temp. during the next 144 hours, °C.	Yield, %
1	0 to +5	23 to 25	12
2	− 2 to 0	23 to 25	28
3	−15 to −10	23 to 25	38
4	−60 to −50	23 to 25	60
5	−60 to −50	1 to 5	60
6	−60 to −50	1 to 5	45

TABLE II

EFFECT OF REACTION TIME ON THE YIELD OF METHYL NITROACETATE

In run No. 9 anhydrous sodium sulfate was omitted. In all ten experiments 90.5 g. (0.5 mole) of dipotassium nitroacetate, 500 ml. (12.38 moles) of methanol, 100 g. (1 mole) of concd. sulfuric acid, and 15 g. (0.1 mole) of anhydrous sodium sulfate (except in 6 and 9), were used.

Run	Time in hr. at −60 to −50°	Yield, %
7	1	25
8	24	40
9	24	29
10	48	45

TABLE III

EFFECT OF THE AMOUNT OF CONCD. SULFURIC ACID ON THE YIELD OF METHYL NITROACETATE

In all these experiments the same conditions and amounts were used as in run No. 4.

Moles concd. H_2SO_4	Yield, %
1	18
1.5	45
2	60
3	60

The data in Table I show that a lower reaction temperature during the first twenty-four hours of

(1) Presented before the Division of Organic Chemistry at the St. Louis Meeting of the American Chemical Society, September 8, 1948.

(2) Present address: General Aniline and Film Corp., New York City, N. Y.

(3) Present address: Picatinny Arsenal, Dover, N. J.

(4) Lyttle and Weisblat, THIS JOURNAL, **69**, 2118 (1947).

(5) Steinkopf, *Ann.*, **434**, 21 (1923).

the reaction increases the yields. While a low reaction temperature is important during the first twenty-four hours, a further extension of the reaction at a low temperature does not increase the yields appreciably as indicated in Table II.

Omission of anhydrous sodium sulfate resulted in lower yields. A 2:1 ratio of concd. sulfuric acid to dipotassium nitroacetate is needed to get optimum yields as indicated by the data in Table III.

Experimental

Preparation of the Dipotassium Salt of Nitroacetic Acid.—In a three-liter flask provided with stirrer, condenser and dropping funnel was placed 1500 ml. (20.2 moles) of freshly prepared 50% potassium hydroxide. When the temperature had risen to 60° on dissolving of the potassium hydroxide, 300 g. (4.91 moles) of nitromethane was added dropwise with vigorous stirring. During the one and one-half hours required for the addition of the nitromethane, the temperature rose to 102°. Ammonia was liberated during the latter half of the addition and the reflux condenser was removed after the entire amount of nitromethane had been added. The reddish brown mixture was then heated until the first crystals appeared. After cooling, the potassium salt which had separated out was filtered and washed with methanol. This first crop weighed 210 g. representing a yield of 44.5%.

Anal. Calcd. for $C_2HNO_4K_2$: K, 43.03. Found: K, 42.61.

The mother liquor was evaporated further and after cooling a second crop of crystals was obtained which weighed 60 g., representing a yield of 12.7%.

Anal. Found: K, 42.43.

Still further evaporation of the mother liquor gave a third crop of crystals (70 g.) which was found by analysis to be 43% contaminated with potassium carbonate which formed in the reaction.

Anal. Found: K, 48.90.

Preparation of Methyl Nitroacetate.—In a one-liter flask fitted with stirrer, thermometer and dropping funnel were placed 90.5 g. (0.5 mole) of dipotassium nitroacetate, 500 ml. (12.38 moles) of methanol and 15 g. (0.1 mole) of anhydrous sodium sulfate. The flask was placed in a Dewar and cooled down to −50 to −60° by a trichloroethylene–dry ice mixture. One hundred grams (1 mole) of concentrated sulfuric acid (d. 1.84) was added dropwise to the mixture during a period of one and one-half hours. The reaction mixture was kept in the Dewar for twenty-four hours with stirring (temp. −50 to −60°) and then for one hundred and forty-four hours at 23–25° with occasional shaking. The precipitated potassium sulfate was then filtered off and the excess methanol was evaporated under vacuum. The oily residue was diluted with ether and neutralized with a 5% solution of sodium carbonate. The ether layer, which contained the ester, was dried and the ether was evaporated. Vacuum distillation of the residue at 15 mm. yielded 36 g. (60%) of the ester, boiling at 93–94°; $n^{20}D$ 1.4245; neut. equiv. calcd. for $C_3H_5O_4N$, 119, found 121.

Preparation of Ethyl Nitroacetate. The procedure was the same as for the synthesis of methyl nitroacetate. Forty grams (60%) of ethyl nitroacetate was obtained, boiling at 105–107° at 25 mm., d^{20}_4 1.11950, $n^{20}D$ 1.4252.

Acknowledgments.—The authors wish to express their appreciation to Mr. L. Friedman for his technical assistance and express their thanks to the General Tire and Rubber Company, Akron, Ohio, for financial assistance in this work.

Summary

An improved synthesis of esters of nitroacetic acid has been presented. The methyl and ethyl esters of nitroacetic acid have been prepared in two steps from nitromethane in 60% yield.

LAFAYETTE, INDIANA RECEIVED APRIL 7, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY]

The Chemistry of Nitroacetic Acid and its Esters. II. The Synthesis of Ethyl α-Nitro-β-(3-indole)-propionate from Gramine and Ethyl Nitromalonate[1]

BY D. I. WEISBLAT AND D. A. LYTTLE

We have recently reported a synthesis of *dl*-tryptophan (V) in which the key intermediate, ethyl α-nitro-β-(3-indole)-propionate (IV), was prepared from gramine and ethyl nitroacetate.[2] A new synthesis of this intermediate, starting with ethyl nitromalonate (I), is described in this communication.

The alkylation of ethyl nitromalonate (I) by gramine (II) under reaction conditions similar to those reported for the alkylation of ethyl nitroacetate[2] gives ethyl α-nitro-α-carbethoxy-β-(3-indole)-propionate (III) in excellent yield. The structure of ethyl nitromalonate, in contrast to that of ethyl nitroacetate, excludes dialkylation[2,3] as a possible side reaction and this, together with the activating effect of the second carbethoxy group, probably accounts for the higher yields and purer product obtained in the present alkylation.

Since powdered sodium hydroxide is an effective catalyst for the dialkylation of ethyl nitroacetate by gramine,[2] it was expected that it would greatly accelerate the present alkylation. Contrary to our expectations, however, it was found that not only sodium hydroxide but basic substances in general cause extensive decomposition. For this reason the rapid removal of dimethylamine, which is formed in the reaction, is essential for optimum yield and purity of product.

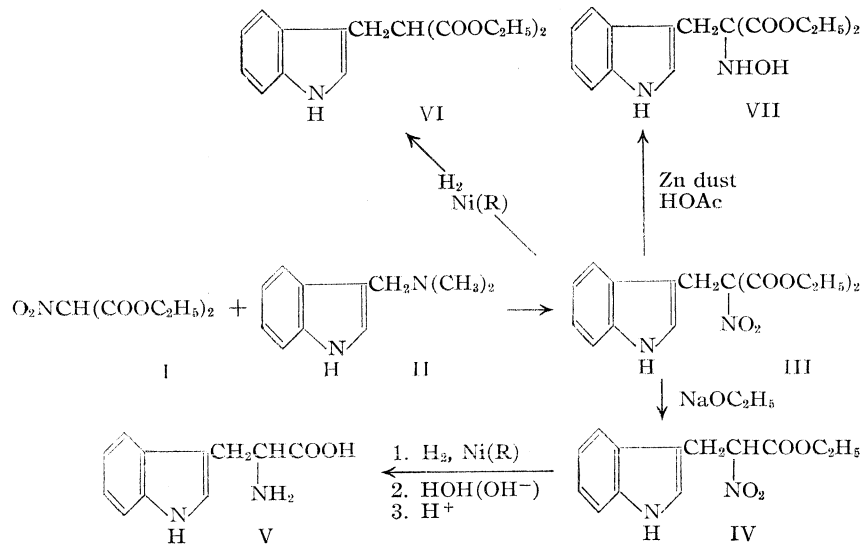
The conversion of III to IV in a yield of 91.6% was readily accomplished by treating a solution of III in ether with one equivalent of sodium in alcohol.[4]

(1) This paper was presented before the Organic Division at the 112th Meeting of the American Chemical Society, New York City, September, 1947.

(2) Lyttle and Weisblat, THIS JOURNAL, **69**, 2118 (1947).

(3) Snyder and Katz, *ibid.*, **69**, 3140 (1947).

(4) Ulpiani, *Gazz. chim. ital.*, **34**, 174 (1904).



Improvements in the reduction of IV and the hydrolysis of ethyl *dl*-tryptophan to *dl*-tryptophan (V) have increased the over-all yield on these steps to 87 from 50% as reported previously.[2]

Attempts to obtain ethyl α-amino-α-carbethoxy-β-(3-indole)-propionate by catalytic reduction of III with Raney nickel and hydrogen at 2500 p. s. i. and 100° were unsuccessful. The hydrogen uptake was almost 4 moles per mole of III, indicating that hydrogenolysis had occurred. The only product isolated was the known ethyl α-carbethoxy-β-(3-indole)-propionate (VI).[5]

Chemical reduction of III with zinc dust and acetic acid gave a product representing only partial reduction of the nitro group, ethyl α-hydroxylamino-β-(3-indole)-propionate (VII), in a yield of 56%.

When the nitration of Arndt and Rose,[6] which consists of treating methyl malonate with fuming nitric acid, was applied to the preparation of ethyl nitromalonate, yields varying from 45 to 76% were obtained. An investigation of this reaction showed that a higher temperature is necessary for optimum yields. When the nitration is allowed to proceed for several hours at 15–20°, consistent yields of around 92% can be obtained.

We have found, however, that ethyl nitromalonate prepared by these nitration procedures invariably is contaminated with oxides of nitrogen which initiate autocatalytic decomposition of the nitro ester. These oxides, which cannot be removed by repeated washing and/or distillation, are completely removed by treatment of the nitro ester with an amide such as urea or acetamide. Ethyl nitromalonate so treated is stable over long periods of time.

Experimental

Ethyl Nitromalonate (I).—Ethyl malonate (80.0 g., 0.5 mole) was placed in a 500-cc. three-necked flask fitted with a dropping funnel, a stirrer, a thermometer and an outlet protected by a drying tube. The flask was cooled by tap water at 12°, and 184 cc. of fuming nitric acid (d. 1.5) was added at a rate sufficient to maintain the temperature between 15 and 20°. The addition required one hour, after which the mixture was allowed to stir for three and one-half hours at 15°. The solution was poured onto 1 l. of ice and water and the ester extracted with 200- and 100-cc. portions of toluene. The combined toluene extracts were washed twice with water, and then with 200-cc. portions of 5% aqueous urea solution until a starch–potassium iodide test for oxides of nitrogen in the wash was negative. The toluene solution was extracted with 10% sodium carbonate solution in portions until acidification of a test portion of extract showed that it contained no nitro ester. The sodium carbonate extracts were combined and washed once with 200 cc. of toluene. The aqueous solution was then carefully acidified to congo red paper with concentrated hydrochloric acid, with cooling by the occasional addition of ice. The ester was collected by extracting with 500-, 200- and 100-cc. portions of toluene. The toluene solution was washed twice with 200-cc. portions of water and then with 5% aqueous urea solution, checking again with starch–potassium iodide test paper for the complete absence of oxides of nitrogen. Drying of the toluene solution was done over magnesium sulfate. The yield of ester was determined by weighing the toluene solution, taking an aliquot, adding an equal volume of alcohol, and titrating the nitro ester with 1 *N* sodium hydroxide to a phenolphthalein end-point. The assay showed that the yield was 94.1 g. or 91.7%. If the analytically pure ester is desired, it may be obtained by concentrating and distilling; b. p. 81–83° at 0.3 mm.; $n^{21}D$ 1.4274.

Ethyl α-Nitro-α-carbethoxy-β-(3-indole)-propionate (III).—Distilled ethyl nitromalonate,[7] 43.3 g. (0.25 mole), 250 cc. of toluene dried by distillation, and gramine,[8] 51.3 g. (0.25 mole) were placed in a 500-cc., three-necked flask fitted with stirrer, nitrogen inlet, thermometer in the mixture, and an efficient reflux condenser. With a vigorous stream of nitrogen[9] passing through the well-stirred mixture, it was heated rapidly to vigorous reflux. Dimethylamine evolution began at about 90 to 95° and was very rapid at the boiling point. Refluxing, nitrogen flow and stirring were continued until evolution of dimethylamine ceased, usually after three hours. The solution was cooled and extracted twice with 50-cc. portions of 10% hydrochloric acid, washed with 50 cc. of water, then extracted with two 50-cc. portions of 5% sodium hydroxide and washed twice with water. The toluene solution was dried over magnesium sulfate and concentrated at reduced pressure. The last traces of solvent were removed by heating at 80° and 0.5 mm. with stirring. There remained 80.5 g. (96.5%) of III as a light red, thick sirup.

Anal. Calcd. for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.29, 57.19; H, 5.14, 5.14; N, 8.45, 8.23.

Ethyl α-Nitro-β-(3-indole)-propionate (IV).—Ethyl α-nitro-α-carbethoxy-β-(3-indole)-propionate, 80.5 g. (0.24 mole), in 500 cc. of anhydrous ether was cooled in an ice-

(5) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 203 (1944).

(6) Arndt and Rose, *J. Chem. Soc.*, 1 (1935).

(7) Equally good results are obtained, however, when a stoichiometric amount of undistilled ester in toluene solution is used.

(8) Kuhn and Stein, *Ber.*, **70**, 567 (1937).

(9) This is necessary to insure rapid and complete removal of dimethylamine. If this is not done, both yield and quality of product are poor.

bath. A solution of 5.55 g. (0.24 mole) of sodium in 260 cc. of absolute alcohol was added slowly, with vigorous stirring, over a period of two hours. Precipitation of the sodium salt of IV and probably some sodium ethylate occurred to form a very thick slurry. This was stirred overnight, then filtered. The salt was washed twice with 125-cc. portions of ether, transferred to a separatory funnel, covered with 200 cc. of ether and acidified with 100 cc. of 10% hydrochloric acid. Vigorous shaking was continued until all the solid had disappeared. The ether layer was separated and the aqueous phase extracted with 100 cc. of ether. The ether solutions were combined and washed with two 200-cc. portions of water. Drying and concentration left 57.9 g. (91.6%) of crystalline IV. The identity of this material and that obtained by alkylation of ethyl nitroacetate was established by a mixed melting point.

DL-Tryptophan.—The reduction of 57.9 g. (0.221 mole) of IV was carried out in an Aminco rocking hydrogenator using 150 cc. of absolute alcohol and 6 g. of Raney nickel catalyst at 100° for one hour. The bomb was heated as rapidly as possible since we have found that a rapid reduction is necessary to avoid undesirable by-products and low yields. The catalyst was removed by filtration and to the filtrate was added 60 g. of 20% sodium hydroxide. The solution was allowed to stand overnight at room temperature. The *p*H was then adjusted to 5.9 with glacial acetic acid and crystalline material separated. After the mixture had stood in the ice-box overnight, the tryptophan was filtered and washed with water, alcohol and ether. The product was dried *in vacuo*. There was thus obtained 39.3 g. (87.1%) of white, crystalline *dl*-tryptophan; m. p. 265° (uncor., dec.).

Ethyl α-Carbethoxy-β-(3-indole)-propionate (VI).—Ethyl α-nitro-α-carbethoxy-β-(3-indole)-propionate (III), 16.72 g. (0.05 mole), in 50 cc. of absolute alcohol was reduced catalytically at 180 atm. and 100° in the presence of approximately 3 g. of Raney nickel. The observed hydrogen absorption was approximately 3.8 moles per mole of III. The oil which remained after filtration and concentration crystallized readily, representing a nearly quantitative yield of VI. An analytical sample was prepared by recrystallizing several times from 75% alcohol, m. p. 62.0–62.5° (uncor.).[5]

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.74; H, 6.52; N, 5.06.

Ethyl α-Hydroxyamino-α-carbethoxy-β-(3-indole)-propionate (VII).—To 3.34 g. (0.01 mole) of III in 25 cc. of glacial acetic acid was added 0.5 cc. of water and then 5 g. of zinc dust in small portions. The temperature was held below 45° during the addition. After forty minutes, the zinc and zinc acetate were removed by centrifugation and washed with glacial acetic acid. Concentration at reduced pressure was followed by partitioning of the crude between water and ether. The ether was washed with 5% sodium hydroxide, then with water. Drying and concentration left 1.80 g. (56%) of crystalline material. After several recrystallizations from alcohol the hydroxylamino ester melted at 131–132° (uncor.).

Anal. Calcd. for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.75. Found: C, 60.16, 59.75; H, 6.41, 6.09; N, 9.00, 9.08.

Acknowledgments.—The authors wish to thank Mr. Jack Richmond for assistance with a portion of the laboratory work, and Mr. Harold Emerson and his associates for some of the microanalyses.

Summary

1. A new synthesis of *dl*-tryptophan employing ethyl nitromalonate and gramine is reported.

2. An improved method for preparing and stabilizing esters of nitromalonic acid is described.

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Some Peptides and Peptide Derivatives Containing Leucine and Alanine

BY W. J. POLGLASE AND EMIL L. SMITH

In order to investigate further the specificity of the enzyme, leucine aminopeptidase,[1] a number of new leucine compounds were required. For a study of the stereochemical specificity[2] of this enzyme, dipeptides containing L-leucine in combination with L- and D-alanine and β-alanine were prepared. We wish to report the synthesis of D-alanyl-L-leucinamide acetate, L-alanyl-L-leucinamide acetate, L-leucyl-L-alaninamide acetate, L-leucyl-D-alaninamide acetate and β-alanyl-L-leucinamide hydrochloride. The preparation of L-alanyl-L-leucine is given in detail since this compound has not been previously synthesized by the carbobenzoxy method. The preparation of L-leucyl-L-alanine and L-leucyl-D-alanine by the carbobenzoxy method has already been described by Bergmann and co-workers.[3] Some additional data on intermediate products in the synthesis of these two peptides have now been obtained and a synthesis from racemic alanine was accomplished.

It has been the practice of most workers when preparing a dipeptide containing a D-amino acid first to resolve a racemic mixture of the amino acid by the use of an optically active base. In the preparation of a dipeptide by the carbobenzoxy method it is often possible to obtain one or two crystalline intermediate compounds as well as the final crystalline dipeptide. Thus, if a carbobenzoxy-L-amino acid is coupled to a DL-amino acid ester there may be as many as three synthetic steps at which to effect separation of the resulting diastereoisomers. We have found this method particularly useful in the preparation of L-leucyl-D-alanine and L-leucyl-L-alanine. Thus, carbobenzoxy-L-leucine was coupled through the azide with the methyl ester of DL-alanine. Carbobenzoxy-L-leucyl-D-alanine methyl ester was readily crystallized from the mixture. The diastereoisomeric compound could not be crystallized from

(1) K. Linderstrøm-Lang, *Z. physiol. Chem.*, **182**, 151 (1929); E. L. Smith and M. Bergmann, *J. Biol. Chem.*, **153**, 627 (1944).

(2) E. L. Smith and W. J. Polglase, *Federation Proc.*, **8**, 252 (1949), and to be published.

(3) M. Bergmann, L. Zervas, J. S. Fruton, F. Schneider and H. Schleich, *J. Biol. Chem.*, **109**, 325 (1935).

the mother liquor but after saponification with alkali, the resulting carbobenzoxy-L-leucyl-L-alanine was crystallized. Reduction by hydrogenation of the carbobenzoxy dipeptides gave the pure dipeptides in both instances. This procedure for the preparation of dipeptides containing a D-amino acid residue is being investigated further with other amino acids.

There appear to be few instances of the preparation of peptides by such methods. However, Behrens, Doherty and Bergmann[4] separated the products resulting from the reduction of acetyldehydrophenylalanyl-L-leucine; they obtained by differential crystallization acetyl-L-phenylalanyl-L-leucine and acetyl-D-phenylalanyl-L-leucine. Recently, Cook, Cox and Farmer[5] coupled *l*-α-bromisovaleryl chloride and DL-N-methylvaline; these products were converted to the hydroxy compounds and then to the lactones. The diastereoisomeric lactones were then separated chromatographically.

The D-alanine used in this work was prepared as described by Fischer.[6] The carbobenzoxy-D-alanine was obtained by an enzymatic resolution of carbobenzoxy-DL-alanine.[7] In the presence of aniline and cysteine-papain, the carbobenzoxy-L-alaninanilide is synthesized and crystallizes from solution; the carbobenzoxy-D-alanine is readily recovered from the mother liquor.[8] The procedure has successfully been used for the resolution of the DL mixtures of derivatives of several amino acids.[9]

Experimental

Preparation of Amino Acid Esters.—The amino acid was dissolved in ten times its weight of anhydrous methanol saturated with anhydrous hydrogen chloride at 0° and allowed to stand at 0° overnight. The reaction mixture was then concentrated to a sirup under reduced pressure and the concentration repeated several times after the addition of anhydrous methanol. The amino acid ester hydrochloride generally crystallized and was suspended in ether and collected by filtration. A solution of the free ester in the desired organic solvent was then prepared as described by Fischer.[10]

Coupling of Amino Acids.—Following the well-known method of Bergmann and Zervas,[7] the amino acid (or amino acid ester) required as the first moiety of the desired peptide was acylated with a 10% excess of carbobenzoxy chloride in the presence of two equivalents of alkali. The resulting compound was converted to the chloride (or azide) and allowed to react with the ester of the amino acid required as the second moiety. The carbobenzoxy dipeptide ester thus obtained was then saponified to the carbobenzoxy dipeptide or ammonolyzed to the carbobenzoxy dipeptide amide. Hydrogenation in the usual manner[7] of a methanolic solution of the carbobenzoxy compound in the presence of acetic acid and water and with palladium as catalyst gave the desired dipeptide or dipeptide amide acetate.

Carbobenzoxy-L-leucyl-D-alanine Methyl Ester.—This was prepared from D-alanine methyl ester hydrochloride and carbobenzoxy-L-leucine azide as described by Bergmann and co-workers,[3] m. p. 129–130°, which is the same as that previously given.[3] The optical rotation has not been reported; $[\alpha]^{27}D$ −1° (*c* 4, ethanol). The same product was obtained from carbobenzoxy-L-leucine azide and racemic alanine methyl ester hydrochloride. An ether solution of carbobenzoxy-L-leucine azide prepared from 15.6 g. of carbobenzoxy-L-leucine hydrazide[3] was added to an ether solution of DL-alanine methyl ester obtained from 5.0 g. of the hydrochloride. The mixture was allowed to stand at room temperature overnight in the hood. The ether solution was then washed with water, *N* hydrochloric acid, saturated bicarbonate and dried over sodium sulfate. The filtered solution was concentrated under reduced pressure to about 70 cc. whereupon the carbobenzoxy-L-leucyl-D-alanine methyl ester crystallized; yield 2.95 g.; m. p. 126–129°. This compound was recrystallized from ethyl acetate-petroleum ether; m. p. 129–130°, unchanged upon admixture with a specimen prepared with pure D-alanine; $[\alpha]^{21}D$ −1° (*c* 4, ethanol).

L-Leucyl-D-alanine.—This was prepared as previously described[3] by saponification of 2.02 g. of carbobenzoxy-L-leucyl-D-alanine methyl ester and reduction of the sirupy carbobenzoxy dipeptide; yield 0.9 g. The peptide was recrystallized from methanol–ethyl acetate; yield 0.7 g.; $[\alpha]^{27}D$ +80° (*c* 1, water). Bergmann, *et al.*,[3] give $[\alpha]^{22}D$ + 76.0 (*c* 2.5, water).

Anal. Calcd. for $C_9H_{18}O_3N_2$: N, 13.86. Found: N, 13.72.

Carbobenzoxy-L-leucyl-D-alaninamide.—Carbobenzoxy-L-leucyl-D-alanine methyl ester, 2.20 g., was dissolved in 30 cc. of methanol previously saturated at 0° with ammonia. After forty hours in a pressure bottle at room temperature, the solution was concentrated under reduced pressure and the amide crystallized. The product was recrystallized from ethanol–ether; needles, yield 1.65 g.; m. p. 181–182°; $[\alpha]^{22}D$ − 6° (*c* 1, ethanol).

Anal. Calcd. for $C_{17}H_{25}O_4N_3$: N, 12.5. Found: N, 12.2.

L-Leucyl-D-alaninamide Acetate.—This was obtained by hydrogenation over palladium of 1 g. of the carbobenzoxy derivative in 20 cc. of methanol containing 1 cc. of acetic acid and 1 cc. of water. The reduction was complete in two hours, the catalyst was removed by filtration and the filtrate concentrated under reduced pressure. The product crystallized after repeated concentration with anhydrous methanol and was recrystallized from methanol–ethyl acetate: needles, yield 0.72 g.; m. p. 250–255° (dec.); $[\alpha]^{22}D$ + 61° (*c* 1, water).

Anal. Calcd. for $C_{11}H_{23}O_4N_3$: N, 16.1. Found: N, 16.0.

Carbobenzoxy-L-leucyl-L-alanine Methyl Ester.—The synthesis of this compound has been described[3] (m. p. 92–93°) but the optical rotation was not reported. We observed m. p. 95–96°; $[\alpha]^{22}D$ −38° (*c* 1, ethanol).

Carbobenzoxy-L-leucyl-L-alanine.—This compound was previously described as a sirup. It was prepared as described[3] by saponification of the methyl ester. The compound crystallized at room temperature in large dodecahedra from a mixture of ethyl acetate, ethyl ether and petroleum ether (boiling range 65–110°): yield quantitative; m. p. 152–153°, $[\alpha]^{27}D$ −25° (*c* 1, ethanol).

Anal. Calcd. for $C_{17}H_{24}O_5N_2$: C, 60.7; H, 7.2; N, 8.33. Found: C, 60.4; H, 7.2; N, 8.44.

This compound was also obtained from the mother liquor of the carbobenzoxy-L-leucyl-D-alanine methyl ester resulting from coupling carbobenzoxy-L-leucine azide with racemic alanine ester. The mother liquor was concentrated to a sirup, dissolved in 20 cc. of acetone and saponi-

(4) O. K. Behrens, D. G. Doherty and M. Bergmann, *J. Biol. Chem.*, **136**, 61 (1940).

(5) A. H. Cook, S. F. Cox and T. H. Farmer, *Nature*, **162**, 61 (1948).

(6) E. Fischer, *Ber.*, **34**, 245 (1899).

(7) M. Bergmann and L. Zervas, *ibid.*, **65**, 1192 (1932).

(8) We are grateful to Dr. William H. Stein of the Rockefeller Institute for Medical Research for the preparation of carbobenzoxy-D-alanine and for his courtesy in permitting us to publish his method of preparation of this compound.

(9) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, **119**, 707 (1937); J. S. Fruton, G. W. Irving, Jr., and M. Bergmann, *ibid.*, **133**, 703 (1940); C. A. Dekker and J. S. Fruton, *ibid.*, **173**, 471 (1948); H. T. Hanson and E. L. Smith, *ibid.*, **179**, 815 (1949).

(10) E. Fischer, *Ber.*, **34**, 433 (1907).

fied with 11 cc. of *N* sodium hydroxide. After forty-five minutes at room temperature the solution was acidified and the acetone removed under reduced pressure. The resulting sirup was extracted into ethyl acetate and this solution extracted with 25 cc. of a saturated solution of sodium bicarbonate. The sodium bicarbonate solution was acidified and extracted with ethyl acetate and this extract dried with sodium sulfate. The ethyl acetate solution was concentrated to a sirup and the product crystallized from ethyl acetate, ethyl ether and petroleum ether (boiling range 65–110°); dodecahedra, yield 0.7 g., m. p. 152–153°, unchanged on admixture with a specimen prepared with L-alanine; $[\alpha]^{25}D$ −25° (*c* 1, ethanol).

L-Leucyl-L-alanine.—This was prepared as described by Bergmann and co-workers,[3] except that the above crystalline compound was the starting material. Three grams of carbobenzoxy-L-leucyl-L-alanine yielded 1.75 g. of the dipeptide. The compound was recrystallized from methanol–ethyl acetate. Fischer (see[3]) recrystallized this dipeptide by dissolving it in a large volume of hot absolute ethanol and collecting successive crops of crystals. We found that the methanol–ethyl acetate mixture gave higher yields of material having the required optical rotation. The dipeptide was dried *in vacuo* at 50°; $[\alpha]^{25}D$ + 22.9° (*c* 5, methanol) identical with that previously found.

Carbobenzoxy-L-leucyl-L-alaninamide.—This was prepared from 2.04 g. of the ester and methanol previously saturated with ammonia at 0°. After forty hours at room temperature in a pressure bottle, the solution was concentrated under reduced pressure to a crystalline mass. This was suspended in ether and filtered; needles, yield 1.76 g. The compound was recrystallized from ethanol–water; m. p. 189°, $[\alpha]^{27}D$ − 26° (*c* 0.6, ethanol).

Anal. Calcd. for $C_{17}H_{25}O_4N_3$: C, 60.9; H, 7.5; N, 12.5. Found: C, 60.9; H, 7.3; N, 12.6.

L-Leucyl-L-alaninamide Acetate.—This was prepared by hydrogenation of 1.03 g. of carbobenzoxy-L-leucyl-L-alaninamide. The reduction was complete in ninety minutes; needles, yield 0.65 g.; m. p. 250–255° (dec.); $[\alpha]^{21}D$ + 4° (*c* 1, water). The compound was dried *in vacuo* at 50°.

Anal. Calcd. for $C_{11}H_{23}O_4N_3$: C, 50.6; H, 8.9; N, 16.1. Found: C, 51.2; H, 9.0; N, 15.9.

Enzymatic Preparation of Carbobenzoxy-D-alanine.[8]—Commercial papain, 10.2 g., was stirred for thirty minutes with 255 cc. of water and filtered. Two hundred cc. of the filtrate was added to a mixture of 112 g. of carbobenzoxy-DL-alanine,[7] 135 cc. of 2 *N* sodium hydroxide, 46 cc. of aniline, 3.0 g. of cysteine and 200 cc. of citrate buffer, *p*H 5.0. The volume of the mixture was adjusted to 1,000 cc. by the addition of water and then incubated for seven days at 40°. The mixture was cooled to 0°, filtered and the precipitate washed twice with 250-cc. quantities of water. The filtrate was boiled and filtered and this filtrate was acidified with 100 cc. of 20% hydrochloric acid. The acidic solution was extracted with ether and the ether solution was extracted with saturated sodium bicarbonate solution. This solution was acidified and extracted with ether, the ether solution was washed with water and dried over sodium sulfate. The solution was then concentrated under reduced pressure to a sirup which crystallized on standing *in vacuo*. The crystalline residue was tritrated at 0° with 200 cc. of 2 *N* hydrochloric acid, filtered and the product dried in air; yield 49.5 g. For recrystallization, the product was dissolved in 200 cc. of ethyl ether and 600 cc. of light petroleum ether was added slowly, in portions. The carbobenzoxy-D-alanine was collected by filtration; m. p. 84–86°, $[\alpha]^{28}D$ + 14.0° (*c* 9, acetic acid). The constants reported by Bergmann and Zervas for carbobenzoxy-L-alanine[7] are: m. p. 84°; $[\alpha]^{17}D$ −14.3° (*c* 9, acetic acid). Hunt and du Vigneaud[11] give $[\alpha]^{27}D$ −13.9° and + 14.0 for the L and D derivatives.

Carbobenzoxy-D-alanyl-L-leucine Methyl Ester.—Carbobenzoxy-D-alanine, 5.0 g., was dissolved in 20 cc. of anhydrous ethyl ether and shaken at 0° with 5.0 g. of phosphorus pentachloride until all but a trace of the latter had dissolved. Light petroleum ether, previously cooled to −50° (*cf.* 11) was added and the oil which precipitated was washed three times with petroleum ether. The oil was then dissolved in 30 cc. of chloroform, previously cooled to −50°. This solution was added to a solution of L-leucine methyl ester (from 8.2 g. of the hydrochloride) in 30 cc. of chloroform. After thirty minutes at 0° and one hour at room temperature, the chloroform solution was washed with water, saturated sodium bicarbonate and *N* hydrochloric acid. The chloroform layer was dried over sodium sulfate and concentrated to a sirup which crystallized upon addition of petroleum ether; yield 5.7 g. The product was recrystallized from ethyl ether–petroleum ether (boiling range 30–60°); m. p. 72–73°; $[\alpha]^{27}D$ −9° (*c* 1, ethanol).

Anal. Calcd. for $C_{18}H_{26}O_5N_2$: N, 8.0. Found: N, 7.9.

Carbobenzoxy-D-alanyl-L-leucinamide.—This was prepared at room temperature by ammonolysis for forty hours with saturated methanol–ammonia of 3.75 g. of the corresponding ester. The amide crystallized upon concentration of the reaction mixture under reduced pressure; needles, yield 2.84 g. The product was recrystallized from ethanol–water; m. p. 187–188°; $[\alpha]^{30}D$ − 6° (*c* 1, ethanol).

Anal. Calcd. for $C_{17}H_{25}O_4N_3$: N, 12.5. Found: N, 12.5.

D-Alanyl-L-leucinamide Acetate.—This was obtained by hydrogenation of 2.25 g. of carbobenzoxy-D-alanyl-L-leucinamide. It crystallized in needles after repeated concentration of the filtered reaction mixture with ethanol; yield 1.61 g. The compound melted at 147°, immediately re-solidified and melted with decomposition at 249–250°; $[\alpha]^{26}D$ − 35° (*c* 1.5, water). The compound was dried *in vacuo* at 25°.

Anal. Calcd. for $C_{11}H_{23}O_4N_3$: C, 50.6; H, 8.9; N, 16.1. Found: C, 50.6; H, 8.9; N, 16.1.

Carbobenzoxy-L-alanyl-L-leucinamide.—Carbobenzoxy-L-alanine, 11.1 g., was converted to the acid chloride and dissolved in chloroform (75 cc.) as described above in the preparation of carbobenzoxy-D-alanyl-L-leucine methyl ester. The chloroform solution was added to a chloroform solution of leucine methyl ester obtained from 9.1 g. of the hydrochloride. After about five minutes, potassium bicarbonate, 5 g. in water, was added and the mixture shaken at frequent intervals. After one hour, the chloroform layer was washed with dilute hydrochloric acid and with water, dried over sodium sulfate and concentrated under reduced pressure to a sirup. The entire product was converted to the amide with saturated methanol–ammonia. After forty hours the solution was concentrated under reduced pressure and the amide crystallized: needles, yield 4.3 g.; m. p. 185–187°. The product was recrystallized from ethanol–water, m. p. 188–189°; $[\alpha]^{30}D$ − 41° (*c* 1, ethanol).

Anal. Calcd. for $C_{17}H_{25}O_4N_3$: N, 12.5. Found: N, 12.6.

L-Alanyl-L-leucinamide Acetate.—This was prepared by hydrogenation of 3.00 g. of carbobenzoxy-L-alanyl-L-leucinamide; needles, yield 2.32 g. The compound was dried at 25° *in vacuo*. It softened at 158° and gradually darkened on further heating, melting at 250°; $[\alpha]^{28}D$ −9° (*c* 2, water).

Anal. Calcd. for $C_{11}H_{23}O_4N_3$: C, 50.6; H, 8.9; N, 16.1. Found: C, 50.9; H, 9.2; N, 16.0.

L-Alanyl-L-leucine.—This compound has been prepared by Fischer[12] but its synthesis by the carbobenzoxy method has not been reported. Carbobenzoxy-L-alanine, 22.3 g., was coupled with leucine methyl ester (from 20 g. of the hydrochloride) as described above in the preparation of carbobenzoxy-L-alanyl-L-leucinamide. The resulting sirupy carbobenzoxy-L-alanyl-L-leucine methyl ester was saponified in 150 cc. of acetone and 45 cc. of *N* sodium

(11) M. Hunt and V. du Vigneaud, *J. Biol. Chem.*, **124**, 699 (1938).

(12) E. Fischer, *Ber.*, **40**, 1754 (1907).

hydroxide. After forty-five minutes at room temperature, the solution was neutralized with *N* hydrochloric acid and the acetone removed by distillation under reduced pressure. The water insoluble sirup was taken into ethyl acetate, and the solution dried and concentrated. The resulting sirup was hydrogenated in 60 cc. of methanol containing 4 cc. of acetic acid and 4 cc. of water with palladium catalyst. The reduction was complete after forty-eight hours. The catalyst was removed by filtration, the filtrate concentrated under reduced pressure to a sirup from which the acetic acid and water were removed by repeated concentration with anhydrous methanol. The product was crystallized from methanol–ether and dried at 75° *in vacuo:* yield 2.60 g.; $[\alpha]^{21}D$ − 17.0° (*c* 5, water). Fischer[12] found $[\alpha]^{20}D$ − 17.2 and − 16.8°.

Carbobenzoxy-β-alanyl-L-leucinamide.—Carbobenzoxy-β-alanine,[13] 6.65 g., in anhydrous ethyl ether, 25 cc., was converted to the acid chloride as previously described[13] and was added to an ether solution of L-leucine methyl ester prepared from 5.9 g. of the hydrochloride. After a few minutes at 0°, 3.5 g. of potassium bicarbonate in water was added and the mixture shaken frequently for an hour during which time the mixture was allowed to come to room temperature. The ether layer was separated and washed with dilute hydrochloric acid and with water. The solution was dried over sodium sulfate and then concentrated under reduced pressure to a sirup. The sirupy product was converted to the amide as described above; needles, yield 5.70 g., m. p. 172–173°. The amide was recrystallized from ethanol–water, m. p. 174–175°.

Anal. Calcd. for $C_{17}H_{25}O_4N_3$: C, 60.9; H, 7.5; N, 12.5. Found: C, 61.0; H, 7.2; N, 12.5.

(13) R. H. Sifferd and V. du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935).

β-Alanyl-L-leucinamide Hydrochloride.—This was prepared by hydrogenation of 2.50 g. of carbobenzoxy-β-alanyl-L-leucinamide. The reduction was complete in three hours and the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to a sirup and this procedure repeated several times after the addition of successive small portions of ethanol. Since the product failed to crystallize as the acetate, the sirup was dissolved in 30 cc. of ethanol and 1 cc. of concentrated hydrochloric acid was added. The compound crystallized as the hydrochloride upon the addition of ether as plates; yield after drying *in vacuo* over sulfuric acid at 25°, 1.55 g.; m. p. 120° with evolution of gas; hygroscopic, $[\alpha]^{26}D$ − 17° (*c* 2, water).

Anal. Calcd. for $C_9H_{20}O_2N_3Cl$: C, 45.5; H, 8.5; N, 17.7. Found: C, 45.3; H, 8.6; N, 17.6.

Acknowledgment.—This investigation was aided by grants from the United States Public Health Service.

Summary

1. The preparation and properties of some dipeptides and dipeptide derivatives containing L-leucine, D- and L-α-alanine and β-alanine are described.

2. L-Leucyl-D-alanine and L-leucyl-L-alanine have been synthesized from L-leucine and racemic alanine.

3. The enzymatic preparation of carbobenzoxy-D-alanine from carbobenzoxy-DL-alanine is described.

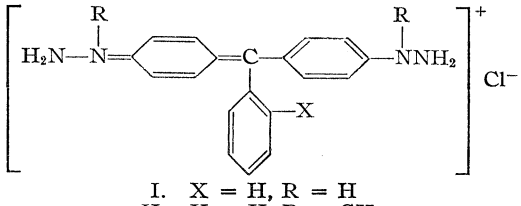
SALT LAKE CITY, UTAH RECEIVED APRIL 30, 1949

[CONTRIBUTION FROM THE BALLISTIC RESEARCH LABORATORIES]

Triphenylmethane Dyes Containing the Hydrazine Group and Their Condensation Products with Aldehydes

BY LESTER P. KUHN AND LOUIS DEANGELIS

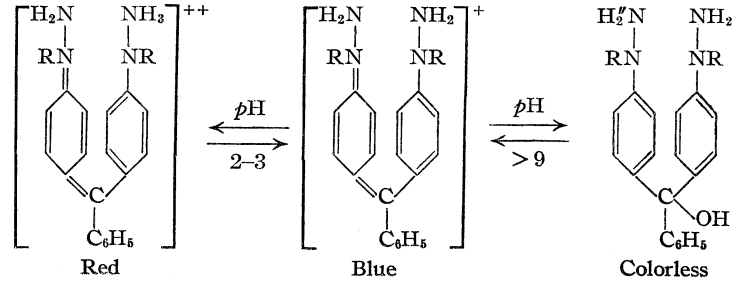
In order to obtain an improved reagent for the determination of aldehydes we sought to prepare a



I. X = H, R = H
II. X = H, R = CH_3
III. X = SO_3^-, R = CH_3

dye which contains a functional group capable of reacting readily with aldehydes and which as a result of its reaction would change color. Schwarzenbach[1] prepared N,N′ substituted phenylhydrazine sulfonphthalein dyes and showed that they are deeply colored stable compounds quite similar in properties to the aniline sulfonphthaleins. More recently *p,p′*-dihydrazinotriphenylmethyl chloride, I, and its N-methyl derivative, II, have been prepared.[2] It was shown that these dyes react readily with aldehydes, but not with ketones, and that the color of the dye solution changes from red to blue or to green. In the present work the preparation of I and II has been repeated, and the new dye III has been prepared. An attempt has been made to further evaluate these compounds as reagents for the determination of aldehydes and also to explain the color changes which are observed.

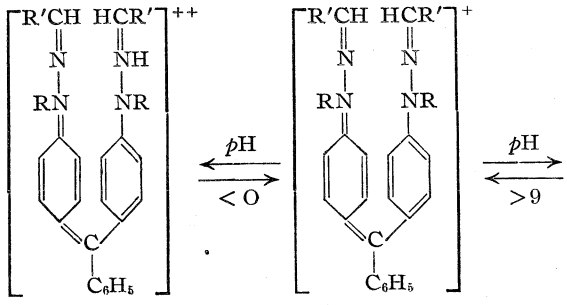
The dyes I, II and III can exist in several different states depending upon the *p*H of the solution in the manner shown here.



(1) Schwarzenbach, *Helv. Chim. Acta*, **20**, 498 (1937).

(2) Ciusa and Ottolino, *Gazz. chim. ital.*, **75**, 171 (1945); *C. A.*, **41**, 4137 (1947).

The hydrazones show a similar behavior



In the hydrazone series the conversion of the singly charged cation to the doubly charged cation requires a relatively concentrated solution of sulfuric or hydrochloric acids whereas in the hydrazine series the change occurs at a *p*H of 2–3. This difference which is due to the stronger basicity of the hydrazine group as compared with the hydrazone makes possible the use of these dyes as extremely good reagents for aldehydes. Ciusa and Ottolino[2] described the hydrazine dye as red and the hydrazone dye as blue or green and did not mention the fact that the color of these compounds depends upon the solution *p*H. Apparently they happened to be working in the *p*H range in which the hydrazine dye is stable in its red form and the hydrazone in its blue form.

A solution of any of the hydrazine dyes may be prepared in either water, methanol, or mixtures of the two and acidified to the point where the red color is obtained. Upon the addition of a drop of solution containing an aldehyde a color change is obtained within a minute. With aliphatic aldehydes the color becomes blue and with aromatic aldehydes it becomes green due to the formation of the hydrazone dye. The results obtained with a number of different aldehydes are given in Table I. Interestingly enough, ketones do not react under the conditions employed except the very readily enolizable ketone, ethyl acetoacetate. Sugars and chloral hydrate were the only aldehydes which did not give a positive test. With this reagent we have been able to detect 2 parts of benzaldehyde in a million parts of methanol.

Figures 1, 2 and 3 show the absorption curves for dyes I, II and III, respectively, in the red and blue forms and also the curves for the hydrazones formed from formaldehyde, acetaldehyde and benzaldehyde.

For the quantitative determination of aldehydes dye III should be used because its hydrazones are more soluble than the hydrazones of dyes I and II. A calibration curve is first prepared by making up solutions of known concentrations of the aldehyde to be determined and excess dye and then obtaining the optical density as a function of concentration. Figure 4 shows the calibration curves for acetaldehyde and benzaldehyde. The latter is a straight line but the former is slightly concave downward because the unreacted hydrazine dye has an appreciable absorption at the wave length where the absorption maximum of the acetaldehyde hydrazone occurs. The concentration of aldehyde in the solution to be analyzed can be obtained by comparing the intensity of color which it yields upon reaction with the reagent with the calibration curve, if the experimental conditions are kept constant. It is beyond the scope of this paper to make a complete evaluation of this reagent

TABLE I

EFFECT OF VARIOUS SUBSTANCES UPON DYES

Compound	Color produced
Formaldehyde	Blue
Acetaldehyde	Blue
Benzaldehyde	Green
Glyoxal	Blue
Furfural	Green
Crotonaldehyde	Green
Chloral hydrate	No change
Anisaldehyde	Green
p-Nitrobenzaldehyde	Green
Glucose	No change
Fenchone	No change[a]
Acetone	Deeper red[b]
Acetophenone	Deeper red[b]
Paraldehyde	Blue
Acetonyl acetone	No change[b]
Methyl glyoxal	Purple
Piperonal	Green
Ethyl acetoacetate	Blue
Cinnamaldehyde	Green
p-Dimethylaminobenzaldehyde	Green

[a] Turns blue after standing for ten minutes. [b] Turns purple after standing for ten minutes.

TABLE II

ABSORPTION MAXIMA OF DYES OF FORM R=D—R[a,b]

R	Triphenylmethane dyes[a]	Sulfonphthalein dyes[b]
NH_2	562	576
$NHNH_2$	580	
$NHCH_3$		604
$N(CH_3)_2$	618	
NCH_3NH_2	590	610
$NHN{=}CH_2$	615	
$NCH_3N{=}CH_2$	625	635
$NHN{=}CHCH_3$	640	
$NCH_3N{=}CHCH_3$	645	660
$NHN{=}CHC_6H_5$	685	
$NCH_3N{=}CHC_6H_5$	700	705
$NHN{=}CHC_6H_4NO_2$-*p*	680	
$NCH_3N{=}CHC_6H_4NO_2$-*p*	695	700
$NHN{=}CHC_6H_4OCH_3$-*p*	705	
$NCH_3N{=}CHC_6H_4OCH_3$-*p*	730	730
$NHN{=}CH{-}CH{=}CH{-}C_6H_5$	710	
$NCH_3N{=}CH{-}CH{=}CH{-}C_6H_5$	735	735

[a] D = $C_6H_4C(C_6H_5)C_6H_4$. [b] D = $C_6H_4C(C_6H_4SO_3)C_6H_4$.

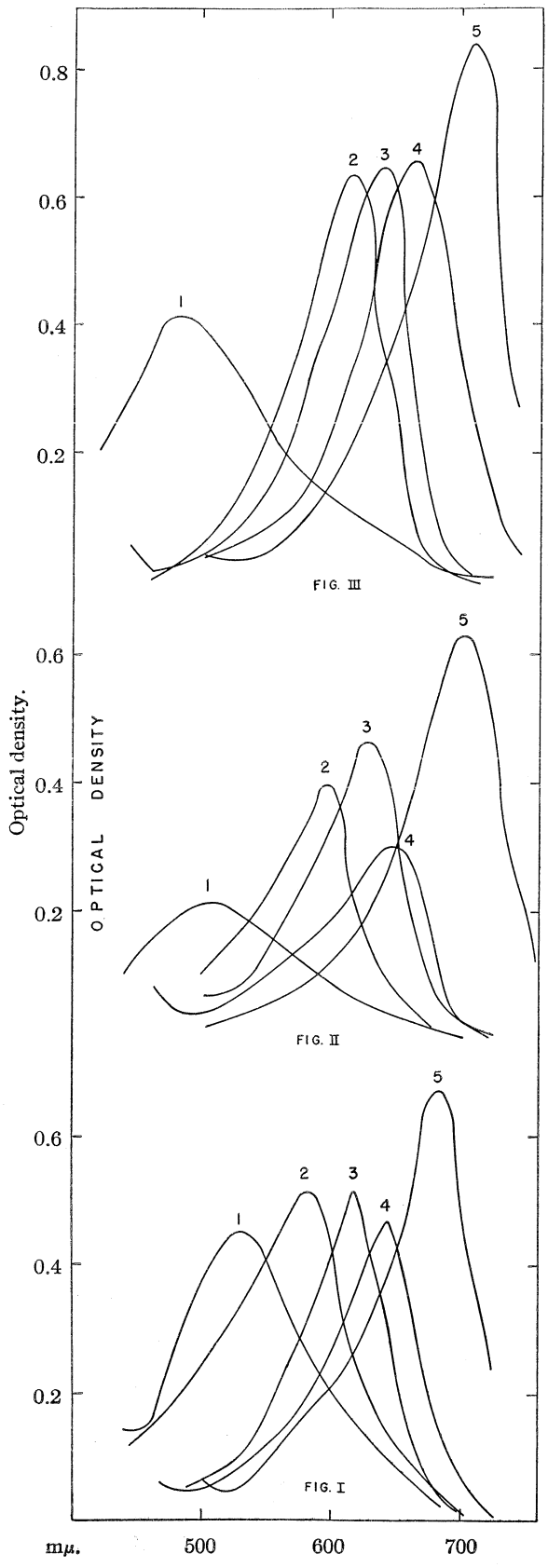


Fig. 3.—Absorption spectrum of III in methanol–water: 1, pH < 2; 2, pH 5; 3, formaldehyde added pH < 2; 4, acetaldehyde added pH < 2; 5, benzaldehyde added pH < 2.

Fig. 2.—Absorption spectrum of II in methanol–water: 1, pH < 2; 2, pH 5; 3, formaldehyde added pH < 2; 4, acetaldehyde added pH < 2; 5, benzaldehyde added pH < 2.

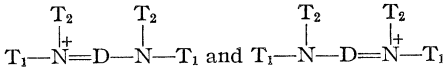
Fig. 1.—Absorption spectrum of I in methanol–water: 1, pH < 2; 2, pH 5; 3, formaldehyde added pH < 2; 4, acetaldehyde added pH < 2; 5, benzaldehyde added pH < 2.

for quantitative determinations but it is rather our intention to indicate the possibility of its use.

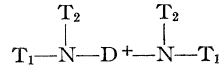
The absorption maxima of the various dyes are given in Table II. The following changes in the dye molecule result in a deepening of the color (bathochromic effect): replacement of the amino group of the diaminotriphenylmethane dye with the hydrazine group, replacement of the hydrogen atom on the nitrogen with methyl, conversion of the hydrazine dye to a hydrazone. The position of the absorption maximum of the hydrazone dyes derived from aldehydes of the general formula, RCHO, is displaced toward the longer wave lengths as R goes through the series H, CH_3, *p*-nitrophenyl, phenyl, *p*-methoxyphenyl, C_6H_5-CHCH.

A number of interesting relationships between the constitution of cyanine dyes and their color have been deduced by Brooker.[3] These relationships have been extended to the dyes of the triphenylmethane series by Branch and co-workers.[4]

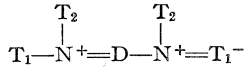
It is of interest to apply these relationships to these new dyes. The dyes in their deeply colored state have a high degree of resonance and it is possible to picture the various structures which contribute to the actual state of the molecule using the symbolism devised by Branch.[4] Let us represent the dye by the symbol $T_1T_2N—D—N—T_1T_2$, where D is $C_6H_4C(C_6H_5)$-C_6H_4, the N's are the auxochromic nitrogen atoms and T_1 and T_2 are the terminal groups bound to these nitrogen atoms. Thus for dye I, T_1 is H and T_2 is NH_2. The various structures contributing to the actual structure of the molecule are



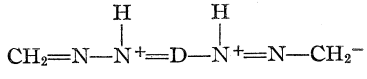
which are the A structures



which is the P structure and

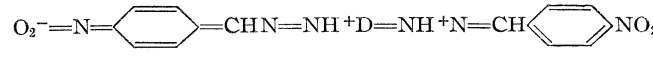


which is the T structure. Contributions from the T structures are possible only if T_1 or T_2 contains a double bond. It may be illustrated by the formaldehyde hydrazone of dye I



Constitutive features which increase the stability of structures A and T have a bathochromic effect upon the dye. The stability of the A structure depends upon the ability of the nitrogen to contribute its unshared electrons to the resonating system and thereby becoming positively charged. This ability depends upon the nature of the substituents on the nitrogen atom, the more electronegative the substituent the less will be the tendency of the nitrogen to donate its unpaired electrons. Since hydrogen is more electronegative than NH_2 which is more electronegative than CH_3, it is in agreement with theory that the hydrazinotriphenylmethane dye absorbs at longer wave length than the amino dye but at slightly shorter wave length than the methylamino dye.

Conversion of the hydrazine dyes to the hydrazone dyes with an aldehyde, RCHO, reduces the basicity of the auxochromic nitrogen and hence reduces the stability of the A structure which should result in a hypsochromic effect. However, it makes possible the existence of the T structures and the net result is a deepening of the color. When R is aromatic the colors are deeper than when R is aliphatic because the polarizability of the benzene ring makes the T structures more stable. The introduction of the electron attracting nitro group into the benzene ring of R would be expected to produce a bathochromic effect since it stabilizes the T structure



Similarly the methoxy group should produce a hypsochromic effect since it tends to yield electrons and become positively charged, and hence reduces the stability of the T structure. Since the expected effects are opposite to those which are actually observed it seems likely that other resonance forms must be considered which make significant contributions to the actual state of the molecule and which influence the color. For the

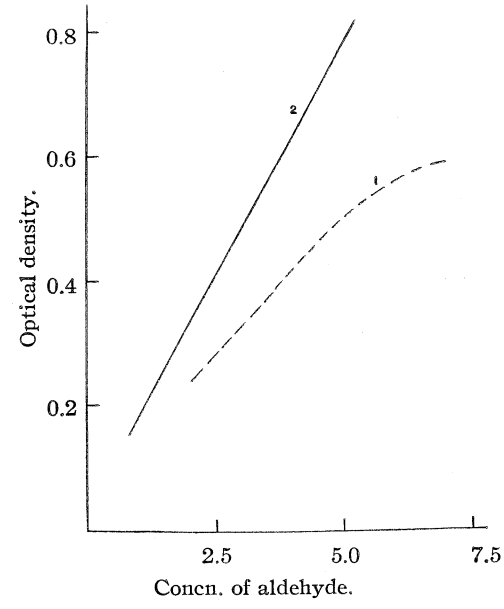
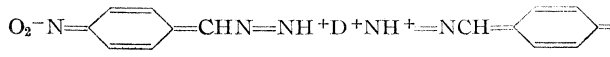


Fig. 4.—Calibration curve for the determination of aldehydes with III pH < 2: 1, acetaldehyde; 2, benzaldehyde.

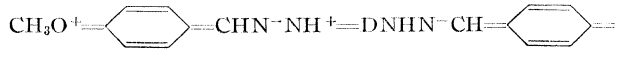
(3) Brooker, *Rev. Modern Phys.*, **14**, 275 (1942).

(4) Tolbert, Branch and Berlenbach, THIS JOURNAL, **67**, 887 (1945); (b) Branch, Tolbert and Lowe, *ibid.*, **67**, 1653 (1945).

nitro compound the structure



which is similar to the P structure may account for the observed hypsochromic effect. The methoxy group would stabilize the form



which like the A structure would produce a bathochromic effect. With molecules of this type a number of different resonance structures can be pictured which make significant contributions to the actual state of the molecule. Some of these structures can be associated with a bathochromic effect and other structures with a hypsochromic effect. The introduction of a substituent may stabilize several different structures which have opposing effects upon the color, and hence it is not easy to predict what the net result will be.

Lengthening the conjugated carbon chain in the terminal group, T_1, has a bathochromic effect as can be seen by comparing the benzaldehyde dyes with the cinnamaldehyde dyes; also the crotonaldehyde compounds are deeper than the acetaldehyde dyes.

Experimental

Dyes I and II were prepared by the reactions

$$C_6H_5CCl_3 + 2C_6H_5CH{=}NNRC_6H_5 \xrightarrow{ZnCl_2} [(C_6H_5CH{=}NNRC_6H_4)_2CC_6H_5]^+Cl^- + 2HCl$$

$$[(C_6H_5CH{=}NNRC_6H_4)_2CC_6H_5]^+ Cl^- + 2H_2O \xrightarrow{H_2SO_4} 2C_6H_5CHO + [(H_2NNRC_6H_4)_2CC_6H_5]^+Cl^-$$

I, R = H
II, R = CH_3

The benzalhydrazone dyes were isolated as green lustrous crystals. The structure of these was not proven; however, evidence for the validity of the assigned structure is based upon the elementary analyses, the method of synthesis and the similarity of properties with the properties of other triphenylmethane dyes whose structures are well known. The dyes I, II and III were prepared by the hydrolysis of the corresponding benzalhydrazones. They were not isolated but were used in the solutions in which they were prepared.

Benzalhydrazone of I.—Benzotrichloride, benzalphenylhydrazone and anhydrous zinc chloride in molar ratio of 1:2:1 were intimately mixed and heated slowly to 80° with constant mixing by hand. The mixture turned green and was maintained at 80° for thirty minutes. After cooling to room temperature the product was broken up and washed with ligroin. It was then dissolved in methanol, precipitated with dilute hydrochloric acid, filtered and washed with dilute hydrochloric acid and air dried. The product was dissolved in chloroform, the chloroform solution washed with dilute hydrochloric acid and then water and dried with calcium chloride. The product was precipitated by the addition of ethyl ether, filtered and washed with ethyl ether. It was finally recrystallized from acetic acid and benzene. The pure product crystallized out after standing for several days. The analytical data suggest that the dye contains 1 mole of water.

Anal. Calcd. for $C_{33}H_{27}N_4ClH_2$: C, 74.5; H, 5.50; N, 10.5. Found: C, 74.0; H, 5.80; N, 10.3.

The benzalhydrazone of II was prepared in the same manner except that benzalphenylmethylhydrazone was used instead of benzalphenylhydrazone. For analysis this dye was converted to its methyl ether by dissolving the dye in methanol and adding sodium methylate solution until the green color disappeared. The methyl ether was precipitated with water, filtered and washed with water and dried over phosphoric anhydride. The methyl ether can be converted back to the original colored dye by the addition of acid.

Anal. Calcd. for $C_{36}H_{34}N_4O$: C, 80.5; H, 6.0; N, 10.4. Found: C, 79.6; H, 6.4; N, 10.4.

The benzalhydrazone of III was prepared in the same manner except that the benzotrichloride was replaced by the pseudo dichloride of *o*-sulfobenzoic acid.

Anal. Calcd. for $C_{36}H_{31}N_4SClO_3$: C, 67.5; H, 5.04; N, 9.00; S, 5.15. Found: C, 67.1; H, 5.44; N, 8.43; S, 5.12.

To hydrolyze, 50 mg. of the dye was dissolved in 25 ml. of methanol, and 25 ml. of 20% by volume aqueous sulfuric acid was added. The solution was heated on a steam-bath for 0.5 to one hour or until the color of the solution has turned from green to red, the volume being kept approximately constant by the addition of 50% methanol. The benzaldehyde resulting from the hydrolysis evaporated off. After filtration the solution may be used as an aldehyde reagent. Its reactivity seems to decrease slowly and after two weeks it reacts sluggishly with aldehydes. We have found that the reagent performs satisfactorily for a period of a week after it has been prepared. For this reason it is advisable to store the dye as the hydrazone and to hydrolyze it as it is needed.

The qualitative tests with the various aldehydes were run by adding a drop of aldehyde to about 5 ml. of the reagent. The calibration curves for the quantitative determination of acetaldehyde and benzaldehyde, respectively, were obtained by measuring into 10-ml. volumetric flasks 3 ml. of the reagent Dye III and varying amounts from 0 to 0.8 ml. of aldehyde solution which contained 1 drop of aldehyde in 400 ml. of aldehyde-free methanol. The flasks were brought up to volume with methanol and were allowed to stand overnight. The readings were taken with a Beckman Spectrophotometer at the wave length where absorption of the dye formed with the particular aldehyde is at a maximum. This of course must be determined in advance using an excess of aldehyde. It was found that the concentration of dye in the reagent should be such that the contents of the flask which contains no aldehyde should have an optical density of 0.03 to 0.04 at the wave length at which the measurements will be taken.

Summary

Three hydrazinotriphenylmethane dyes have been prepared and have been tested with various aldehydes to yield the corresponding hydrazones. An explanation has been provided for the color change accompanying this reaction which corrects misconceptions of previous workers. The absorption of these compounds in the visible spectral region has been measured. The usefulness of these dyes as reagents for the qualitative determination of aldehydes has been demonstrated and the possibility of using them for quantitative measurements has been indicated. The relationship between the color and constitution of these compounds has been discussed and principles set forth by previous workers on other dyes have been extended.

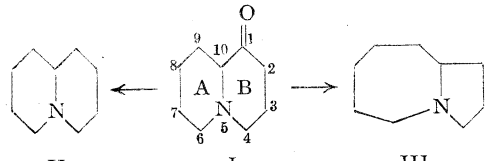
ABERDEEN, MARYLAND RECEIVED DECEMBER 30, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Rearrangement of α-Aminoketones During Clemmensen Reduction. I. Bicyclic Compounds Containing a Bridge-head Nitrogen[1]

BY NELSON J. LEONARD AND WILLIAM C. WILDMAN

The Clemmensen reduction of 1-ketoquinolizidine (I) leads not to the normal product, quinolizidine (II),[2] but to the rearrangement product, 1-azabicyclo[5.3.0]decane (III).[3] We have now established that this reductive rearrangement proceeds with ketone-ring (B) contraction.

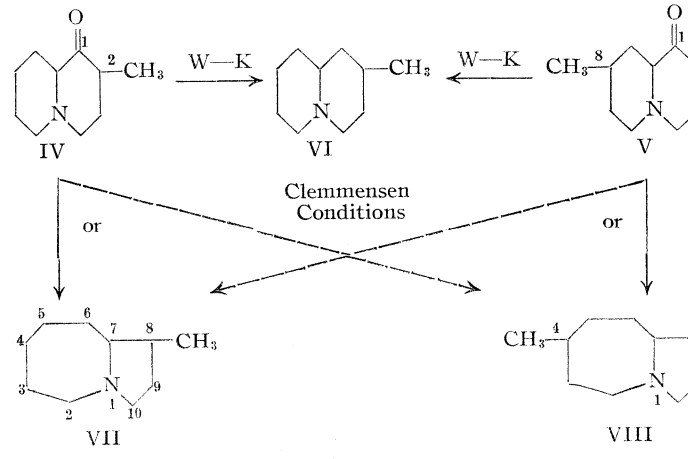


II I III

Quinolizidine (II),[4] the parent nucleus of the *Lupin* alkaloids, was first synthesized by Clemo, Ramage and Raper in 1932.[5] The compound was also synthesized satisfactorily in the same laboratory[2] by the Clemmensen reduction of 2-ketoquinolizidine and by the Wolff–Kishner reduction of 1-ketoquinolizidine (I). However, when the Clemmensen method was applied to I, an isomer of II was obtained, the structure of which was unknown until proved through an unequivocal synthesis by Prelog and Seiwerth[3] to be 1-azabicyclo[5.3.0]decane (III). No clearly outlined mechanism for this unusual rearrangement has been proposed, but Prelog and Seiwerth suggested that the first step might be a cleavage of the α–C–N bond in the acid medium, followed by an intramolecular condensation of the secondary amino group with the carbonyl group and reduction to give the new ring system. The work of Cromwell[6] indicates that α-aminoketones are not as readily cleaved as β-aminoketones in acid medium. Nevertheless, if cleavage is involved as the initial step in the rearrangement, it is conceivable that α,β-unsaturation might develop. The secondary amine could then add intramolecularly in a 1,4-manner to the unsaturated ketone. In other words, the conversion of I to III does not indicate whether it is ring A or ring B which contracts from a six to a five-membered ring. A logical way to begin the study of the mechanism of the rearrangement is to learn which ring contracts and which expands.

The "labelling" of either ring with a methyl group provides an attractive means of following contraction or expansion. Clemo and his coworkers have provided the model compounds, for they carried out Clemmensen reductions of 1-keto-2-methylquinolizidine (IV)[7] and 1-keto-8-methylquinolizidine (V).[8] The products of Clemmensen reduction were not identical with each other and were not identical with the normal (Wolff–Kishner) reduction product of each: 2-methylquinolizidine (VI).[9]

The Clemmensen reduction products are therefore represented as VII and VIII, but the question as to which rearranged amine resulted from which aminoketone could not be decided until the amines were synthesized by an unequivocal method. We have now completed unequivocal syntheses of VII and VIII, and it is the comparison of these amines with the Clemmensen reduction products of IV and V which enables us to state that the ketonic ring (B) contracts. In brief, identical physical properties were exhibited by the derivatives of 8-methyl-1-azabicyclo[5.3.0]decane (VII) (picrate, m. p. 181–182°; picrolonate, m. p. 189–190°) and the Clemmensen reduction product of IV (picrate, m. p. 182°; picrolonate, m. p. 189°)[7]; by the derivatives of 4-methyl-1-azabicyclo[5.3.0]decane (VIII) (picrate, m. p. 189°; picrolonate, m. p. 138–139°) and the Clemmensen reduction product of V (picrate, m. p. 189°; picrolonate, m. p. 138°).[8] The established course of



IV VI V VII VIII

(1) Supported in part by a grant from the Research Board of the University of Illinois.

(2) Clemo, Metcalfe and Raper, *J. Chem. Soc.*, 1429 (1936).

(3) Prelog and Seiwerth, *Ber.*, **72**, 1638 (1939).

(4) Known alternatively as norlupinane, octahydropyridocoline, and 1-azabicyclo[4.4.0]decane.

(5) Clemo, Ramage and Raper, *J. Chem. Soc.*, 2959 (1932).

(6) Cromwell, *Chem. Rev.*, **38**, 83 (1946), and primary refereuces

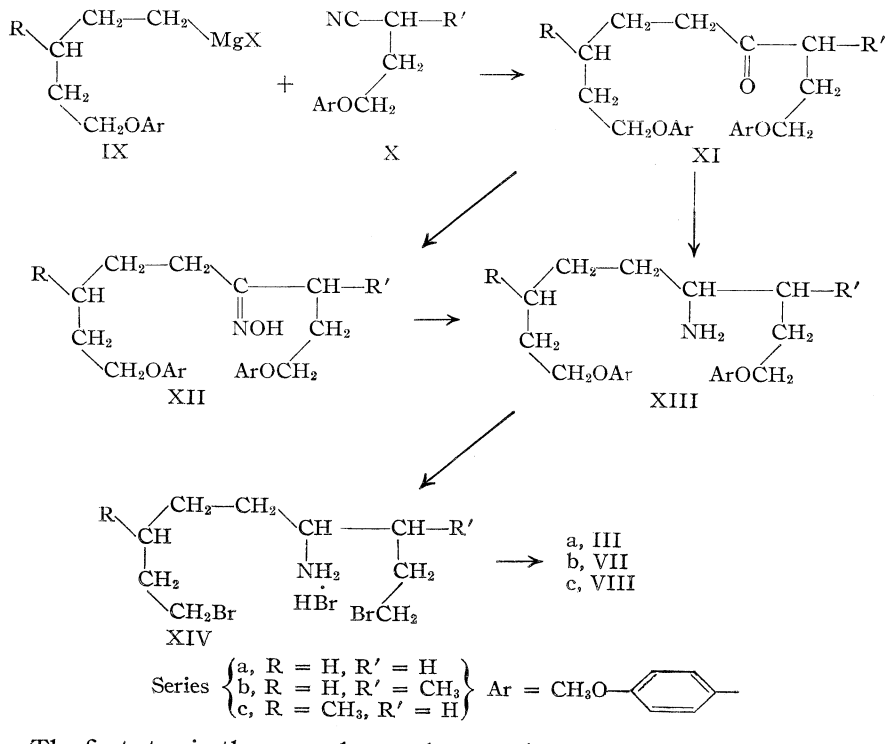
(7) Clemo and Metcalfe, *J. Chem. Soc.* 1518 (1937).

(8) Clemo, Cook and Raper, *ibid.*, 1183 (1938).

(9) The product of Wolff–Kishner reduction of IV was described as 2-methyloctahydropyridocoline (picrate, m. p. 158°; picrolonate, m. p. 219°)[7]; that from V, as 8-methyloctahydropyridocoline (picrate, m. p. 150°; picrolonate, m. p. 197°).[8] Both products should be named 2-methyloctahydropyridocoline (or 2-methylquinolizidine). Even if they were not actually identical, they could only be different racemates represented by the same structure (VI).

the Clemmensen reduction is thus indicated by the unbroken arrows in the accompanying diagram (IV → VII and V → VIII).

Unequivocal methods of synthesis of VII and VIII were realized by applying certain modifications to the general method which Prelog and his co-workers devised for the preparation of bicyclic compounds containing a bridge-head nitrogen.[3,10,11] Our modified method was checked by a "control" run: the synthesis of the known compound, 1-azabicyclo[5.3.0]decane (III), through the intermediates IXa, Xa, XIa, XIIa, XIIIa, and XIVa. The methyl-substituted products VII and VIII were then prepared by the similar reaction series b and c. The use of the terminal aryloxy group in the intermediates (IX, X, XI, and XIII) was suggested by our desire to work with crystalline and easily separable compounds. The utilization of the *p*-methoxyphenoxy group specifically was guided by the finding of Ziegler and his co-workers[12] that certain *p*-methoxyphenyl ethers were cleaved by acid more readily than the analogous phenyl ethers. The use of the *p*-methoxyphenoxy group insured facile acid cleavage of XIII to XIV.



The first step in the general procedure employed for the synthesis of III, VII and VIII was the Grignard reaction. The halide precursors of the Grignard reagents IXa and IXc were made by condensation of hydroquinone monomethyl ether with 1,5-dichloropentane and 1,5-dibromo-3-methylpentane,[13] respectively. The nitriles Xa and Xb were made by methods previously described for the phenoxy analogs. The reaction between the Grignard reagents (IX) and the nitriles (X) proceeded normally, but special precautions were necessary in the hydrolysis and isolation to insure the maximum yield of each ketone, 1,9-bis-(*p*-methoxyphenoxy)-4-nonanone (XIa), 1,9-bis-(*p*-methoxyphenoxy)-3-methyl-4-nonanone (XIb), and 1,9-bis-(*p*-methoxyphenoxy)-3-methyl-6-nonanone (XIc). Oximes (XII) were formed from each ketone, and the oximes could be reduced with sodium and ethanol to the corresponding amines (XIII). However, the conversion of the ketones (XI) to the amines (XIII) was accomplished more efficiently by hydrogenation in liquid ammonia over Raney nickel catalyst at high temperature and pressure. 4-Amino-1,9-bis-(*p*-methoxyphenoxy)-nonane (XIIIa) was obtained in crystalline form without difficulty. Although the other two amines (XIIIb and XIIIc) were not readily crystallizable, suitable crystalline derivatives were found in the hydrochloride monohydrate of 4-amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane (XIIIb) and in the half ammonium oxalate salt of 6-amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane (XIIIc). No attempt was made to isolate the α,ω-dibromoamine hydrobromides (XIV) which were obtained by hydrobromic acid cleavage of XIII, although the quantitative recovery of hydroquinone in a trial run indicated that cleavage was proceeding satisfactorily. The crude α,ω-dibromoamine hydrobromides (XIV) were converted to the 1-azabicyclo[5.3.0]decanes (III, VII, VIII) by intramolecular dialkylation of the primary amine group in dilute aqueous sodium hydroxide. The final products (III, VII, VIII) were characterized by the formation of suitable derivatives. Although diastereoisomeric racemates might have been expected from both 8-methyl-1-azabicyclo[5.3.0]-decane (VII) and 4-methyl-1-azabicyclo[5.3.0]-decane (VIII), single derivatives were isolated in every case.

With the establishment of the fact that the ketone ring contracts during the Clemmensen reduction of the 1-ketoquinolizidines (I, IV, V), it be-

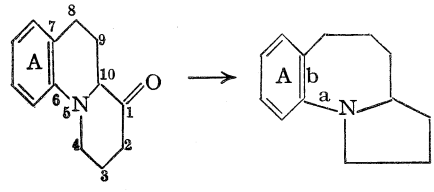
(10) Prelog and Bozicevic, *Ber.*, **72**, 1103 (1939).

(11) Prelog and Zalan, *Helv. Chim. Acta*, **27**, 531 (1944).

(12) (a) Ziegler and Weber, *Ber.*, **70**, 1275 (1937); (b) Ziegler, Weber and Gellert, *ibid.*, **75**, 1715 (1942).

(13) Leonard and Wicks, THIS JOURNAL, **68**, 2402 (1946).

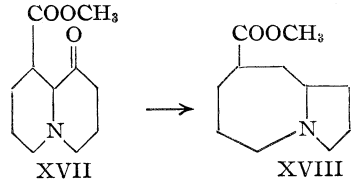
comes possible to assign correct structures to the Clemmensen reduction products of several analogous compounds investigated by Clemo and his co-workers. The product of Clemmensen reduction (which differed from the normal or Wolff–Kishner product)[14] of 1-keto-6,7-benzoquinolizidine (XV)[15] therefore has the structure: benzo-[b]-1-azabicyclo[5.3.0]decane (XVI). The product of Clemmensen reduction (which differed from the Wolff–Kishner product)[14] of 1-keto-6,7-hexa-



XV XVI

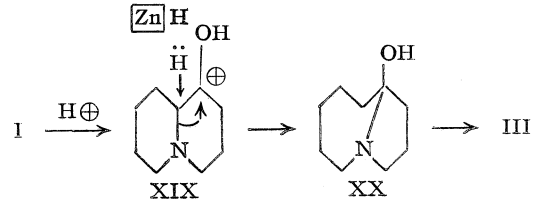
(a, ring A fully saturated)

hydrobenzoquinolizidine (XVa)[16] is therefore hexahydrobenzo[b]-1-azabicyclo[5.3.0]decane(XVIa). The product of Clemmensen reduction of methyl 9-ketoquinolizidine-1-carboxylate (XVII) (which was degraded by Clemo, Ramage and Raper[17] to 1-azabicyclo[5.3.0]decane (III)) must possess the structure: methyl 1-azabicyclo[5.3.0]-decane-5-carboxylate (XVIII).



XVII XVIII

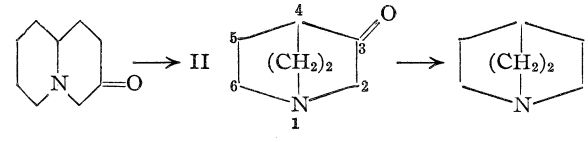
These examples serve as illustrations of a rearrangement which appears to be general in scope. The products of the rearrangement can be accounted for by an elaboration of the suggestion of Prelog and Seiwerth[3]



XIX XX

The first step would involve the migration of the R_2N- group to the geometrically-fixed, adjacent carbonium carbon (formed from the carbonyl group in acid solution),[18a] with the subsequent or simultaneous attack of hydrogen at the newly-formed carbonium ion of the α-carbon (XIX → XX). Reductions of the type represented by the second step, conversion of XX to III, appear to occur readily.[18b,c]

The limitations, the confining structural features of the α-substituted ketones, and a study of the proposed mechanism of the rearrangement constitute the subject matter of succeeding articles. At present, it is important to mention the fact that rearrangement was found not to occur in the Clemmensen reduction of at least two related α-aminoketones of the bicyclic, bridge-head-nitrogen type. Clemmensen reduction of 3-ketoquinolizidine (XXI) gave a low yield of the normal product, quinolizidine (II),[19a] and similar reduction of 3-ketoquinuclidine (XXII) gave quinuclidine (XXIII).[19b]



XXI XXII XXIII

Clemmensen reduction of β-aminoketones of the bicyclic, bridge-head-nitrogen type invariably produced unrearranged products.[2,20]

Experimental[21,22]

Halides

1-Bromo-3-(*p*-methoxyphenoxy)-propane.—The procedure used for the condensation of hydroquinone monomethyl ether with α,ω-dihaloalkanes was based on the method of Ziegler and Weber[12a] for phenoxyalkyl halides. The yields were similar for all compounds synthesized in this manner. The following synthesis is representative of the series. A solution of 28 g. (0.5 mole) of potassium hydroxide in 350 ml. of methanol was added over a period of one hour to a stirred solution of 62 g. (0.5 mole) of hydroquinone monomethyl ether (Tennessee Eastman Corporation) and 400 g. (1.98 moles) of 1,3-dibromopropane at reflux temperature. The reaction mixture was boiled under reflux until the solution was neutral to litmus (about six hours). The solution was cooled, and sufficient water was added to dissolve the potassium bromide. The non-aqueous layer was washed twice with water, dried over magnesium sulfate, and distilled. Three hundred grams of 1,3-dibromopropane was recovered. The 1-bromo-3-(*p*-methoxyphenoxy)-propane was obtained as a light yellow oil, b. p. 120–130° (1 mm.); yield, 75 g. (61.5%). The crude product was redistilled for analysis, b. p. 126–127° (1 mm.); $n^{20}D$ 1.5463; d^{20}_4 1.3788.

Anal. Calcd. for $C_{10}H_{13}O_2Br$: C, 49.00; H, 5.34; MR_D 55.85. Found: C, 49.25; H, 5.47; MR_D 56.31.

1-Bromo-3-methyl-5-(*p*-methoxyphenoxy)-pentane.—B. p. 133–134° (0.5 mm.); $n^{20}D$ 1.5311; d^{20}_4 1.2829.

Anal. Calcd. for $C_{13}H_{19}O_2Br$: C, 54.37; H, 6.66; MR_D 68.69. Found: C, 54.46; H, 6.93; MR_D 69.27.

(14) Clemo, Cook and Raper, *J. Chem. Soc.*, 1318 (1938).

(15) Alternative name: 1-keto-6,7-benzo-1,2,3,4,8,9-hexahydropyridocoline.[14]

(16) Alternative name: 1-ketododecahydro-6,7-benzopyridocoline.[14]

(17) Clemo, Ramage and Raper, *J. Chem. Soc.*, 3190 (1931).

(18) (a) Whitmore, *Chem. Eng. News*, **26**, 668 (1948); (b) Alexander and Wildman, THIS JOURNAL, **70**, 1187 (1948); (c) Bunnett and Marks, *ibid.*, **71**, 1587 (1949).

(19) (a) Clemo, Morgan and Raper, *J. Chem. Soc.*, 1743 (1935); (b) Clemo and Metcalfe, *ibid.*, 1989 (1937).

(20) Lions and Willison, *J. Proc. Roy. Soc. N. S. Wales*, **73**, 240 (1940).

(21) All melting points are corrected. Microanalyses were performed by Miss Emily Davis, Mrs. Jane Wood and Mr. Maurice Dare.

(22) The calculated molecular refractivities do not take into account exaltations due to the benzene ring and the *para*-methoxyl group.

1-Chloro-5-(*p*-methoxyphenoxy)-pentane.—B. p. 153–154° (2 mm.); $n^{20}D$ 1.5209; d^{20}_4 1.1107.

Anal. Calcd. for $C_{12}H_{17}O_2Cl$: C, 63.01; H, 7.49; *MR*D 62.18. Found: C, 63.14; H, 7.24; *MR*D 62.68.

1-Bromo-2-(*p*-methoxyphenoxy)-ethane.—In order to obtain this compound pure, it was necessary to depart from the procedure described above in one important particular. The organic layer was washed with 5% sodium hydroxide and then twice with water before the drying and distilling operations. The 1-bromo-2-(*p*-methoxyphenoxy)-ethane was obtained as a light yellow oil, b. p. 105–108° (2 mm.), which solidified upon standing. Recrystallization from ethanol gave colorless platelets, m. p. 51.5–52.5°.

Anal. Calcd. for $C_9H_{11}O_2Br$: C, 46.77; H, 4.79. Found: C, 46.82; H, 4.82.

Nitriles

Ethyl α-Cyano-γ-(*p*-methoxyphenoxy)-butyrate.—The ester was prepared by the procedure of Robinson and Watt[23] for the condensation of phenoxyethyl bromide with ethyl cyanoacetate, with the exception that twice the recommended pressure was employed. A mixture of 92.4 g. (0.40 mole) of 1-bromo-2-(*p*-methoxyphenoxy)-ethane, 56.0 g. (0.40 mole) of anhydrous potassium carbonate, and 226 g. (2.0 moles) of ethyl cyanoacetate was heated under reflux at 130° and 120 mm. for twenty-two hours. The reaction mixture was cooled, and sufficient water was added to dissolve the inorganic salts. The ester layer was washed with water until neutral and was fractionally distilled. The first fraction contained 116 g. of unreacted ethyl cyanoacetate, b. p. 95–98° (14 mm.). The second fraction consisted mainly of unreacted 1-bromo-2-(*p*-methoxyphenoxy)-ethane, 37 g., b. p. 80–135° (1 mm.). The condensation product boiled at 166–170° (1 mm.); yield 51.0 g. (81% based on unrecovered halide). The crude product was redistilled for analysis, b. p. 169–170° (1 mm.); $n^{20}D$ 1.5083; d^{20}_4 1.1431.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32; *MR*D 67.95. Found: C, 64.14; H, 6.57; N, 5.48; *MR*D 68.66.

Ethyl α-Cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyrate.—The sodium derivative of ethyl-α-cyano-γ-(*p*-methoxyphenoxy)-butyrate was prepared by the addition of 52.6 g. (0.20 mole) of ethyl α-cyano-γ-(*p*-methoxyphenoxy)-butyrate to an ethanolic solution of 0.2 mole of sodium ethoxide from the reaction of 4.6 g. (0.20 mole) of sodium with 200 ml. of absolute ethanol. Eighty-five grams (0.60 mole) of methyl iodide was added over a period of one-half hour at reflux temperature to the stirred solution of the sodio-derivative. The mixture was refluxed for five hours. The ethanol and methyl iodide were removed by distillation. The oily residue was washed with water, and the water layer was extracted twice with ether. The combined ester and ether layers were dried over magnesium sulfate and distilled. The ethyl α-cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyrate was obtained as a colorless liquid, b. p. 162–163° (0.5 mm.); $n^{20}D$ 1.5024; d^{20}_4 1.1413; yield 50.5 g. (91%).

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05; *MR*D 72.77. Found: C, 65.06; H, 6.79; N, 4.91; *MR*D 72.13.

α-Cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyric Acid.—A solution of 45 g. (0.162 mole) of ethyl α-cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyrate in 100 ml. of ethanol was treated with one equivalent of 30% aqueous potassium hydroxide and allowed to stand at room temperature for six hours. The mixture was neutralized with one equivalent of 6 *N* hydrochloric acid. The cyano acid was separated, and the aqueous solution was extracted twice with ether. The cyano acid and ether extracts were combined and dried over magnesium sulfate. The ether was removed under reduced pressure. The residual yellow oil was caused to crystallize by standing twelve hours at 0°. The α-cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyric acid was isolated by filtration. The filtrate (15.1 g.) was composed largely of unreacted ester which was resaponified and worked up in the same manner. The total yield of the crude cyano acid was 36 g. (89.3%). For analysis a small portion was recrystallized twice from hot water to yield white needles, m. p. 80–81°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.86; H, 6.14; N, 5.64.

1-(*p*-Methoxyphenoxy)-3-cyanobutane (Xb).—Sixty grams (0.24 mole) of crude α-cyano-α-methyl-γ-(*p*-methoxyphenoxy)-butyric acid was heated at 200° for two hours. The liquid was cooled, washed once with 5% sodium carbonate solution and once with water, dried over magnesium sulfate, and distilled. The 1-(*p*-methoxyphenoxy)-3-cyanobutane was obtained as a colorless liquid, b. p. 146–149° (1.3 mm.); yield 37 g. (75%). The nitrile solidified upon standing. For analysis a small portion was recrystallized from ether as colorless platelets, m. p. 46–47°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.38; H, 7.53; N, 6.64.

1-Cyano-3-(*p*-methoxyphenoxy)-propane (Xa).—The following procedure was that employed by von Braun[24] for the preparation of the phenoxy homolog. A solution of 77.0 g. (0.314 mole) of 1-bromo-3-(*p*-methoxyphenoxy)-propane and 65 g. (1.0 mole) of potassium cyanide in 520 ml. of 70% ethanol was boiled under reflux for six hours. The ethanol was removed by distillation. The nitrile was dissolved in 100 ml. of ether, washed twice with water, and dried over anhydrous magnesium sulfate. The nitrile boiled at 150–153° (1 mm.); yield 45 g. (75%). The nitrile solidified upon standing. Recrystallization of a small portion from ethanol yielded colorless platelets, m. p. 37–38°.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 69.10; H, 6.85; N, 7.33. Found: C, 69.24; H, 6.70; N, 7.45.

Ketones

1,9-bis-(*p*-Methoxyphenoxy)-4-nonanone (XIa).—A solution of 8 g. (0.042 mole) of 1-cyano-3-(*p*-methoxyphenoxy)-propane in 35 ml. of anhydrous ether was added with stirring to a Grignard reagent prepared from 1.25 g. (0.052 mole) of magnesium, 11.4 g. (0.05 mole) of 1-chloro-5-(*p*-methoxyphenoxy)-pentane, and 35 ml. of anhydrous ether. The mixture was boiled under reflux for five hours and then was decomposed at 0° by the slow addition of 80 ml. of 1.2 *N* hydrochloric acid. The crude ketone was isolated by filtration. The ether layer of the filtrate was separated, washed twice with water, and dried over anhydrous magnesium sulfate. The ether was evaporated, and the oily residue was crystallized from ethanol. The combined crude ketone was obtained as colorless platelets from ethanol, m. p. 72–75°; yield 10.0 g. (61.8%). For analysis a small portion was recrystallized twice from ethanol, m. p. 80–81°.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.56; H, 8.06.

1,9-bis-(*p*-Methoxyphenoxy)-3-methyl-4-nonanone (XIb).—A solution of 10.2 g. (0.05 mole) of 1-(*p*-methoxyphenoxy)-3-cyanobutane in 40 ml. of anhydrous ether was added to a Grignard reagent prepared from 1.44 g. (0.06 mole) of magnesium, 14.8 g. (0.065 mole) of 1-(*p*-methoxyphenoxy)-5-chloropentane, and 30 ml. of anhydrous ether. The mixture was boiled under reflux for five hours and then decomposed at 0° by the slow addition of 100 ml. of 1.2 *N* hydrochloric acid. The crude ketone was isolated by filtration. The ether layer of the filtrate was separated, washed twice with water, and dried over anhydrous magnesium sulfate. The ether was evaporated, and the oil residue was crystallized from an ethyl acetate–petroleum ether mixture. The combined crude ketone was dissolved in boiling ethyl acetate and allowed to cool to 50°. One gram of non-ketonic material, m. p. 127–

(23) Robinson and Watt, *J. Chem. Soc.*, 1536 (1934).

(24) von Braun, *Ber.*, **42**, 2047 (1909).

128°, was isolated by filtration, but it was not investigated further. The 1,9-bis-(*p*-methoxyphenoxy)-3-methyl-4-nonanone was obtained as white rosettes upon the addition of petroleum ether to the cold ethyl acetate solution, m. p. 42–43°; yield 10.2 g. (51%).

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.15; H, 8.02.

1,9-bis-(*p*-Methoxyphenoxy)-3-methyl-6-nonanone (XIc).—A solution of 4.76 g. (0.025 mole) of 1-cyano-3-(*p*-methoxyphenoxy)-propane in 20 ml. of anhydrous ether was added with stirring to a Grignard reagent prepared from 0.72 g. (0.03 mole) of magnesium, 9.2 g. (0.032 mole) of 1-bromo-3-methyl-5-(*p*-methoxyphenoxy)-pentane, and 20 ml. of anhydrous ether. The mixture was boiled under reflux for five hours and then decomposed at 0° by the slow addition of 50 ml. of 1.2 *N* hydrochloric acid. The ether layer was separated, washed twice with water, and dried over anhydrous magnesium sulfate. After removal of the solvent by distillation, the ketone was obtained as an oil which could not be induced to crystallize, yield 8.4 g. (84%).

Oximes

One gram (0.0025 mole) of the ketone in 15 ml. of 50% methanol was heated under reflux for eighteen hours with 0.6 g. (0.0086 mole) of hydroxylamine hydrochloride and 1.2 g. (0.0147 mole) of anhydrous sodium acetate. The oxime crystallized upon cooling and was washed with water. Recrystallization from 95% ethanol yielded 0.6 g. (60%).

1,9-bis-(*p*-Methoxyphenoxy)-4-nonanone Oxime (XIIa).—Needles, m. p. 76–77°.

Anal. Calcd. for $C_{23}H_{31}NO_6$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.93; H, 7.84; N, 3.57.

1,9-bis-(*p*-Methoxyphenoxy)-3-methyl-4-nonanone Oxime (XIIb).—Platelets, m. p. 76.5–77°.

Anal. Calcd. for $C_{24}H_{33}NO_6$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.36; H, 8.20; N, 3.46.

1,9-bis-(*p*-Methoxyphenoxy)-3-methyl-6-nonanone Oxime (XIIc).—Platelets, m. p. 78–79°.

Anal. Calcd. for $C_{24}H_{33}NO_6$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.65; H, 8.29; N, 3.63.

Amines

A mixture of 12.5 g. of the ketone and 50 ml. of liquid ammonia was hydrogenated over Raney nickel catalyst at 150° and 150–200 atmospheres for five hours. The amine was dissolved in ethanol, and the catalyst was separated by filtration.

4-Amino-1,9-bis-(*p*-methoxyphenoxy)-nonane (XIIIa).—The ethanol was evaporated, and the residual light yellow oil was caused to crystallize by the addition of cold ether. The pure amine was obtained in approximately 60% yield as needles upon recrystallization from anhydrous ether, m. p. 71–72°.

Anal. Calcd. for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.62. Found: C, 71.13; H, 8.48; N, 3.72.

4-Amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane (XIIIb).—After removal of the ethanol by distillation, the amine was obtained as a red oil which could not be crystallized. The hydrochloride was prepared by the addition of five drops of the amine to a solution of 2 ml. of 50% ethanol and three drops of concentrated hydrochloric acid. The crude product was recrystallized from hot water as colorless platelets, m. p. 104–105°. Chemical behavior, infrared spectrum and analysis proved the compound to be **4-amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane hydrochloride monohydrate** (yield, *ca.* 60%).

Anal. Calcd. for $C_{24}H_{36}ClNO_4 \cdot H_2O$: C, 63.24; H, 8.40; N, 3.07. Found: C, 63.35; H, 8.63; N, 3.08.

6-Amino-1,9-bis-(*p*-methoxyphenoxy)-3-methylnonane (XIIIc).—After removal of the ethanol by distillation, the amine was obtained as a red oil which could not be induced to crystallize. The oxalate was chosen as a derivative. A 30% ethanolic solution of anhydrous oxalic acid was added dropwise to a solution of five drops of the amine in 5 ml. of ethanol. The monoammonium monoamine oxalate was obtained as white needles, m. p. 194–196° (yield, *ca.* 40%).

Anal. Calcd. for $C_{26}H_{39}N_2O_8$: C, 61.52; H, 7.75; N, 5.52. Found: C, 61.80; H, 7.81; N, 5.87.

α,ω-Dibromoamine Hydrobromides

A solution of 9 g. of the amine (XIII) in 190 ml. of glacial acetic acid was saturated with hydrogen bromide. The solution was treated with 190 ml. of 48% hydrobromic acid and boiled under reflux for seventy-two hours. The solvents were removed by distillation under reduced pressure. The residue was dissolved in 50% ethanol and evaporated to dryness under reduced pressure. The α,ω-dibromoamine hydrobromide was not purified but was used directly in the next step.

1-Azabicyclo[5.3.0]decanes

The method of preparation of the tertiary amines (III, VII, VIII) was essentially that of Prelog, Cerkovnikov and Ustricev[25] for the synthesis of bicyclic amines possessing a bridge-head-nitrogen atom. The steam volatile tertiary base was acidified with 10% hydrochloric acid. The water was removed by distillation under reduced pressure. The residue was treated with 20 ml. of 2 *N* sodium hydroxide, extracted twice with ether, and the ethereal solution was dried over anhydrous magnesium sulfate. The ethereal solution was used for the preparation of derivatives.

1-Azabicyclo[5.3.0]decane (III) Picrate.—Prepared in ether and recrystallized twice from methanol, the picrate formed yellow needles which melted with decomposition at 213–214° (reported, 213–214°,[3] 213°[2]).

8-Methyl-1-azabicyclo[5.3.0]decane (VII) Picrate.—Prepared in ether and recrystallized twice from methanol, the picrate formed yellow needles which melted with decomposition at 181–182°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.65. Found: C, 50.46; H, 5.93; N, 14.46.

4-Methyl-1-azabicyclo[5.3.0]decane (VIII) Picrate.—Prepared in ether and recrystallized twice from methanol, the picrate formed yellow needles which melted with decomposition at 189°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.65. Found: C, 50.21; H, 5.99; N, 14.93.

8-Methyl-1-azabicyclo[5.3.0]decane (VII) Picrolonate.—Prepared in ether and recrystallized twice from ethanol, the picrolonate formed yellow needles which melted at 189–190°.

4-Methyl-1-azabicyclo[5.3.0]decane (VIII) Picrolonate.—Prepared in ether and recrystallized twice from ethanol, the picrolonate formed deep yellow clusters of small prisms, m. p. 138–139°.

Summary

8-Methyl-1-azabicyclo[5.3.0]decane (VII) has been synthesized by an unequivocal method and has been shown to be identical with the Clemmensen reduction product of 1-keto-2-methylquinolizidine (IV).

4-Methyl-1-azabicyclo[5.3.0]decane (VIII) has been synthesized by a similar method and has been shown to be identical with the Clemmensen reduction product of 1-keto-8-methylquinolizidine (V).

By these comparisons, it has been established that it is the ketonic ring which undergoes contraction during the Clemmensen reduction-rearrangement of 1-ketoquinolizidines.

URBANA, ILLINOIS RECEIVED FEBRUARY 21, 1949

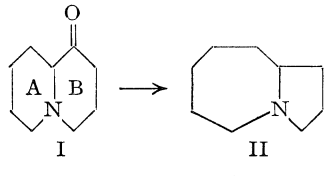
(25) Prelog, Cerkovnikov and Ustricev, *Ann.*, **535**, 37 (1938).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

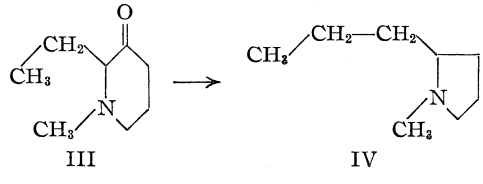
Rearrangement of α-Aminoketones During Clemmensen Reduction. II. Contraction of a Six-membered Ring in the Monocyclic Series

BY NELSON J. LEONARD AND WILLIAM V. RUYLE[1]

In the first article in this series[2] proof was provided that the Clemmensen reduction–rearrangement of 1-ketoquinolizidine (I) to 1-azabicyclo-[5.3.0]decane (II) proceeds through contraction of the six-membered *ketone ring* (B) to a five-membered ring. Since it was also established that contraction is the general fate of the ketonic ring in 1-ketoquinolizidines subjected to Clemmensen reduction, it was of interest to determine if a closely analogous *monocyclic* tertiary α-aminoketone (III) behaved similarly under Clemmensen conditions. Accordingly, the model compound 1-methyl-2-ethyl-3-piperidone (III) has been synthesized and has been subjected to Clemmensen reduction. The fact that the product obtained was 1-methyl-2-*n*-propylpyrrolidine (IV) indicates that the reductive rearrangement is not limited to the bicyclic series, and that ring contraction occurs in the monocyclic series when the amino and carbonyl groups are homocyclic.

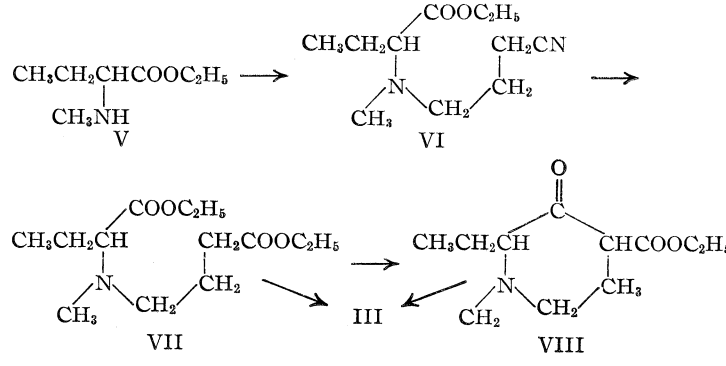


I II



III IV

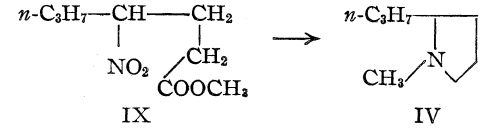
The synthesis of the cyclic aminoketone (III) used in this study was carried out by a series of reactions similar to those employed by Clemo and Ramage[3] in the synthesis of bicyclic aminoketones and by Prill and McElvain[4] in the synthesis of monocyclic aminoketones. Ethyl α-methylaminobutyrate (V) was obtained by condensation of methylamine with α-bromobutyric acid, followed by esterification. Treatment of V with γ-bromobutyronitrile in the presence of anhydrous potassium carbonate furnished α-carbethoxypropyl-γ′-cyanopropylmethylamine (VI), and ethanolysis of VI gave the diester VII.



V VI VII III VIII

Ring closure of the diester (VII) was accomplished by the Dieckmann reaction under two different sets of conditions. When sodium ethoxide was used,[4a] the keto ester (VIII) was isolated as the hydrochloride, which was then hydrolyzed and decarboxylated to give the hydrochloride of III in 60% yield (based on the diester). When potassium was used,[3] the intermediate keto ester (VIII) was not isolated but was immediately hydrolyzed and decarboxylated to give 1-methyl-2-ethyl-3-piperidone (III) in 50% yield. The Clemmensen reduction of 1-methyl-2-ethyl-3-piperidone resulted in a 71% yield of an amine which possessed properties different from those of 1-methyl-2-ethylpiperidine but identical with those of 1-methyl-2-propylpyrrolidine (IV).[5–7]

For direct comparison with the Clemmensen reduction product of III, a sample of 1-methyl-2-propylpyrrolidine (IV) was prepared by the reductive cyclization of methyl γ-nitroheptanoate (IX).[8] The hydrogenation was carried out in dioxane solution over copper oxide–chromium oxide catalyst at 260° and 250 atmospheres. The result was somewhat surprising in that the desired product (IV) was obtained directly, indicating that the process had included N-methylation (by the methanol available from cleavage of the ester).



IX IV

The products of Clemmensen reduction of III and reductive cyclization of IX were identical (see Table I).

As the monocyclic aminoketone III corresponds

(1) Present address: Merck and Company, Inc., Rahway, New Jersey.

(2) Leonard and Wildman, THIS JOURNAL, **71**, 3089 (1949).

(3) Clemo and Ramage, *J. Chem. Soc.*, 437 (1931).

(4) (a) Prill and McElvain, THIS JOURNAL, **55**, 1233 (1933); (b) McElvain, *ibid.*, **46**, 1721 (1924).

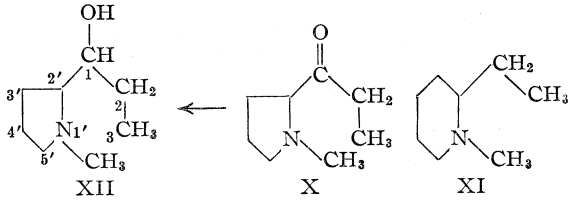
(5) Löffler, *Ber.*, **43**, 2038 (1910).

(6) Hess and Anselm, *ibid.*, **54**, 2110 (1921).

(7) Craig, THIS JOURNAL, **55**, 2543 (1933).

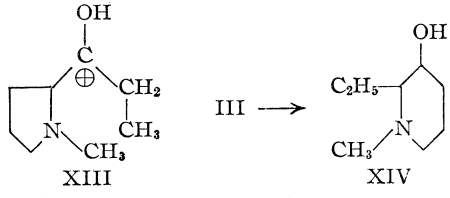
(8) Leonard and Beck, *ibid.*, **70**, 2504 (1948).

to 1-ketoquinolizidine (I) with the non-ketonic ring (A) opened, so the monocyclic aminoketone, 1-methyl-2-propionylpyrrolidine (X), is a model of 1-ketoquinolizidine (or, more accurately, of 1-ketoöctahydropyrrocoline) with the ketonic ring (B) opened. If X were to undergo analogous rearrangement during Clemmensen reduction, the product would be 1-methyl-2-ethylpiperidine (XI), and the process of *non-ketonic ring* expansion from five to six members would effect essentially the reverse of the process (III → IV) of *ketonic ring* contraction from six to five members. 1-Methyl-2-propionylpyrrolidine (X) was prepared



XII X XI

and subjected to Clemmensen reduction. In several runs representing variations in conditions, the only product isolated was 1-(1′-methyl-2′-pyrrolidyl)-1-propanol (XII). Complete reduction did not occur, nor did rearrangement occur. The difference in the behavior of X in the Clemmensen reaction as compared with III (and I)[9] might be rationalized on the basis of the absence in X of the apparently important geometrical directing effect,[2] and thus the carbonium carbon-1 (XIII) may capture a hydride ion (to give XII) before the nitrogen can attack. On a statistical basis, the nitrogen has less opportunity to approach carbonium carbon-1 in X than it does in III where their positions are both fixed by the ring structure. Among the structural features which determine whether rearrangement accompanies reduction, evidently the coexistence of the amino and carbonyl groups in the same ring is important.



XIII XIV

The possibility of the rearrangement (III → IV) proceeding through an ethyleneimonium ion intermediate,[10] formed after Clemmensen conversion of 1-methyl-2-ethyl-3-piperidone (III) to the carbinol (XIV) or corresponding chloro compound, has not been neglected. However, such a sequence seems unlikely since compound XIV was recovered unchanged when subjected to Clemmensen reduction conditions—a behavior similar to that of most secondary alcohols.[11] 1-Methyl-2-ethyl-3-hydroxypiperidine (XIV) as obtained both by catalytic and by sodium and ethanol reduction of III was used in the attempted, unsuccessful conversion (XIV → IV). Our findings are similar to those of von Braun and Weissbach[12] in the α-thiaketone series. These workers found that 4-ketoisothiochroman underwent reduction-rearrangement under Clemmensen conditions to give 1-methyl-1,2-dihydroisothionaphthene, but that 4-hydroxyisothiochroman and 4-chloroisothiochroman did not undergo rearrangement under the same conditions, giving instead isothiochroman. The parallel behavior of the α-amino- and α-thiaketones merits further investigation.

Experimental[13,14]

Ethyl α-Methylaminobutyrate (V).—A mixture of 56 g. (0.34 mole) of α-bromobutyric acid and 1.5 l. of a 35% solution of methylamine in water was stirred at room temperature for four days. The excess methylamine and water were removed by distillation at water pump pressure, with the receiver immersed in a dry ice–ethanol mixture. In this way, 1.34 l. of aqueous methylamine solution (29% methylamine) was recovered. The recovered material was used in a subsequent run without serious diminution of yield. To the residue remaining after removal of the methylamine was added 39 g. of potassium hydroxide in 50% aqueous solution and 200 ml. of 95% ethanol, and the mixture was evaporated to dryness *in vacuo*. In order to effect complete removal of methylamine and water, the residue was treated with 150 ml. of ethanol and was evaporated to dryness *in vacuo*. This process was repeated twice, and the residue at this stage consisted of small colorless crystals suspended in a viscous sirup. The mixture was stirred with 500 ml. of absolute ethanol until the sirupy material was in solution; the crystalline material remained undissolved. The mixture was saturated with dry hydrogen chloride and was allowed to stand overnight. After refluxing for one and one-half hours, the mixture was distilled *in vacuo* almost to dryness. The residue was cooled in an ice–salt-bath and overlayered with 300 ml. of ether. To the well-stirred mixture was added slowly a cold solution of 50 g. of potassium hydroxide in 50 ml. of water, while the temperature was maintained below 10°. The flask was stoppered and shaken vigorously. The yellow ether layer was decanted from the alkaline slurry, which was in turn shaken successively with one 200-ml. portion and three 100-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. After removal of ether by distillation, the product was fractionally distilled, b. p. 64–65.5° (20 mm.); $n^{20}D$ 1.4174; yield, 30.4 g. (63%).

The **picrate** formed slowly in ether solution, and was recrystallized from ether containing a very small amount of methanol, m. p. 103–104.5°.

(9) Prelog and Seiwerth, *Ber.*, **72**, 1638 (1939).

(10) For representative papers on ethyleneimonium ions, see: Cromwell and Cram, THIS JOURNAL, **65**, 301 (1943); Cromwell and Witt, *ibid.*, **65**, 308 (1943); Kerwin, Ullyot, Fuson and Zirkle, *ibid.*, **69**, 2961 (1947); Bartlett, Ross and Swain, *ibid.*, **69**, 2971 (1947); Schultz and Sprague, *ibid.*, **70**, 48 (1948); Fuson and Zirkle, *ibid.*, **70**, 2760 (1948).

(11) It was recognized that existing evidence shows that the Clemmensen reduction of >CO to >CH₂ does not proceed by way of the carbinol (Martin, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 156), but the possibility was not precluded that the α-aminoketones might exhibit unique behavior. The mechanism which was proposed in Paper I for change in ring size in the bicyclic compounds does not require the interim formation of the carbinol and hence continues valid for both bicyclic and monocyclic types.

(12) von Braun and Weissbach, *Ber.*, **62**, 2416 (1929).

(13) All melting points are corrected. Microanalyses were performed by Miss Emily Davis, Mrs. Jane Wood and Mr. Maurice Dare.

(14) The assistance of Dr. Gerhard Leubner is gratefully acknowledged.

Anal. Calcd. for $C_{13}H_{18}N_4O_9$: C, 41.71; H, 4.85; N, 14.97. Found: C, 41.77; H, 4.96; N, 15.04.

α-Carbethoxypropyl-γ'-cyanopropylmethylamine (VI).—A stirred mixture of 59.0 g. (0.407 mole) of ethyl α-methylaminobutyrate, 60.2 g. (0.406 mole) of γ-bromobutyronitrile, and 58.0 g. (0.42 mole) of finely ground anhydrous potassium carbonate was heated in an oil-bath at 100° for one and one-half hours. After cooling, 150 ml. of water was added to the mixture to dissolve the inorganic salts, and the organic layer was separated. The aqueous layer was extracted three times with 30-ml. portions of ether, which were combined with the organic layer. The ethereal solution was dried and the ether was removed. The residue was distilled *in vacuo*. After a considerable forerun, b. p. 28–120° (2 mm.), the product was collected, b. p. 120–122° (2 mm.); yield, 54.6 g. (63.5%); $n^{20}D$ 1.4450. Fractional distillation of the forerun resulted in recovery of approximately 17% of each of the unchanged reactants.

The **picrate**, prepared in ether and recrystallized from ether–ethanol, melted at 78–82°. Repeated recrystallization failed to improve the melting point.

Anal. Calcd. for $C_{17}H_{23}N_5O_9$: C, 46.26; H, 5.25. Found: C, 46.38; H, 5.24.

α-Carbethoxypropyl-γ'-carbethoxypropylmethylamine (VII).—A solution of 54.6 g. (0.257 mole) of α-carbethoxypropyl-γ'-cyanopropylmethylamine in 225 ml. of absolute ethanol, cooled in an ice-bath and protected from moisture, was saturated with dry hydrogen chloride. The solution was warmed to approximately 35° for one and one-half hours and was then heated under reflux for two and one-half hours. After cooling, the ammonium chloride was collected and washed with absolute alcohol. The combined filtrate and washings were concentrated to a small volume *in vacuo*, and the residue taken up in 60 ml. of water. The solution was overlayered with 50 ml. of ether. The mixture was cooled in an ice-bath, and 50% aqueous potassium hydroxide was added until a distinctly alkaline reaction was given. The aqueous layer was extracted three times with 50-ml. portions of ether. The ethereal solution was dried and the ether was removed. The product distilled at 119–120° (2 mm.); yield, 55.9 g. (84%); $n^{20}D$ 1.4391.

Anal. Calcd. for $C_{13}H_{25}NO_4$: C, 60.20; H, 9.72; N, 5.40. Found: C, 60.38; H, 9.85; N, 5.39.

Attempts to prepare the picrate and picrolonate in ether or ethanol failed.

Dieckmann Ring Closure of α-Carbethoxypropyl-γ'-carbethoxypropylmethylamine

A. With Potassium: 1-Methyl-2-ethyl-3-piperidone (III).—Potassium metal (10.0 g., 0.256 gram atom) was powdered under 50 ml. of dry xylene in a 200-ml. round-bottomed, three-necked flask fitted with stirrer, dropping funnel, and reflux condenser protected by a calcium chloride tube. With the temperature of the heating bath maintained at 105–115°, 14.5 g. (0.056 mole) of α-carbethoxypropyl - γ' - carbethoxypropylmethylamine dissolved in 20 ml. of dry xylene was added over a period of fifty minutes while the mixture was stirred rapidly. The mixture was stirred for an additional three hours at the same temperature. After cooling, 15 ml. of absolute ethanol was added cautiously to destroy excess potassium, then 40 ml. of water was added. The layers were separated, and the xylene layer was extracted with three 10-ml. portions of water. To the aqueous extracts was added 70 ml. of concentrated hydrochloric acid, and the mixture was heated under reflux on a steam-bath for two and one-half hours. The mixture was concentrated *in vacuo* to a small volume. The dark red, semi-crystalline residue was taken up in 40 ml. of water and was overlayered with 50 ml. of ether. To the cooled mixture was added with stirring an excess of a saturated aqueous solution of sodium hydroxide. The layers were separated and the aqueous layer was extracted several times with small portions of ether. After drying the ether solution, the ether was removed and the colorless product was distilled at 80–85° (14 mm.); yield, 4.04 g. (51%). A small sample was redistilled for analysis, b. p. 64° (5 mm.); $n^{20}D$ 1.4620.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71. Found: C, 67.94; H, 10.94.

The **picrate** was made in ether solution and was recrystallized from absolute ethanol, m. p. 131.5–132.5°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.90; N, 15.13. Found: C, 45.35; H, 5.06; N, 15.05.

The **picrolonate**, prepared similarly, melted with decomposition at 165–166°.

Anal. Calcd. for $C_{18}H_{23}N_5O_6$: C, 53.33; H, 5.72. Found: C, 53.55; H, 5.69.

B. With Sodium Ethoxide: 1-Methyl-2-ethyl-4-carbethoxy-3-piperidone (VIII) Hydrochloride.—Sodium ethoxide[15] was prepared from 2.23 g. (0.097 gram atom) of sodium in a 100-ml. Claisen flask fitted with stirrer, dropping funnel, and receiver, and protected from atmospheric moisture. To the sodium ethoxide was added 25.16 g. (0.097 mole) of the diester. The stirred mixture was heated gradually in an oil-bath. At 120° (bath temp.) ethanol began to distil, and in a period of thirty minutes the temperature was raised to 145° and maintained there for fifteen minutes, after which no more ethanol distilled. The cooled reaction mixture was dissolved in 75 ml. of water, and the solution was made acid to congo red with hydrochloric acid, while the temperature was kept below 10°. The solution was then neutralized to litmus with potassium carbonate, and was extracted with ether until the extracts no longer gave a red color with ferric chloride solution. The combined ether extracts were dried and then concentrated to a volume of about 50 ml. Dry hydrogen chloride was passed into the solution until precipitation of the hydrochloride was complete; yield, 18.71 g. (77%); m. p. 158–160°. After one recrystallization from absolute ethanol–ether mixture, the product melted, with decomposition, at 162–163° and weighed 16.02 g. (66%).

Anal. Calcd. for $C_{11}H_{20}ClNO_3$: C, 52.90; H, 8.07; N, 5.61. Found: C, 53.03; H, 8.32; N, 5.66.

1-Methyl-2-ethyl-3-piperidone Hydrochloride.—1-Methyl-2-ethyl-4-carbethoxy-3-piperidone hydrochloride was hydrolyzed and decarboxylated by heating with 6 *N* hydrochloric acid on a steam-bath for three hours. Removal of excess hydrochloric acid by distillation *in vacuo* and recrystallization of the residue from dry acetone gave a 91% yield of 1-methyl-2-ethyl-3-piperidone hydrochloride, m. p. 133–134°.

Anal. Calcd. for $C_8H_{16}ClNO$: C, 54.08; H, 9.08; N, 7.88. Found: C, 54.35; H, 9.30; N, 7.59.

The **picrate** prepared from this hydrochloride had the same melting point as the picrate prepared from the free base in procedure A, and there was no depression of melting point when the two were mixed.

Reductive Cyclization of Methyl γ-Nitroheptanoate (IX).—Twenty and three-tenths grams of methyl γ-nitroheptanoate (0.1 mole) dissolved in 65 ml. of purified dioxane was hydrogenated in the presence of copper chromite catalyst at 260° and 250 atmospheres.[8] About 65% of the theoretical amount of hydrogen was taken up in four hours. After removal of the catalyst by filtration, the bulk of the dioxane was removed by distillation through a six-inch Fenske column. The product distilled at 138–146°; yield, 4.5 g. (36%). A considerable amount of higher boiling material remained in the distilling flask. A final distillation of the product from metallic sodium yielded 2.8 g. of amine, b. p. 145–146° (742 mm.); $n^{20}D$ 1.4378; d^{15}_4 0.823. The picrate, picrolonate and chloroaurate are described in Table I.

Clemmensen Reduction of 1-Methyl-2-ethyl-3-piperidone Hydrochloride.—Mossy zinc (36 g.) was washed with 5% hydrochloric acid and was then shaken for five minutes with a mixture of water (65 ml.), concentrated hydrochloric acid (4 ml.) and mercuric chloride (4 g.).

(15) Hauser and Hudson, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 279.

TABLE I

	[a]Product of Clemmensen reduction of 1-methyl-2-ethyl-3-piperidone	[a]Product of Reductive cyclization of methyl γ-nitro-heptanoate	Reported for 1-methyl-2-propylpyrrolidine
B. p., °C. (mm.)	146–147 (742)	145–146 (742)	146–147 (761)[5]
Density, 15°	0.825	0.823	0.815[5]
$n^{20}D$	1.4380	1.4378	.....
Picrate, m. p., °C.	123–124	123–124	124,[5] 125[6]
Picrolonate, m. p. °C.	169.5–171	168–169.5	.....
Chloroaurate, m. p., °C.	76–77	75–77	76[5]
Chloroplatinate, m. p., °C.	145–146.5	.....	145–146[5]

[a] Admixture of the corresponding derivatives caused no depression in melting point.

The solution was decanted from the amalgam, which was then washed once with distilled water by decantation. To the amalgam was added cautiously a solution of 1-methyl-2-ethyl-3-piperidone hydrochloride (4.0 g.) in 40 ml. of concentrated hydrochloric acid. After the vigorous initial reaction had subsided, the mixture was heated under reflux for twelve hours. (This period of time was found to be sufficient and was used in subsequent comparative experiments.) At intervals of three hours, 10-ml. portions of concentrated hydrochloric acid were added. After cooling, the solution was decanted, and the residual amalgam was washed with small portions of water. The excess hydrochloric acid was removed from the solution and aqueous washings *in vacuo*. The residual viscous sirup was made strongly alkaline with a solution of 50 g. of potassium hydroxide in 200 ml. of water. The resulting slurry of zinc salts was subjected to steam distillation. The first 40-ml. fraction of distillate appeared to contain most of the organic product, and was collected separately from the subsequent 200 ml. of distillate. The first fraction was saturated with potassium hydroxide with cooling, and was then extracted five times with 10-ml. portions of ether. The ethereal solution was dried and the ether was removed. The product distilled at 143–146° (743 mm.); yield, 1.87 g. (65.3%). Mineral oil was added to the distilling flask, and the last traces of product were forced over by heating strongly. The picrate (4.9% of theory) prepared from this fraction melted at 121–123° without recrystallization, and the melting point was not depressed on admixture with the picrate prepared from the main fraction. A small amount (1.1% of theory) of the same picrate was isolated from the second fraction of steam distillate. The total yield of the product and its picrate was thus 71.3%. A final distillation of the product from metallic sodium furnished material having the physical constants shown in Table I.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.58; H, 13.41; N, 10.74.

Picrate, pale yellow needles from absolute ethanol.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.45; H, 5.74; N, 15.67.

Picrolonate, small yellow prisms from absolute ethanol.

Anal. Calcd. for $C_{18}H_{25}N_5O_5$: C, 55.23; H, 6.44; N, 17.89. Found: C, 55.06; H, 6.47; N, 17.66.

Catalytic Hydrogenation of 1-Methyl-2-ethyl-3-piperidone Hydrochloride. 1-Methyl-2-ethyl-3-hydroxypiperidine (XIII) Hydrochloride.—The hydrochloride (1.5 g.) of 1-methyl-2-ethyl-3-piperidone was dissolved in 50 ml. of absolute ethanol and was subjected to hydrogenation at 2.5 atmospheres at 25° in the presence of 0.2 g. of platinum oxide catalyst. Slightly more than the theoretical amount of hydrogen was taken up in one hour. After removal of the catalyst by filtration and the solvent by distillation *in vacuo*, the residue was dissolved in hot, dry acetone. Colorless prisms formed slowly on cooling. After a second recrystallization from acetone, the colorless, hygroscopic prisms melted at 109–111°, and weighed 0.62 g. (41%). The compound gave negative Benedict and Tollens tests.

Anal. Calcd. for $C_8H_{18}ClNO$: C, 53.47; H, 10.10; N, 7.80. Found: C, 53.47; H, 10.33; N, 7.68.

The **picrate**, prepared from the hydrochloride by liberating the free base, extracting into ether, and treating the ether solution with ethereal picric acid, crystallized from ethanol–ether as short needles, m. p. 105–108°.

Anal. Calcd. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.25; H, 5.67; N, 15.27.

The mother liquors obtained from the recrystallization of the hydrochloride could not be made to yield more crystalline material. The sirupy residue remaining after removal of solvent gave negative Benedict and Tollens tests. The sirup was converted to the free base, and thence to the **picrate**, which weighed 1.04 g. (33%) and melted at 104–106°. Recrystallization from ethanol–ether mixture raised the melting point to 107–109.5°.

Anal. Calcd. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.19; H, 5.73; N, 15.33.

Admixture of the two picrates (m. p.'s 105–108° and 107–109.5°) gave no depression in melting point. From appearance and solubility characteristics, the two picrates were identical. On occasions, when ethanol–ether solution of the picrate were cooled in the refrigerator for several days, the compound crystallized in the form of small prisms which melted at 113–116°. Admixture with the lower melting form produced a melting range of 105–116°. Although the rather wide melting ranges of these picrates might indicate mixtures of the two possible diastereoisomers, the formation of the two diastereoisomeric entities has not been shown definitely.

Catalytic hydrogenation of the free base, 1-methyl-2-ethyl-3-piperidone, was attempted, but the absorption of hydrogen was much slower and less complete than in the case of the hydrochloride, and the product appeared to contain considerable unchanged ketone.

Reduction of 1-Methyl-2-ethyl-3-piperidone with Sodium and Ethanol.—Three grams of the hydrochloride of 1-methyl-2-ethyl-3-piperidone was converted to the base, and the aminoketone was dissolved in 40 ml. of absolute ethanol contained in a 200-ml. round-bottomed flask bearing a reflux condenser. Sodium (8.0 g.) in small pieces was dropped through the condenser at a rate sufficient to maintain rapid reflux. Toward the end of the addition it was necessary to heat the mixture to cause the sodium to dissolve. Twenty-five milliliters of water was added, and the mixture was subjected to steam distillation. The distillate was collected as long as it showed an alkaline reaction to litmus (approx. 160 ml.), and was then acidified with hydrochloric acid and evaporated to dryness *in vacuo*. The residue was basified with a saturated aqueous solution of potassium hydroxide, extracted into ether, and the extracts were dried. After removal of the ether, the product distilled at 73–77° (4 mm.); $n^{20}D$ 1.4800; yield, 1.4 g. (58%).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.08; H, 11.97. Found: C, 67.37; H, 12.21.

The **picrate**, recrystallized from ethanol–ether mixture, melted at 104.5–108°, and the melting point was not depressed by admixture with the picrate of the catalytic hydrogenation product. The hydrochloride crystallized from acetone as colorless prisms, whose melting point and mixed melting point (109–111°) were the same as the hydrochloride of the catalytic hydrogenation product.

Treatment of 1-Methyl-2-ethyl-3-hydroxypiperidine under Clemmensen Conditions.—The hydrochloride was subjected to the Clemmensen reduction in the same manner as was 1-methyl-2-ethyl-3-piperidone hydrochloride. Sixty per cent. of the starting material was recovered from the reaction mixture as the picrate. No other product was isolated.

The free base obtained from the sodium reduction of the amino-ketone likewise was unchanged when subjected to Clemmensen conditions.

2-Propionylpyrrole.—This compound was prepared by the method of Oddo[16] in a yield of 35%, b. p. 227–230°, m. p. 50–52°.

1-(2′-Pyrrolidyl)-1-propanol.—By sodium and ethanol reduction of 2-propionylpyrrole,[17] a 22% yield of 1-(2′-pyrrolidyl)-1-propanol was obtained, b. p. 97–100° (17 mm.). Recrystallization from petroleum ether gave colorless hygroscopic needles, m. p. 48–50°.

1-Methyl-2-propionylpyrrolidine (X).—By the method of Hess,[18] a 78% yield of the compound was obtained, b. p. 70–72° (12 mm.), $n^{20}D$ 1.4611. The **picrate**, recrystallized from ethanol as orange leaflets, melted at 103–104°. The free base gave a positive Tollens test in the cold, but a negative Benedict test, even when heated.

Clemmensen Reduction of 1-Methyl-2-propionylpyrrolidine.—The free base (1.27 g.), when subjected to the Clemmensen reduction in the usual manner, yielded 0.79 g. (62%) of a liquid which boiled at 79–80° (13 mm.). The boiling point reported for 1-(1′-methyl-2′-pyrrolidyl)-1-propanol (XII) is 83° (14–15 mm.),[19] and the analytical figures were consistent with the assignment of this structure to the product.

(16) Oddo, *Gazz. chim. ital.*, **39**, I, 649 (1909); *Ber.*, **43**, 1012 (1910).

(17) Hess, *ibid.*, **46**, 3113 (1913).

(18) Hess, *ibid.*, **46**, 4104 (1913).

(19) Hess, Merck and Uibrig, *ibid.*, **48**, 1886 (1915).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.08; H, 11.97. Found: C, 67.18; H, 12.26.

The compound has no effect on Tollens reagent. The **picrate**, recrystallized from ethanol, melted at 149–150.5° with sintering at 145° (reported, 153–154° with sintering at 150°).[17]

Anal. Calcd. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.21; H, 5.68; N, 15.31.

Summary

It has been established that Clemmensen reduction of 1-methyl-2-ethyl-3-piperidone results in the formation of the rearrangement product, 1-methyl-2-*n*-propylpyrrolidine.

The Clemmensen reduction–rearrangement of α-aminoketones, which was previously recognized only in the bicyclic series (1-ketoquinolizidines), has thus been shown to occur in the monocyclic series (six-membered ring). It can be said that ring contraction occurs in the monocyclic series when the α-amino and carbonyl groups are homocyclic.

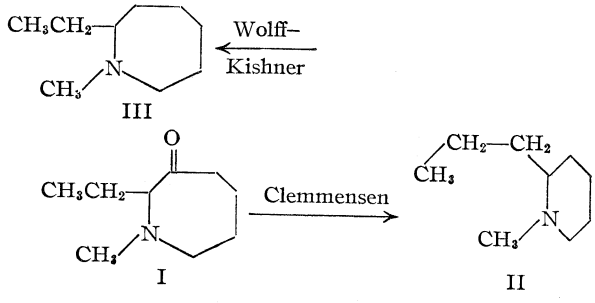
URBANA, ILLINOIS RECEIVED FEBRUARY 21, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Rearrangement of α-Aminoketones During Clemmensen Reduction. III. Contraction of a Seven-membered Ring in the Monocyclic Series

BY NELSON J. LEONARD AND ERIC BARTHEL, JR.

Since the fact has been established that under Clemmensen reduction conditions the six-membered ring in 1-methyl-2-ethyl-3-piperidone undergoes contraction to a five-membered ring with the formation of 1-methyl-2-*n*-propylpyrrolidine,[1] we wished to determine whether the seven-membered homolog (I) would undergo contraction to a six-membered ring. This information would constitute the beginning of our knowledge concerning



the possible effect of ring size in limiting the rearrangement process. Accordingly, 1-methyl-2-ethyl-1-azacycloheptan-3-one (I) has been prepared and has been subjected to Clemmensen reduction. The product obtained was identified as the rearranged product, 1-methyl-2-*n*-propylpiperidine (II).

The synthesis of I was accomplished by a method similar to that used by Prill and McElvain[2] for the compound lacking the 2-ethyl group. Ethyl α-methylaminobutyrate[1] was condensed with δ-chlorovaleronitrile to give α-carbethoxypropyl-δ′-cyanobutylmethylamine. Ethanolysis of the cyanoester produced the diester, α-carbethoxypropyl-δ′-carbethoxybutylmethylamine. Dieckmann ring closure of the diester furnished 1-methyl-2-ethyl-1-azacycloheptan-3-one (I), isolated as the hydrochloride in 52% yield. The normal carbonyl reduction product of I, 1-methyl-2-ethylazacycloheptane (III), was obtained by the Wolff–Kishner method; the Clemmensen reduction product of I was isomeric with III. The Clemmensen product and its derivatives had the properties requisite for 1-methyl-2-*n*-propylpiperidine (*dl*-N-methylconiine) (II),[3,4] and identity was fully established by direct comparison with an authentic sample of II.

The results indicate that the Clemmensen reduction-rearrangement of monocyclic α-aminoketones is not limited to contraction of six-membered rings.

Experimental[5]

δ-Chlorovaleronitrile.—Sixty-eight and five-tenths grams of 95% potassium cyanide (1.0 mole) was dissolved

(1) Leonard and Ruyle, THIS JOURNAL, **71**, 3094 (1949).

(2) Prill and McElvain, *ibid.*, **55**, 1233 (1933).

(3) Lukes and Smetackova, *Coll. Czech. Chem. Commun.*, **6**, 231 (1934).

(4) Hess and Eichel, *Ber.*, **50**, 1396 (1917).

(5) All melting points are corrected. Microanalyses were performed by Miss Emily Davis, Mrs. Jane Wood and Mr. Maurice Dare.

in 1.2 l. of commercial absolute methanol and to this solution was added 660 g. (5.2 moles) of 1,4-dichlorobutane.

The mixture was refluxed on the steam-bath with stirring for seventeen hours. The flask was cooled in an ice-bath and the precipitated salts were collected and washed with absolute methanol. The solvent was removed by distillation and the dark purple residue was subjected to fractional distillation under reduced pressure. 1,4-Dichlorobutane (501 g.), b. p. 61–65° (27–28 mm.), was recovered and the product was collected at 115–118° (28 mm.); $n^{20}D$ 1.4447; yield, 71.7 g. (61% based on potassium cyanide).

α-Carbethoxypropyl-δ′-cyanobutylmethylamine.—A vigorously stirred mixture of 28.4 g. (0.242 mole) of δ-chlorovaleronitrile, 35.1 g. (0.242 mole) of ethyl α-methylaminobutyrate,[1] and 34.5 g. (0.25 mole) of finely ground anhydrous potassium carbonate was heated at 120–130° for twenty-four hours. The mixture was cooled and 100 ml. of water was added to dissolve the inorganic material. The organic layer was separated and the aqueous layer was extracted with three 50-ml. portions of ether, which were combined with the organic layer. The ethereal solution was dried and the ether was removed. The residue was distilled *in vacuo;* b. p. 110–112° (0.4 mm.); $n^{20}D$ 1.4482; yield, 44.7 g. (82%).

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.97; H, 9.97; N, 12.52.

Attempts to prepare the picrate and picrolonate in ether or ethanol failed.

α-Carbethoxypropyl-δ′-carbethoxybutylmethylamine.—A solution of 44.7 g. (0.197 mole) of α-carbethoxypropyl-δ′-cyanobutylmethylamine in 250 ml. of absolute ethanol, cooled in an ice-bath and protected from moisture, was saturated with dry hydrogen chloride. The solution was allowed to stand at room temperature (*ca.* 25°) for two hours and was heated under reflux for two hours. After cooling, the precipitated ammonium chloride was collected and washed with absolute ethanol. The combined filtrate and washings were concentrated to a small volume under reduced pressure. The residue was taken up in 80 ml. of water, the solution was cooled in an ice-bath, and 15% aqueous potassium hydroxide solution was added until the solution was definitely alkaline to litmus paper. The organic layer was separated and the aqueous layer was extracted with two 50-ml. and two 25-ml. portions of ether. The organic layer and ether extracts were combined and dried, and the ether was removed. The product was collected at 125–128° (1.1 mm.); $n^{20}D$ 1.4427; yield, 38.5 g. (71.5%).

Anal. Calcd. for $C_{14}H_{27}NO_4$: C, 61.51; H, 9.96; N, 5.12. Found: C, 61.77; H, 9.77; N, 5.32.

The picrate and picrolonate could not be prepared in ether or ethanol.

Dieckmann Ring Closure of α-Carbethoxypropyl-δ′-carbethoxybutylmethylamine. 1-Methyl-2-ethyl-1-azacycloheptan-3-one (I) Hydrochloride.—Sodium ethoxide[6] was prepared from 3.24 g. of sodium in a 1-l. round-bottomed, three-necked flask fitted with a mercury seal stirrer and a Vigreux fractionating column. A thermometer was inserted in the head of the column and the side arm was attached to a condenser set for downward distillation. The system was protected from moisture. A solution of 38.5 g. (0.141 mole) of the aminodiester in 600 ml. of dry xylene was added. The stirred mixture was heated sufficiently to cause gentle refluxing in the column. Periodically the temperature was raised and the mixture of ethanol and xylene was distilled until the thermometer registered the boiling point of pure xylene. At the end of thirty hours, no more ethanol distilled over. The cooled residue was extracted with four 30-ml. portions of water and was made slightly acid with dilute hydrochloric acid. The xylene layer was extracted with 40-ml. portions of dilute hydrochloric acid until the aqueous extract gave a negative enol test with ferric chloride solution. Concentrated hydrochloric acid (100 ml.) was added to the combined aqueous extracts and the solution was refluxed for two and a quarter hours. A test with ferric chloride solution for the enol function was negative at this time. The reaction mixture was concentrated by evaporation *in vacuo*, cooled in an ice-bath, and made distinctly alkaline to litmus by the slow addition of a saturated aqueous solution of potassium hydroxide. The basic solution was extracted with eight 25-ml. portions of ether. The extracts were combined and dried. Dry hydrogen chloride was passed through the ethereal solution with the formation of a thick, viscous, yellowish gum. The ether was decanted and the residue was recrystallized from ethanol–ether; yield, 14.1 g. (52%) of colorless elongated prisms, m. p. 162.5–163°.

Anal. Calcd. for $C_9H_{18}ClNO$: C, 56.39; H, 9.46; N, 7.31. Found: C, 56.57; H, 9.55; N, 7.07.

The **picrate**, made from the ethereal solution, crystallized from dilute ethanol as bright yellow needles, m. p. 169–169.5°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.25; N, 14.58. Found: C, 47.11; H, 5.24; N, 14.87.

The **picrolonate**, prepared similarly, crystallized as golden-yellow needles, m. p. 164.5–165.5°, from absolute ethanol.

Anal. Calcd. for $C_{19}H_{25}N_5O_6$: C, 54.41; H, 6.01; N, 16.70. Found: C, 54.39; H, 6.22; N, 16.72.

1-Methyl-2-ethyl-1-azacycloheptan-3-one (I).—Four grams (0.029 mole) of anhydrous potassium carbonate dissolved in 10 ml. of water was added to 5 g. (0.026 mole) of the aminoketone hydrochloride in 10 ml. of water. The organic layer which separated was collected in 10 ml. of ether and the aqueous layer was extracted with two additional 10-ml. portions of ether. The extracts were combined and dried and the ether was removed. Distillation of the residue yielded 3.37 g. (84%) of the free base, b. p. 91–92° (13 mm.); $n^{20}D$ 1.4696.

Wolff-Kishner Reduction of 1-Methyl-2-ethyl-1-azacycloheptane-3-one. 1-Methyl-2-ethylazacycloheptane (III).—A mixture of 3.4 g. (0.022 mole) of the aminoketone, 4.2 g. (0.074 mole) of potassium hydroxide, 3 ml. of 85% hydrazine hydrate, and 30 ml. of triethylene glycol was heated at 140–145° under reflux for one hour. The condenser was then set for downward distillation and the temperature of the bath was increased slowly to 250° and was maintained at that point until distillation ceased. The organic matter was removed from the aqueous portion of the distillate by extraction with two 10-ml. portions of ether. After drying, the ether was removed and the residue was distilled, yielding 1.30 g. (42%) of basic material, b. p. 174–175° (755 mm.); $n^{20}D$ 1.4472.

Anal. Calcd. for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 76.96; H, 13.67; N, 10.48.

The **picrate**, formed in ether, crystallized from absolute ethanol as yellow needles, m. p. 166.5–167.5°.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.63; H, 6.07; N, 15.23.

Clemmensen Reduction of 1-Methyl-2-ethyl-1-azacycloheptan-3-one.—Mossy zinc (27 g.) was amalgamated by shaking for five minutes with 3 g. of mercuric chloride, 3 ml. of concentrated hydrochloric acid, and 35 ml. of water. The solution was decanted from the amalgam, which was then washed once with distilled water. Four grams (0.021 mole) of the aminoketone in 40 ml. of concentrated hydrochloric acid was added cautiously to the amalgam. The mixture was heated under gentle reflux for twelve hours. At intervals of two hours, 15-ml. portions of concentrated hydrochloric acid were added and, after seven hours, there was added 20 g. of mossy zinc, amalgamated as before with 2 g. of mercuric chloride, 2 ml. of concentrated hydrochloric acid, and 30 ml. of water. At the end of twelve hours, the aqueous layer was decanted and the residual metal was washed once with distilled water. The solution and washings were concentrated by evaporation *in vacuo*. The resulting viscous sirup was made strongly alkaline to litmus by the addi-

(6) Hauser and Hudson, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 279.

TABLE I

	[a]Product of Clemmensen reduction of 1-methyl-2-ethyl-1-azacycloheptan-3-one	Product of Wolff–Kishner reduction of 1-methyl-2-ethyl-1-azacycloheptan-3-one	[a]1-Methyl-2-*n*-propylpiperidine prepared according to Lukes and Smetackova[3]	Reported for 1-methyl-2-*n*-propylpiperidine (*dl*-N-methylconiine)
B. p., °C. (mm.)	163–165 (759)	174–175 (755)	167–168 (757)	175.5[3]; 174[4]
$n^{20}D$	1.4491	1.4472	1.4500	1.4522[3]
Hydrochloride, m. p., °C.	168–168.5	.....	169–169.5	165–167[3]; 165–166[4]
Picrate, m. p., °C.	108.5–109	166.5–167.5	109.3–109.8	112–114[3]; 110.5[4]
Chloroaurate, m. p., °C.	88.5–90.5	.....	88.5–89.5	90[3]; 91[4]
Chloroplatinate, m. p., °C.	194.5–196	.....	196–197	197[3]; 194[4]

[a] The melting points of mixtures of the corresponding derivatives showed no depression.

tion of a saturated aqueous solution of potassium hydroxide. The white slurry thus obtained was subjected to steam distillation until the distillate was no longer basic to litmus paper. The organic layer was separated and the aqueous layer was extracted with four 40-ml. portions of ether. The organic layer and extracts were combined and dried and the ether was removed. Distillation of the residue yielded 1.49 g. (50%) of basic material, b. p. 61–63° (13 mm.); 163–165° (759 mm.); $n^{20}D$ 1.4491.

Anal. Calcd. for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 76.13; H, 13.68; N, 9.99.

The **picrate** was prepared in ether and recrystallized from dilute ethanol as long light-yellow needles, m. p. 108.5–109°.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.75; H, 6.19; N, 15.29.

The **chloroplatinate** was prepared by adding an aqueous solution of the amine hydrochloride to an aqueous solution of platinum chloride and was recrystallized from dilute ethanol as bright orange prisms, m. p. 194.5–196°.

The **chloroaurate** was prepared similarly, yielding greenish yellow needles, m. p. 88.5–90.5°.

The **hydrochloride** was formed in ether and deposited white needles when recrystallized from acetone, m. p. 168–168.5°.

1-Methyl-2-pyridone.—This compound was prepared by the method of Prill and McElvain[7] in a yield of 83%, b. p. 134–136° (18 mm.); $n^{20}D$ 1.5679.

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 419.

1-Methyl-2-piperidone.—Fifty-five and four-tenths grams of 1-methyl-2-pyridone was dissolved in 200 ml. of glacial acetic acid and the solution was hydrogenated at 2–3.5 atmospheres and 26° in the presence of 0.5 g. of platinum oxide catalyst. Slightly more than the theoretical amount of hydrogen was taken up in seventeen hours. The catalyst was removed by filtration and the solvent was removed by evaporation under reduced pressure. Distillation of the residue yielded 50.36 g. (87.5%) of product, b. p. 102–106° (15 mm.); $n^{20}D$ 1.4711.

1-Methyl-2-*n*-propylpiperidine.—The method of Lukes and Smetackova[3] was used in the preparation of this material from 1-methyl-2-piperidone in a yield of 9.7%; b. p. 167–168° (757 mm.); $n^{20}D$ 1.4500. The derivatives of 1-methyl-2-*n*-propylpiperidine were made in the same manner as were the derivatives of the product of the Clemmensen reduction of 1-methyl-2-ethyl-1-azacycloheptan-3-one. They are listed in Table I.

Summary

It has been established that Clemmensen reduction converts 1-methyl-2-ethyl-1-azacycloheptan-3-one to the rearrangement product, 1-methyl-2-*n*-propylpiperidine (*dl*-N-methylconiine). The process involves ring contraction from seven to six members.

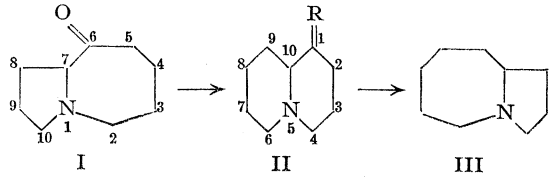
URBANA, ILLINOIS RECEIVED FEBRUARY 23, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Rearrangement of α-Aminoketones During Clemmensen Reduction. IV. Contraction of a Seven-membered Ring in the Bicyclic Series

BY NELSON J. LEONARD AND WILLIAM C. WILDMAN[1]

In a previous communication[2] the authors showed that the rearrangement of 1-ketoquinolizidine (IIb) to 1-azabicyclo[5.3.0]decane (III), under conditions of the Clemmensen reduction, proceeds with contraction of the ketonic ring and expansion of the non-ketonic ring, and a mechanism was suggested for this transformation. Now we have shown that the 1-azabicyclo[5.3.0]decane ring system can be transformed to the quinolizidine ring system by the same process. The Clemmensen reduction of 6-keto-1-azabicyclo[5.3.0]-decane (I) produced the rearrangement product, quinolizidine (1-azabicyclo[4.4.0]decane) (IIa).



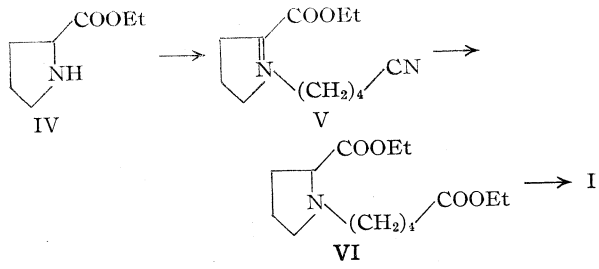
I II III

(a, R = H_2; b, R = O)

The synthesis of I was accomplished by the Dieckmann ring closure of ethyl δ-N-(2-carbethoxypyrrolidyl)-valerate (VI) without isolation of the intermediate ketoester. The diester VI was obtained by ethanolysis of δ-N-(2-carbethoxypyrrolidyl)-valeronitrile (V), product of the condensa-

(1) Present address: Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

(2) Leonard and Wildman, THIS JOURNAL, 71, 3098 (1949).



tion of ethylproline (IV) with δ-bromovaleronitrile.

The normal carbonyl reduction product of 6-keto-1-azabicyclo[5.3.0]decane (I) was obtained by the Wolff–Kishner method and was identified as 1-azabicyclo[5.3.0]decane (III). The Clemmensen reduction product of I was the result of rearrangement and was identified as quinolizidine (IIa). Authentic samples of IIa and III were available for direct comparison with these reduction products. The conversion of I to IIa under Clemmensen conditions thus proceeds with the contraction of the seven-membered ketonic ring and expansion of the five-membered non-ketonic ring. The contraction of a seven-membered ring has also been observed in the Clemmensen reduction of a monocyclic α-aminoketone.[3]

Experimental[4]

δ-Bromovaleronitrile.—A solution of 783 g. (3.62 moles) of tetramethylene bromide, 47.0 g. (0.724 mole) of potassium cyanide, and 600 ml. of methanol was heated under reflux for twenty-four hours. The methanol was removed by distillation. The residue was washed twice with water, dried over anhydrous magnesium sulfate, and fractionally distilled. After removal of the excess tetramethylene bromide, the δ-bromovaleronitrile was obtained as a colorless liquid, b. p. 114–115° (12 mm.); $n^{21.5}D$ 1.4795; yield, 50.0 g. (42.7%).

Ethyl Proline.—The ester was prepared by the procedure of Kapfhammer and Matthes[5] except that the ethanolic solution of proline ethyl ester hydrochloride was concentrated, redissolved in 100 ml. of absolute ethanol, and resaturated with hydrogen chloride. The solution then was concentrated under reduced pressure and treated with ether and anhydrous ammonia as described.[5] This modification resulted in yields as high as 80%.

δ-N-(2-Carbethoxypyrrolidyl)-valeronitrile.—A mixture of 20.0 g. (0.14 mole) of proline ethyl ester, 22.7 g. (0.14 mole) of δ-bromovaleronitrile, and 22.1 g. (0.16 mole) of anhydrous potassium carbonate was heated at 100° for six hours. The reaction mixture was cooled, and water was added to dissolve the inorganic salts. The cyano ester was separated, and the aqueous layer was extracted with ether. The cyano ester and ether extract were combined, washed with water, dried over anhydrous magnesium sulfate, and distilled. The nitrile was obtained as a colorless liquid, b. p. 102–103° (0.5 mm.); $n^{20}D$ 1.4630; d^{20}_4 1.0333; yield, 23.1 g. (74%).

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.28; H, 8.99; N, 12.50; *MR*D 60.75. Found: C, 64.38; H, 9.00; N, 12.65; *MR*D 59.76.

Ethyl δ-N-(2-Carbethoxypyrrolidyl)-valerate.—A solution of 22.6 g. (0.105 mole) of δ-N-(2-carbethoxypyrrolidyl)-valeronitrile in 125 ml. of absolute ethanol, cooled in ice and protected from moisture, was saturated with dry hydrogen chloride. The solution was allowed to stand at room temperature for two hours and then was boiled under reflux for two hours. The ammonium chloride was removed by filtration, and the ethanolic solution of the diester was concentrated under reduced pressure. The residue was dissolved in 50 ml. of water, cooled to 0°, and made alkaline with 15% potassium hydroxide solution. The organic layer was separated, and the aqueous solution was extracted with ether. The diester and the ether extract were combined, dried over anhydrous magnesium sulfate, and distilled. The product was obtained as a colorless liquid, b. p. 110–113° (0.3 mm.); $n^{20}D$ 1.4563; d^{20}_4 1.0413; yield, 16.2 g. (60%).

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16; *MR*D 71.90. Found: C, 62.01; H, 9.31; N, 5.37; *MR*D 70.88.

Dieckmann Ring Closure of Ethyl δ-N-(2-Carbethoxypyrrolidyl)-valerate. 6-Keto-1-azabicyclo[5.3.0]decane.—Sodium ethoxide[6] was prepared from 1.36 g. (0.058 mole) of sodium in a 500-ml. three-necked flask fitted with a mercury-sealed stirrer, a dropping funnel, and a Vigreux fractionating column. A thermometer was inserted in the head of the column, and the side-arm was set for downward distillation. A solution of 15.9 g. (0.058 mole) of the diester in 200 ml. of dry xylene was added to the sodium ethoxide at 25°. The solution was caused to reflux gently in the Vigreux column. The bath temperature was raised periodically, and the ethanol–xylene mixture was distilled until the boiling point of pure xylene was attained. At the end of eighteen hours no ethanol was found in the distillate. The solution was cooled and extracted three times with water. The xylene layer then was extracted with dilute hydrochloric acid until ferric chloride reagent gave a negative test for the enol function. The aqueous extracts were combined and refluxed three hours with 50 ml. of concentrated hydrochloric acid. The solution was concentrated *in vacuo*, cooled to 0°, and made basic with 30% potassium hydroxide solution. The amino ketone was extracted with ether and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure through a ten-inch column packed with glass helices. The 6-keto-1-azabicyclo[5.3.0]decane was obtained as a colorless liquid, b. p. 105–106° (12 mm.); yield, 2.43 g. (27.4%). The amino ketone darkened rapidly on standing. To prevent further decomposition, it was dissolved in absolute ether, and the solution was saturated with dry hydrogen chloride.

6-Keto-1-azabicyclo[5.3.0]decane Picrate.—Prepared in ether and recrystallized three times from ethanol, the picrate formed golden needles, m. p. 170–171°.

Anal. Calcd. for $C_{15}H_{18}N_4O_8$: C, 47.12; H, 4.75; N, 14.66. Found: C, 47.11; H, 4.87; N, 14.54.

6-Keto-1-azabicyclo[5.3.0]decane Picrolonate.—Prepared in ether and recrystallized from ethanol, the picrolonate formed orange platelets, m. p. 165–166°.

Anal. Calcd. for $C_{19}H_{23}N_5O_6$: C, 54.67; H, 5.55; N, 16.78. Found: C, 54.70; H, 5.65; N, 16.97.

Clemmensen Reduction of 6-Keto-1-azabicyclo[5.3.0]-decane. Quinolizidine.—Seven grams of mossy zinc was amalgamated with 1 g. of mercuric chloride, 1 ml. of concentrated hydrochloric acid, and 15 ml. of water. The mixture was swirled for five minutes. The aqueous layer was decanted, and the zinc was washed once with water. A mixture of 1 g. (0.0053 mole) of 6-keto-1-azabicyclo-[5.3.0]decane hydrochloride, 7 g. (0.107 mole) of amalgamated zinc, and 20 ml. of concentrated hydrochloric acid was refluxed for ten hours. An additional 10 ml. of acid was added every two hours during this time. The solution was cooled and made basic with 50% sodium hydroxide solution. The zinc hydroxide was removed by filtration using Super-Cel as a filtering aid. The filtrate was distilled until no basic material was found in the distillate. The distillate was saturated with potassium carbonate and extracted four times with ether. The ethereal

(3) Leonard and Barthel, *ibid.*, **71**, 3098 (1949).

(4) All melting points are corrected.

(5) Kapfhammer and Matthes, *Z. physiol. Chem.*, **223**, 43 (1934).

(6) Hauser and Hudson, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 279.

solution of the amine was dried over anhydrous magnesium sulfate and used for the preparation of derivatives.

Quinolizidine Picrate.—Prepared in ether and recrystallized from methanol, the picrate formed yellow elongated plates, m. p. 197.5–198.5°.

Quinolizidine Picrolonate.—Prepared in ether and recrystallized from ethanol, the picrolonate formed orange plates, m. p. 244–245° (dec.).

Quinolizidine Methiodide.—Prepared in ether and recrystallized from ethanol–ether, the methiodide formed colorless cubes, m. p. 329–330° (dec.).

Wolff–Kishner Reduction of 6-Keto-1-azabicyclo[5.3.0]decane. 1-Azabicyclo[5.3.0]decane.—A solution of 0.5 g. (0.0026 mole) of 6-keto-1-azabicyclo[5.3.0]decane hydrochloride, 1 g. (0.017 mole) of hydrazine hydrate (85%) and 1.5 g. (0.027 mole) of potassium hydroxide in 10 ml. of triethylene glycol was refluxed for one hour. The solution was then distilled until no basic material was found in the distillate. The distillate was saturated with potassium carbonate, extracted twice with ether, and dried over anhydrous magnesium sulfate. The derivatives were prepared from the ethereal solution.

1-Azabicyclo[5.3.0]decane Picrate.—Prepared in ether and recrystallized three times from methanol, the picrate formed yellow elongated plates, m. p. 213–214°. The melting point of a mixture with authentic 1-azabicyclo-[5.3.0]decane picrate[2] was not depressed.

1-Azabicyclo[5.3.0]decane Methiodide.—Prepared in ether and recrystallized from ethanol–ether, the methiodide formed colorless needles, m. p. 282–283°.

Quinolizidine.—Quinolizidine was prepared by the method of Boekelheide and Rothchild[7] from diethyl β-(2-pyridyl)-ethyl malonate in 70% yield, b. p. 72° (12 mm.); $n^{20}D$ 1.4765. The picrate, picrolonate and methiodide were prepared and were recrystallized from the same solvents as were the derivatives of the Clemmensen reduction product of 6-keto-1-azabicyclo[5.3.0]decane: **picrate**, m. p. 197–198°; **picrolonate**, m. p. 244–245° (dec.); **methiodide**, m. p. 329–330° (dec.). No depressions in melting points were observed when corresponding derivatives of the amines from the two syntheses were mixed.

Summary

It has been established that Clemmensen reduction converts 6-keto-1-azabicyclo[5.3.0]decane to the rearrangement product, quinolizidine.

(7) Boekelheide and Rothchild, THIS JOURNAL, **69**, 3149 (1947).

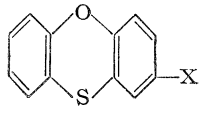
URBANA, ILLINOIS RECEIVED MARCH 28, 1949

[CONTRIBUTION FROM THE PITTSFIELD LABORATORY, APPARATUS DEPARTMENT, GENERAL ELECTRIC COMPANY]

Vinyl Compounds: Phenoxathiin and Dibenzothiophene Derivatives

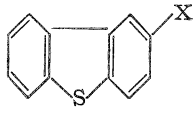
BY RALPH G. FLOWERS AND LEOLA WILLS FLOWERS

During an investigation of the properties of different polymeric materials, several phenoxathiin and dibenzothiophene derivatives were prepared. Interest in these compounds was centered upon the role played by the sulfur atom in determining their electrical properties. The vinylphenoxathiin was synthesized by the hydrogenation of the ketone to the carbinol with subsequent dehydration.



I, X = —$COCH_3$
II, X = —$CHOHCH_3$
III, X = —$CH{=}CH_2$

A similar scheme was carried out in the synthesis of the vinyldibenzothiophene.



IV, X = —$COCH_3$
V, X = —$CHOHCH_3$
VI, X = —$CH{=}CH_2$

The 2-acetylphenoxathiin (I) was prepared by a Friedel–Crafts reaction, using a modification of the work reported by Suter, McKenzie and Maxwell.[1] 2-(α-Hydroxyethyl)-phenoxathiin (II), prepared by the hydrogenation of I, was dehydrated in the vapor phase to 2-vinylphenoxathiin (III), m. p. 39.5–41°. The low melting point of this monomer allows it to be used for impregnation applications as well as in the form of its polymer and copolymers.

A number of investigators[2] have prepared the 2-acetyldibenzothiophene (IV) which we have hydrogenated to the 2-(α-hydroxyethyl)-dibenzothiophene (V). No evidence of catalyst poisoning was observed during the hydrogenation of these sulfur compounds or in subsequent runs using the same bombs with other materials. Two methods for the dehydration of V to 2-vinyldibenzothiophene (VI) were carried out in the present work. VI is also a low melting monomer, m. p. 45.0–45.5°, which may be utilized under the same conditions as those for III.

Experimental[3]

2-Acetylphenoxathiin (I).—One hundred thirty-five grams of anhydrous aluminum chloride and 300 cc. of carbon disulfide were placed in a 2-liter, 3-necked flask, equipped with an efficient stirrer, separatory funnel, condenser and a thermometer. A mixture of 200 g. of phenoxathiin in 700 cc. of carbon disulfide and 85 g. of acetyl chloride was added dropwise through the separatory funnel. The addition of the reactants took about six hours after which the mixture was allowed to stand one-half hour.

A yellow precipitate, which was obtained by hydrolyzing the mixture with ice and hydrochloric acid, was collected in a Büchner funnel and washed several times before drying. The fraction which distilled over at 165–185° at 1 mm. was recrystallized two times from ethyl alcohol: 74 g., 31% yield, of I was obtained which had a melting point of 111–112°.

2-(α-Hydroxyethyl)-phenoxathiin (II).—Seventy and one-half grams of I, dissolved in 1 liter of absolute methyl alcohol, and 5 g. of copper–chromium oxide catalyst[4] were placed in a glass lined, high pressure bomb. The reaction was carried out in the presence of hydrogen at 160° at

(1) Suter, McKenzie and Maxwell, THIS JOURNAL, **58**, 719 (1936).

(2) (a) Burger, Waterman and Lutz, *ibid.*, **60**, 2628 (1939); (b) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1939); (c) Burger and Bryant, *ibid.*, **4**, 119 (1939).

(3) Analyses were made by Miss F. Durkee of this Laboratory and by Dr. Carl Tiedcke.

(4) Adkins, "Reactions of Hydrogen," Univ. of Wisconsin Press, Madison, Wisconsin.

pressures ranging from 2000 to 2400 p.s.i. with shaking for five hours. The reaction mixture was filtered to remove the catalyst. After the solvent had been distilled off, 64 g. (90% yield) was crystallized out of ligroin as small white needles, m. p. 65–67°.

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.84; H, 4.95. Found: C, 68.59; H, 4.99.

2-Vinylphenoxathiin (III).—Forty-seven grams of II was dissolved in 100 cc. of benzene, and introduced into the top of a vertical stainless steel column 1″ in diameter and 18 in. long. This reaction column was packed with alumina pellets[5] and maintained at a temperature of 340–360° and a pressure of 10–20 mm. The reaction products were collected in an ice-cooled receiver and then recrystallized from alcohol: 35 g., 79% yield, of III was obtained which had a melting point of 39.5–41°. The infrared absorption spectrum of this compound was marked by the absence of absorption bands due to the contributions of the carbonyl and hydroxyl groups.

Anal. Calcd. for $C_{14}H_{10}OS$: C, 74.33; H, 4.47. Found: C, 74.30; H, 4.69.

Polymers of III.—This monomer was found to polymerize very readily with heat or with any of several catalysts.[6] Such catalysts as boron trifluoride, benzoyl peroxide, *t*-butyl hydroperoxide and potassium persulfate were employed. These polymers were precipitated from benzene solution with methyl alcohol as white powders having softening points of about 200°.

A disk of polyvinylphenoxathiin prepared by heating the monomer in an open beaker at 130° for one hour, was hard, transparent and brittle at room temperature but it was very pliable at temperatures above 200°. The electrical properties of the disk were determined at 25°. At 60 cycles, the polymer had a power factor of 0.108% and a dielectric constant of 3.42. At one megacycle, the power factor was 0.15% and the dielectric constant was 3.34.

Copolymers of III.—One part of III was copolymerized with 0.8 part vinyl acetate, 1.0 part acenaphthylene, 1.0 part styrene, 0.6 part acrylonitrile, 1.0 part maleic anhydride and 0.35 part butadiene.[7] The butadiene–III copolymer was made by polymerizing in an emulsion. This product formed a tough, pliable film with good electrical properties.

2-(α-Hydroxyethyl)-dibenzothiophene (V).—Ninety-eight grams of IV, dissolved in 1400 cc. of absolute methyl alcohol, was heated with shaking in the presence of a copper–chromium oxide catalyst and 2000 p. s. i. of hydrogen. After reacting for five hours at 130°, the product was filtered to remove the catalyst and then recrystallized from dilute alcohol: 90 g., 91% yield, of white needles, m. p. 61.0–62.0° was obtained.

Anal. Calcd. for $C_{14}H_{12}OS$: C, 73.65; H, 5.26; S, 14.03. Found: C, 73.87; H, 5.13; S, 13.85.

2-Vinyldibenzothiophene (VI).—Thirty-eight grams of V was dissolved in 200 cc. of benzene and this solution was then added dropwise into the top of the vertical reaction column. The column was packed with alumina pellets[5] and maintained at a temperature of 325–350° and a pressure of 10 mm. during the reaction. The product was recrystallized from ethyl alcohol as small white needles, m. p. 45.0–45.5°; 17.5 g., 50% yield, was obtained from the conversion.

In an alternative procedure V and *p-t*-butylcatechol, as a polymerization inhibitor, were gently heated in a porcelain crucible until molten. Anhydrous copper sulfate was added to the mixture and heated a few minutes longer. The product was then recrystallized from alcohol.

Anal. Calcd. for $C_{14}H_{10}S$: C, 79.96; H, 4.76; S, 15.23. Found: C, 79.98; H, 4.77; S, 15.09.

Polymers of VI.—Products with high softening points and good electrical properties were prepared by polymerizing the monomer, both with catalysts and with heat alone. In one example VI was placed in a 125° oven for forty hours to give a hard brittle mass. This polymer when molded into a disk at 150° and 20,000 p.s.i. had a power factor of 0.1% and a dielectric constant of 2.8 at one megacycle.

Copolymers of VI.—Copolymers which are white powders with softening points ranging from 174° to above 220° were obtained by polymerizing one part of VI with one part of the following monomers: styrene, vinyl acetate, N-vinylcarbazole, N-vinylphthalimide, acrylonitrile and acenaphthylene.

Acknowledgment.—The authors wish to thank Mr. E. D. Elliott, Jr., of this Laboratory for his work on the emulsion polymerization of 2-vinylphenoxathiin.

Summary

The synthesis and properties are given for 2-(α-hydroxyethyl)-phenoxathiin, 2-vinylphenoxathiin, 2-(α-hydroxyethyl)-dibenzothiophene and 2-vinyldibenzothiophene. Polymers and copolymers have been prepared from the 2-vinylphenoxathiin and from the 2-vinyldibenzothiophene.

PITTSFIELD, MASS. RECEIVED MARCH 3, 1949

(5) Harshaw Chemical Company, Cleveland, Ohio.

(6) Flowers and Flowers, U. S. Patent 2,449,527; *C. A.*, **43**, 904 (1949).

(7) Flowers and Flowers, U. S. Patent 2,449,528; *C. A.*, **43**, 1223 (1949).

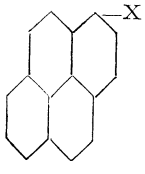
[CONTRIBUTION FROM THE PITTSFIELD LABORATORY, APPARATUS DEPARTMENT, GENERAL ELECTRIC COMPANY]

The Preparation and Properties of 1-Vinylpyrene

BY RALPH G. FLOWERS AND FRANK S. NICHOLS

The synthesis and investigation of the properties of 1-vinylpyrene (I) was undertaken as part of a program in which various polymerizable aromatic compounds were being studied. Interest in the physical and particularly the electrical properties of polymers having large aromatic nuclei stimulated the present work on the vinylpyrene.

Two different methods for the preparation of I were successfully carried out. In the first method, 1-acetylpyrene (II) was hydrogenated to the 1-(α-hydroxyethyl)-pyrene (III) with subsequent dehydration to I.



I X = —CH=CH$_2$
II X = —COCH$_3$
III X = —CHOHCH$_3$
IV X = —CHO
V X = —CH=CHCOOH

Bachmann and Carmack[1] prepared II as yellow crystals, m. p. 80–90°, and III as pale yellow crystals, m. p. 112–112.5°, from the hydrogenation of II with aluminum isopropoxide. The method used in the present work was to hydrogenate II in the presence of a copper–chromium oxide catalyst.[2] Some ethylpyrene is formed, even under the mildest conditions, when II is treated with more than equimolecular amounts of hydrogen. An excellent yield of 1-ethylpyrene was prepared by using a large amount of hydrogen. This is in agreement with results reported by Homer Adkins for aryl- and poly-aryl carbinols bearing an aryl group in the 2 position with respect to the hydroxy group.[3]

The second procedure for the preparation of I involved the treatment of 1-pyrenylaldehyde (IV) with malonic acid to give the 1-pyrenylacrylic acid (V) which was decarboxylated to I.

IV was prepared from phosphorus oxychloride, formylmethylaniline and pyrene as described by Vollman, *et al.*[4] Bergmann and Bograchov[4] prepared V from IV using piperidine as the condensation catalyst. The decarboxylation of V to I was attempted by the method of Walling and Wolfstirn[5] by which they decarboxylated cinnamic acids. The method, however, was not satisfactory in this case as the product obtained was almost entirely polymerized. A vapor phase modification of this method gave good results and has the added advantage that continuous rather than batch reactions may be carried out.

(1) Bachmann and Carmack, THIS JOURNAL, **63**, 2494 (1941).
(2) Adkins, "Reactions of Hydrogen," Wisconsin Press, 1937, p. 12.
(3) Adkins, *ibid.*, p. 69.
(4) Bergmann and Bograchov, THIS JOURNAL, **62**, 3016 (1940).
(5) Walling and Wolfstirn, *ibid.*, **69**, 852 (1947).

Experimental

1-(α-Hydroxyethyl)-pyrene (III).—Twenty-four grams of II, 0.119 mole, dissolved in 120 cc. of absolute methyl alcohol was agitated with 1.4 g. of copper–chromium oxide catalyst[2] and 0.12 mole of hydrogen for seven hours at 80° in a 270-cc. bomb. The initial pressure of 260 pounds per square inch fell to zero during this time; 17 g., 70% yield, of III, m. p. 113°, was obtained on recrystallization from benzene.

1-Ethylpyrene.—Twelve grams of II, 0.059 mole, dissolved in 120 cc. of absolute methyl alcohol was placed in a 270-cc. bomb with 0.7 g. of copper–chromium oxide catalyst. 0.55 mole of hydrogen was introduced into the bomb which was then agitated for one-half hour at 83–88°; 10 g., 83% yield, of the ethyl compound was obtained which had a melting point of 95° as previously reported.[6]

1-Vinylpyrene (I) from III.—Sixty-two grams of III dissolved in 200 cc. of dioxane was added dropwise into the top of a vertical stainless steel column 1/2 in. in diameter and 18 in. long. The column was packed with alumina pellets[7] and was maintained at a temperature of 340–360° and a pressure of 6 mm. during the reaction. Much charring of the product was observed under these conditions; 10 g., 18% yield, of light yellow 1-vinylpyrene, m. p. 87–89°, along with a considerable quantity of polymer was obtained.

Anal.[8] Calcd. for $C_{18}H_{12}$: C, 94.69; H, 5.30. Found: C, 94.35; H, 5.69.

1-Vinylpyrene (I) from V.—Nine grams of V in 150 cc. of benzene and 25 cc. of quinoline were allowed to pass down through a stainless steel column packed with copper borate–alumina pellets.[5] The temperature of the tube was kept at 520–580° and a pressure of 10–20 mm. was maintained on the system during the reaction. The product was washed with cold 2.4 *N* hydrochloric acid and then several times with water. The benzene was removed and the residue taken up with alcohol. This alcohol solution was boiled with activated charcoal and filtered; 5 g., 66% yield, of I, m. p. 87–89°, crystallized out of the light yellow solution.

Polymers of 1-Vinylpyrene.—Six grams of I dissolved in benzene was treated with boron trifluoride etherate to give a quantitative yield of a white powder, softening point about 220°, when precipitated out with methyl alcohol. This powder was molded into a disk at 160° using 40,000 p. s. i. pressure. This polymer had a dielectric constant of 3.2 and a power factor of 0.07% at one megacycle.

Polyvinylpyrene was also prepared by heat alone and with catalysts such as benzoyl peroxide and *t*-butyl perbenzoate.

Copolymers of 1-Vinylpyrene.—Copolymers have been obtained by polymerizing one part of I with one part of each of the following monomers: vinyl acetate, styrene, acenaphthylene, N-vinylphthalimide, N-vinylcarbazole, acrylonitrile and maleic anhydride. The softening points of these copolymers ranged from 155° for styrene and 180° for vinyl acetate to above 220° for the acenaphthylene and maleic anhydride products.

Summary

The properties of 1-vinylpyrene and its preparation by two methods have been described. Polymers and copolymers of 1-vinylpyrene have been made.

PITTSFIELD, MASS. RECEIVED MARCH 3, 1949

(6) Vollmann, Becker, Corell, Streeck and Langbein, *Ann.*, **531** 1–159 (1937); *C. A.*, **32**, 1492 (1938).
(7) Harshaw Chemical Company, Cleveland, Ohio.
(8) Analyses were made by Dr. Carl Tiedcke.

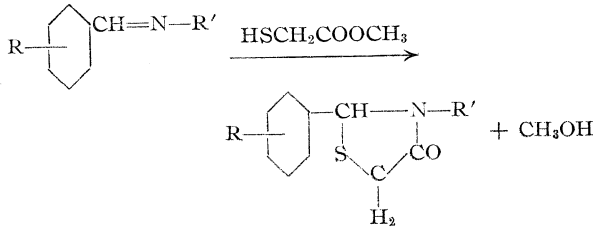
[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of 4-Thiazolidones. III. The Reaction of Methyl Thioglycolate with Benzylidene Dialkylaminoalkylamines

BY ALEXANDER R. SURREY

Recently it has been shown that 2,3-diaryl- and/or 3-alkyl-2-aryl-4-thiazolidones may be easily prepared by the reaction of thioglycolic acid[1] or of thioglycolic esters[1d] with Schiff bases. In continuation of a general investigation on the synthesis of 4-thiazolidones, a series of 2-aryl-3-dialkylaminoalkyl derivatives was prepared to make them available for pharmacological studies.

A convenient method of synthesis,[1b] involving the reaction of methyl thioglycolate with the appropriate benzylidene dialkylaminoalkylamine (Table I), was employed for this purpose. However, in some instances the intermediate anils were not isolated and the crude material was used directly in the next step.



In contrast to the benzylidene anilines,[1b] the anils in the present series react with a thioglycolic ester to give good yields of the 2,3-disubstituted 4-thiazolidones. When the reaction was carried out in refluxing Skellysolve E (b. p. 120°) with a separator connected to the apparatus, the methanol which formed during the reaction was collected as a distinct layer in the separator. Heating was discontinued when no further separation of methanol was noted, which in most instances approached the theory. With lower-boiling petroleum fractions as a solvent, the reaction proceeded in the expected manner. However, the separation of methanol could not be observed.

In most cases, after removal of the solvent by distillation, the crude residue was dissolved in ether, and the 2-aryl-3-dialkylaminoalkyl-4-thiazolidone was extracted with dilute hydrochloric acid. The base obtained from the acid extract was then converted to the crystalline hydrochloride (Table II).

In the preparation of 3-(3-diethylamino-2-hydroxypropyl)-2-phenyl-4-thiazolidone two isomeric crystalline bases and hydrochlorides were obtained. Although two possible racemic mixtures can also be formed in the preparation of the corresponding 2-(4-methoxyphenyl) derivative, only one compound was isolated.

(1) (a) Erlenmeyer and Oberlin, *Helv. Chim. Acta*, **30**, 1329 (1947); (b) Surrey, THIS JOURNAL, **69**, 2911 (1947); (c) Surrey, *ibid.*, **70**, 4262 (1947); (d) Troutman and Long, *ibid.*, **70**, 3436 (1947).

Preliminary pharmacological studies[2] indicate that several of the 2-aryl-3-dialkylaminoalkyl-4-thiazolidones reported in this paper show marked local anesthetic activity. 3-(2-Dibutylaminoethyl)-2-(4-chlorophenyl)-4-thiazolidone, (Win 2126) 3-(2-dibutylaminoethyl-2-(3,4-methylenedioxyphenyl)-4-thiazolidone (Win 2777) and 3-(2-diethylaminoethyl-2-(3,4-methylenedioxyphenyl)-4-thiazolidone (Win 2125) are the most active compounds studied in this series. Win 2777 is much more active than procaine while Win 2125 is as active as procaine and also shows activity as a topical anesthetic (cornea). The compounds reported are very stable to heat, acid or base and in most instances are non-irritating.

Experimental[3]

Preparation of Benzylidene-dialkylaminoalkylamines. (Table I).—Equimolecular quantities of the appropriate aromatic aldehyde and dialkylaminoalkylamine in benzene were refluxed with a water separator connected to the apparatus. When the reaction was completed the benzene was removed and the product was distilled under reduced pressure.

Preparation of 2-Aryl-3-dialkylaminoalkyl-4-thiazolidone Hydrochlorides.—The general procedure for the preparation of the compounds described in Table II is described below.

Equimolecular quantities (0.1 mole) of the benzylidene dialkylaminoalkylamine (Table I) and methyl thioglycolate[4] in 150 ml. of Skellysolve E were refluxed until approximately the theoretical amount of methanol was collected in a separator connected to the apparatus. After distilling the solvent *in vacuo*, the residue was dissolved in ether, and the desired product was extracted with dilute hydrochloric acid solution. The base, obtained from the acid extracts, was dissolved in acetone and alcoholic hydrogen chloride was added. Where necessary, dry ether was added and the solution was allowed to stand at room temperature. The solid hydrochloride which precipitated was purified by recrystallization.

3-(3-Diethylamino-2-hydroxypropyl)-2-phenyl-4-thiazolidone.—A solution of 23.4 g. of benzylidene 3-diethylamino-2-hydroxypropylamine and 11 g. of methyl thioglycolate in 150 ml. of Skellysolve E was treated as described above. The crude crystalline hydrochloride (16 g.) melted at 120–125°. After several recrystallizations from isopropanol, the product melted at 155.6–160.9° cor.

Anal. Calcd. for $C_{16}H_{25}ClN_2O_2S$: S, 9.29; Cl^-, 10.30. Found: S, 9.23; Cl^-, 10.12.

A sample of the hydrochloride was converted to base which solidified on standing. After recrystallization from Skellysolve A it melted at 58.8–60° cor.

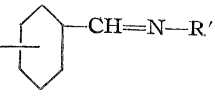
Anal. Calcd. for $C_{16}H_{24}N_2O_2S$: S, 10.37. Found: S, 10.55.

(2) The author is indebted to Dr. F. P. Luduena and Miss J. Sherndal for the local anesthetic testing, the details of which will be published elsewhere.

(3) All melting points and boiling points are uncorrected unless otherwise specified. The corrected melting point determinations and analyses recorded were performed by the analytical staff of these laboratories under the direction of M. E. Auerbach.

(4) Baker, *et al.*, *J. Org. Chem.*, **12**, 144 (1947).

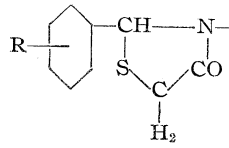
TABLE I

BENZYLIDENE DIALKYLAMINOALKYLAMINES, 

R	R′	B. p., °C.	Mm.	$n^{25}D$	Nitrogen analyses, %[a] Calcd.	Found
H	$CH_2CH_2N(CH_3)_2$	132–133	12	1.5330	15.91	15.61
H	$CH_2CH_2N(C_2H_5)_2$	82–83[b]	0.1	1.5231	13.73	13.61
4-Cl	$CH_2CH_2N(C_4H_9)_2$	147–150	.5	1.5198	9.50	9.36
4-OCH_3	$CH_2CH_2N(C_2H_5)_2$	120–125	.3	1.5367	11.96	11.83
3,4-Di-OCH_3	$CH_2CH_2N(C_2H_5)_2$	140–145	.35	1.5460	10.59	10.29
3,4-O_2CH_2	$CH_2CH_2N(C_2H_5)_2$	132–133	.2	1.5463	11.29	11.07
4-N-$(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	140–150	.2–0.4	1.5778	11.31	11.31[c]
H	$CH_2CH_2CH_2N(C_2H_5)_2$	105	.1	1.5196	12.85	12.80
3,4-O_2CH_2	$CH_2CH_2CH_2N(C_2H_5)_2$	155	.4	1.5402	10.68	10.64
H	$CH_2CHOHCH_2N(C_2H_5)_2$	137–139	.6	1.5313	11.97	11.62
4-OCH_3	$CH_2CHOHCH_2N(C_2H_5)_2$	160–163	.3	1.5419	10.61	10.50

[a] Basic nitrogen by the Toennies and Callan method [*J. Biol. Chem.*, **125**, 259 (1938)]. [b] Described in German Patent 559,500, June 26, 1928, b. p. 128° at 7 mm. [c] Titrated for only two nitrogen atoms by this method.

TABLE II

2-ARYL-3-DIALKYLAMINOALKYL-4-THIAZOLIDONES,  HYDROCHLORIDES

R	R′	Yield, %	Recryst. solvent	M. p., °C. (cor.)	Analyses, % Sulfur Calcd.	Found	Chlorine[a] Calcd.	Found	Win No.
H	$CH_2CH_2N(CH_3)_2$	70	Ethanol	219.2–221.1	11.18	11.08	12.37	12.20	2035
H	$CH_2CH_2N(C_2H_5)_2$	78[b]	Isopropanol	152–153.2	10.18	10.18	11.26	10.96	2131
4-Cl	$CH_2CH_2N(C_4H_9)_2$	53	Acetone	118.4–120.2	7.91	7.74	8.75	8.61	2126
4-OCH_3	$CH_2CH_2N(C_2H_5)_2$	50	Isopropanol	152.2–153.2	9.29	9.41	10.28	10.01	2530
3,4-Di-OCH_3	$CH_2CH_2N(C_2H_5)_2$	45	Isopropanol	137–138	8.55	8.38	9.48	9.45	2501
3,4-O_2CH_2	$CH_2CH_2N(C_2H_5)_2$	56	Isopropanol	144.8–146.4	8.93	8.88	9.88	9.75	2125
3,4-O_2CH_2	$CH_2CH_2N(C_4H_9)_2$	24[c]	Acetone-ether	125.5–127.3	7.71	7.52	8.52	8.52	2777
3,4,5-Tri-OCH_3	$CH_2CH_2N(C_2H_5)_2$	37[c]	Isopropanol	165.7–166.5	7.92	7.97	8.76	8.75	2503
4-$N(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	66	Isopropanol	161–162.4	8.96	8.92	9.91	9.67	2195
4-NO_2	$CH_2CH_2N(C_2H_5)_2$	53[c]	Ethanol	194.1–194.9	8.91	9.10	9.85	9.66	2502
4-NH_2	$CH_2CH_2N(C_2H_5)_2$	54	Isopropanol	185.5–186.5	9.72	9.55	10.75	10.58	2531
H	$CH_2CH_2CH_2N(C_2H_5)_2$	30	Isopropanol	151.2–153.2	9.75	9.72	10.78	10.64	2095
3,4-O_2CH_2	$CH_2CH_2CH_2N(C_2H_5)_2$	10[d]	Isopropanol	171.6–173.8	8.60	8.43	9.51	9.32	2687
H	$CH_2CHOHCH_2N(C_2H_5)_2$		Ethanol-ether	143.2–144	9.30	9.22	10.28	10.22	2130
4-OCH_3	$CH_2CHOHCH_2N(C_2H_5)_2$	30	Isopropanol	168.7–170.5	8.58	8.38	9.48	9.37	2124

[a] Ionic chlorine. [b] The base of this compound was reported by Troutman and Long, Ref. 1d. [c] Yield based on substituted benzaldehyde. [d] Yield of crude base was 74%.

The hydrochloride prepared from the crystalline base melted at 160–161°.

In another experiment the crude base solidified on standing. It was recrystallized from Skellysolve A, m. p. 74.2–75.6° cor.

Anal. Found: S, 10.42.

The hydrochloride prepared from this base melted at 143.2–144° cor. A mixed melting point with the higher melting hydrochloride was depressed.

3-(2-Diethylaminoethyl)-2-(4-nitrophenyl)-4-thiazolidone Hydrochloride (Win 2502).—A mixture of 30.2 g. of 4-nitrobenzaldehyde and 23.6 g. of 2-diethylaminoethylamine in 150 ml. of Skellysolve E was refluxed for three hours (2.4 ml. of water collected). After allowing to cool, 21.8 g. of methyl thioglycolate was added to the reaction mixture and refluxing continued for seventeen hours. At the end of this time approximately 9 ml. of methanol had separated. The solvent was decanted from the oily layer which separated and the latter was dissolved in 250 ml. of acetone and filtered with Norite. Alcoholic hydrogen chloride was added to the filtrate to give 45 g. of a yellow solid. Recrystallization from ethanol yielded 38 g. (53%) of product melting at 194.1–194.9° cor.

2-(4-Aminophenyl)-3-(2-diethylaminoethyl)-4-thiazolidone Hydrochloride (Win 2531).—A mixture of 36 g. of the above nitro base, 150 ml. of water, 250 ml. of ethanol, 140 g. of iron filings and 3.6 ml. of acetic acid was refluxed with stirring for one hour. An additional 7 ml. of acetic acid was added and refluxing continued for two hours longer. The mixture was basified with sodium carbonate and filtered hot. The ethanol was removed by distillation and the aqueous mixture was extracted with ether. After drying and removing the ether by distillation 25 g. of the crude base was obtained which yielded 18 g. of hydrochloride.

A sample of this hydrochloride was converted to the base which solidified on standing. After recrystallization from Skellysolve B it melted at 62.8–64.4° cor.

Anal. Calcd. for $C_{15}H_{23}N_3OS$: S, 10.93. Found: S, 11.02.

Acknowledgment.—The author wishes to thank Miss Marcia K. Rukwid for her valuable technical assistance.

Summary

The preparation of a series of 2-aryl-3-dialkylaminoalkyl-4-thiazolidones by the reaction of methyl thioglycolate with several benzylidene dialkylaminoalkylamines is reported.

Several of the compounds reported showed marked local anesthetic activity.

RENSSELAER, N. Y. RECEIVED DECEMBER 17, 1948

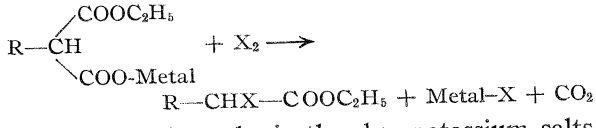
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF TEXAS]

A New Method for the Preparation of α-Bromoesters[1]

BY J. R. DICE AND J. N. BOWDEN[2]

The reaction of the metal salts of carboxylic acids with chlorine or bromine to yield an alkyl or aryl halide and carbon dioxide[3] is well known. Recently, Hunsdiecker[4] employed this reaction in the preparation of α-bromo aliphatic acids from the half-esters of ω,ω′-dicarboxylic acids. There are no reports in the literature of the use of the metal salts of the half acid esters of alkylmalonic acids in this synthesis.

It was reasoned that if one mole of halogen would react with the metal salts of the monoesters of alkylmalonic acids in the same manner as with simple carboxylic acid salts, the product would be an α-haloester.



$$R-CH(COOC_2H_5)(COO\text{-Metal}) + X_2 \longrightarrow R-CHX-COOC_2H_5 + \text{Metal-X} + CO_2$$

To test this hypothesis the dry potassium salts of the monoesters of several alkylmalonic acids were treated with bromine. Although the expected α-bromoesters were obtained, the yields in most experiments were relatively low. In general, bromination of acid chlorides[5] would be a preferred route to these compounds. Compounds prepared by the new method were ethyl α-bromobutyrate, ethyl α-bromoisovalerate, ethyl α-bromocyclohexylacetate, ethyl α-bromocaproate and ethyl α-bromo-β-phenylpropionate.

Although silver salts have been used most frequently in the reaction, other metal salts such as mercury, copper or potassium also have been used successfully.[6] In this study the potassium salts were utilized throughout and carbon tetrachloride was used as solvent.

With the potassium salt of monoethyl malonate we obtained the same result in carbon tetrachloride as that reported by Freund[7] for aqueous solution; *i. e.*, a mixture of ethyl bromoacetate and ethyl dibromoacetate was formed. In this reaction hydrogen bromide was evolved during the addition of bromine. The liberation of hydrogen bromide is apparently caused by a substitution reaction which occurs prior to or simultaneously with decarboxylation. Substitution does not follow decarboxylation, since ethyl bromoacetate does not react visibly with bromine under the conditions of our experiment.

Experimental

Potassium Salts of Monoesters of Alkyl Malonic Acids.—The ethyl alkylmalonates used were prepared from ethyl malonate (b. p. 198° at 746 mm.) and the respective alkyl halides essentially as described by Adams and Johnson,[8] and they were redistilled before use. Potassium salts of the mono acid esters of these compounds were synthesized following the procedure of Freund.[7] To a solution of 0.15 mole of diethyl alkylmalonate in 100 ml. of absolute alcohol was added, with stirring, a solution of 8.7 g. (0.15 mole) of potassium hydroxide in 100 ml. of absolute alcohol. The solution was allowed to stand at room temperature for four to twelve hours; the *p*H of the final mixture had a value between 7 and 8 as measured with *p*-Hydrion paper. Any solids which formed were assumed to be the dipotassium salt of the alkylmalonic acid and were removed by filtration.

TABLE I

ETHYL α-BROMOESTERS

α-Bromoesters	Yield,[a] %	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4
Acetate[b]	23	165–168	749		
Butyrate	36	177–180	745		
Caproate	67	208–209	748[c]	1.4468	1.2210
iso-Valerate	30	185–187	754[d]	1.4392	1.2325[e]
Cyclohexyl-acetate[f]	45	133–136	13	1.4708	1.1466
β-Phenyl-propionate	80	155–159	15	1.5180[g]	

[a] All yields are based on the weight of diethyl alkylmalonate employed. [b] Hydrogen bromide was evolved during the bromine addition and a 20% yield of ethyl dibromoacetate (b. p. 185–192° (749 mm.)) also was obtained. [c] 111–113° at 25 mm. [d] 105–115° at 25 mm. [e] Schleicher, *Ann.*, 267, 116 (1892), reported d^{12}_{12} to be 1.2276. [f] J. v. Braun, *Ber.*, 2184 (1923). [g] This compound decomposed on standing for twenty-four hours, so a density determination was not obtained.

(1) This work was supported by a grant from the Research Institute, the University of Texas, Project 186.

(2) From the M. A. Thesis of J. N. Bowden.

(3) Kleinberg, *Chem. Rev.*, **40**, 381 (1947).

(4) Hunsdiecker and Hunsdiecker, *Ber.*, **75**, 291 (1942).

(5) *Cf.* Bagard, *Bull. Soc. Chim. France*, [4] **1**, 310 (1907); Ingold, *J. Chem. Soc.*, **119**, 316 (1921); Schwenk and Papa, THIS JOURNAL, **70**, 3626 (1948).

(6) Hunsdiecker, Hunsdiecker and Vogt, U. S. Patent, 2,176,181 (1939); see also ref. 4.

(7) Freund, *Ber.*, **17**, 780 (1884).

(8) Adams and Johnson, "Elementary Laboratory Experiments in Organic Chemistry," The Macmillan Co., New York, N. Y., 1943, p. 329.

The alcohol was distilled until only a thick sirup remained in the flask. The last traces of solvent were removed *in vacuo* and the resulting crystals were placed in a vacuum desiccator for twelve hours. The salts were used without further purification.

Preparation of α-Bromoesters.—The dried, finely pulverized, potassium salt was mixed with 100 ml. of carbon tetrachloride. The ice-cold mixture was stirred vigorously while a solution of 25 g. (0.15 mole) of bromine in 50 ml. of carbon tetrachloride was added dropwise over a period of two to four hours. The bromine was decolorized rapidly at the start of the reaction, but persisted after all of the bromine solution had been added. The mixture was filtered and the solvent was removed in a current of air. The residue was distilled at reduced pressure to give in every case a colorless, strongly lachrymatory liquid. The yields and physical constants of the compounds prepared are given in Table I.

Summary

The reaction of the potassium salts of monoethyl alkylmalonates with bromine provides a new method of preparing α-bromoesters.

RECEIVED APRIL 12, 1949

[CONTRIBUTION FROM THE VIRUS LABORATORY, UNIVERSITY OF CALIFORNIA[1]]

The Apparent Sulfur in Cucumber Virus 4

BY C. A. KNIGHT

Rather extensive chemical analyses have been made of tobacco mosaic virus (TMV) and several of its strains; and cucumber viruses 3 and 4 (CV3 and CV4) have been included in these studies.[2] The consideration of CV3 and CV4 as strains of TMV has been based on their mutual possession of an uncommon size and shape, on weak but definite serological cross reactions, on a common unusual resistance to heat and desiccation, and on possession of apparently identical quantities of protein and pentosenucleic acid.[3-5] On the other hand, it has not been possible to perform one of the tests of strain relationship, the cross-protection test, for as yet no common host has been reported for TMV and the cucumber viruses. Furthermore, it appears that the particles of CV3 and CV4 differ slightly but significantly in size from those of TMV and some of its other strains.[6,7] However, whether they are actually distantly related strains of TMV as supposed, or whether they are distinct viruses, it seems evident that the facts revealed from their study could ultimately be brought to bear on problems of the relationship of biological, serological, and physical properties to the chemical composition and structure of the virus, or of biologically active proteins in general. As a consequence of this viewpoint, it seemed imperative to determine the nature of the sulfur in CV3 or in CV4, for, while the sulfur of TMV and of most extensively studied proteins has been shown to occur mainly in well-known sulfur-containing amino acids, the sulfur apparently present in CV3 and CV4 has eluded identification.[3,8]

It will be shown in the present report that CV4 differs decidedly from TMV and some of its strains in that CV4 probably contains no sulfur at all.

Materials and Methods

Preparation of Virus.—Highly purified preparations of CV4 were obtained from the expressed juice of appropriately diseased cucumber plants by differential centrifugation as previously described.[3] The salt content of the preparations was reduced to a very low level by handling the virus in distilled water during two or more cycles of centrifugation, by dialysis against flowing distilled water, or by electrodialysis. These preparations were then frozen and dried *in vacuo*, and then further dried to constant weight at 110° in a drying oven.

Sulfur Analyses.—The first sulfur values for highly purified, dried preparations of CV3 and CV4 were those of Bawden and Pirie in which a range of 0.0 to 0.6% sulfur was reported.[9] No explanation of the possible significance of this range of results was advanced, and the value recorded later by Bawden appears to be a mean of the earlier determinations, namely, 0.3%.[4] A figure of 0.85% sulfur was given by Knight and Stanley as the mean of 8 analyses made on 3 different preparations of CV4.[3] Since that time and including the individual analyses leading to the figure just given, a total of forty-one analyses have been made by three different analysts on thirteen of our preparations. The analyses were made by the customary Carius pressure-tube method and yielded an average of 0.6% sulfur, but the individual values obtained ranged from 0.07 to 1.26%. Furthermore, a given analyst obtained with the same preparations of virus, but on different occasions, sulfur values which differed by as much as 50%. Also, different analytical laboratories, analyzing portions of the same sample of virus, reported results equivalent to three- to ten-fold differences in sulfur content. No analyst was consistently high or low in his results.

Despite this confusing situation, the results seemed to indicate that there is some sulfur in CV4, but that it is for some unknown reason, inherently difficult to obtain a reliable estimate of its quantity.

Attempts to Identify Sulfur in CV4.—A series of tests made on numerous preparations of CV4 over a period of several years has established the absence from this virus of amounts greater than traces of the amino acids, cys-

(1) This investigation was begun in the laboratories of the Rockefeller Institute for Medical Research, Princeton, N. J. Presented in part before the Division of Biological Chemistry at the 115th Meeting of the American Chemical Society at San Francisco, March 28–April 1, 1949.

(2) C. A. Knight, *J. Biol Chem.*, **171**, 297 (1947).

(3) C. A. Knight and W. M. Stanley, *ibid.*, **141**, 29 (1941).

(4) F. C. Bawden, "Plant Viruses and Virus Diseases," second ed., Chronica Botanica Company, Waltham, Mass., 1943, p. 162.

(5) C. A. Knight and W. M. Stanley, *J. Biol. Chem.*, **141**, 39 (1941).

(6) J. D. Bernal and I. Fankuchen, *Nature*, **139**, 923 (1947).

(7) C. A. Knight and G. Oster, *Arch. Biochem.*, **15**, 289 (1947).

(8) C. A. Knight, Abstracts, Meeting of the American Chemical Society, September 8–12, 1941.

(9) F. C. Bawden and N. W. Pirie, *Brit. J. Exptl. Path.*, **18**, 275 (1937).

teine, methionine and thiolhistidine.[10] Cysteine and cystine were ruled out by the failure of CV4 to give a positive nitroprusside test either in the presence or absence of cyanide, the failure of CV4 to reduce uric acid reagent, and by the fact that these amino acids were not detected in the Baernstein determination of sulfur amino acids.[3,8,11-13] Methionine was eliminated from consideration by its failure to appear in the Baernstein separation, the Kolb and Toennies color reaction,[14] or in microbiological assays.[2] It should be noted also that the Baernstein method yielded no sulfate sulfur at all when applied to several of the samples. At one time, it was thought that positive color tests for thiolhistidine were obtained[8] but in more carefully controlled experiments these were not secured, which, coupled with the failure of thiolhistidine to appear in the Baernstein separation, make its presence in CV4 very dubious. Some microbiological tests for biotin, kindly made on a hydrolysate of CV4 by Dr. William Trager, indicated that this sulfur-containing vitamin was absent.

While the tests mentioned above did not preclude the possible presence in CV4 of some rarely occurring or previously unknown sulfur component, it nevertheless seemed advisable to test next for the possible presence of some element other than sulfur, but related to it, such as selenium.

Tests for Selenium in CV4.—When CV4 was digested and treated with codeine sulfate according to the procedure of Gortner and Lewis[15] or some modification of it, a blue color indicative of the presence of selenium was obtained. This color was not secured under comparable conditions with tobacco mosaic virus. However, application of the more specific distillation method of Klein[16] showed no detectable selenium in a 100-mg. sample of CV4. In a control experiment, using this method, the addition to a sample of the virus of 25 micrograms of selenium in the form of sodium selenite resulted in a recovery of 22 micrograms. The absence of selenium from CV4 was further confirmed by examination of the emission spectrum of the virus by Dr. G. I. Lavin. This test showed the absence of even traces of selenium from CV4. Therefore, it can be concluded that selenium is not present in CV4, although no explanation has yet been found for the positive codeine color reaction given by this virus.

The absence of tellurium, as well as selenium, was also indicated by failure to detect either of these elements when the test of Drew and Porter[17] was applied to 500 mg. of virus.

In view of the foregoing, it seemed pertinent to return to the potential sulfur in CV4 and to seek a decisive test which would indicate whether or not this element was present. The use of radiosulfur was selected for this purpose.

Experiments with Sulfur 35.—It had been found that radioactive phosphorus was incorporated into tobacco mosaic virus when mosaic-diseased tobacco plants cultured in sand were fed a nutrient solution to which had been added disodium phosphate containing radioactive phosphorus.[18] It seemed likely, therefore, that if CV4 contained sulfur, a radioactive isotope of that element could be introduced into the virus by a similar procedure. For this purpose, about 100 young cucumber plants growing in sand culture were inoculated with CV4, and starting the following day and continuing for about thirty days, the plants were watered with 17 parts of Spencer's medium nitrogen nutrient solution[19] to which had been added 1 part of potassium chloride solution containing S^{35}.[20] Each plant received about 100 ml. of solution every other day. A day after the last feeding, the plants were harvested, frozen and subsequently processed for CV4 by the usual methods.[3] The virus was handled in diminishing concentrations of phosphate buffer through successive cycles of centrifugation, starting with 0.1 *M* and working down through 0.05, 0.01 *M* and going finally to water, from which the preparation was frozen and dried. A portion of partially purified virus, containing a small but visible amount of green impurity, was reserved for radioactivity measurements. The highly purified, dried virus was white in color.

In order to compare the results obtained with CV4 to those procurable in the case of a strain of tobacco mosaic virus known to contain sulfur, an experiment similar to that just described was performed with tobacco mosaic virus grown in three Turkish tobacco plants.[21]

The sulfur in the various fractions was converted to sulfate by Carius oxidation and precipitated from the digests as benzidine sulfate.[22] Measurements of S^{35} activity were made in a Lauritzen electroscope[23] using the methods of Henriques and co-workers.[22] Carrier sulfur was used when necessary and all samples of benzidine sulfate measured for radioactivity came within the weight range of 6.7 to 7.1 mg.

The data, which are summarized in Table I, indicate that a negligible quantity of the S^{35} supplied to the cucumber plants appeared in the highly purified CV4. On the other hand, the partially purified virus, which contained a visible trace of green impurity, was found to possess 45 times the radioactivity of the highly purified virus. This, and the considerable amount of radioactivity found in the sap and in the plant residue after ex-

TABLE I

DISTRIBUTION OF S^{35} ACTIVITY IN CV4, TOBACCO MOSAIC VIRUS AND OTHER FRACTIONS

Mg. S supplied to plants in nutrient solution in CV4 expt.	17,292
Mg. S in 200 mg. isolated CV4 on basis of 0.6% S	1.2
Total units[a] S^{35} supplied to plants	132,000,000
Total units S^{35} found in 200 mg. of CV4	31
Per cent. of theory of S^{35} found in CV4	0.33
Total units of S^{35} in plant sap from which CV4 was isolated	2,170,000
Units of S^{35} found in dried plant residue after extraction of CV4	18,500,000
Mg. S supplied to plants in nutrient solution in TMV experiment	433
Mg. S in 27 mg. isolated TMV on basis of 0.2% S	0.054
Total units S^{35} supplied to plants	2,590,000
Total units S^{35} found in 27 mg. of TMV	178
Per cent. of theory of S^{35} found in TMV	55

[a] Results are expressed in terms of electroscope divisions per minute.

(10) A sample of thiolhistidine was kindly provided by Dr. V. du Vigneaud.

(11) H. D. Baernstein, *J. Biol. Chem.*, **115**, 25, 33 (1936).

(12) B. Kassel and E. Brand, *ibid.*, **125**, 145 (1938).

(13) M. L. Anson, *J. Gen. Physiol.*, **25**, 355 (1942).

(14) J. J. Kolb and G. Toennies, *J. Biol. Chem.*, **131**, 401 (1939).

(15) R. A. Gortner, Jr., and H. B. Lewis, *Ind. Eng. Chem., Anal. Ed.*, **11**, 198 (1939).

(16) A. K. Klein, *J. Assn. Off. Agr. Chem.*, **26**, 346 (1943).

(17) H. D. K. Drew and C. R. Porter, *J. Chem. Soc.*, 2091 (1929).

(18) W. M. Stanley, *J. Gen. Physiol.*, **25**, 881 (1942).

(19) E. L. Spencer, *Plant Physiol.*, **12**, 825 (1937).

(20) One irradiated unit no. 17 was obtained from the U. S. Atomic Energy Commission. The target material in this unit was 25 g. of potassium chloride. This was dissolved in 9 liters of distilled water and 8 liters of the resulting solution was employed in the CV4 experiment and a portion of the remaining liter was used in the TMV test.

(21) It was not feasible to make this parallel experiment in cucumber plants since no virus known to contain sulfur has been isolated from this source in a highly purified state.

(22) F. C. Henriques, Jr., G. B. Kistiakowsky, C. Margnetti and W. G. Schneider, *Ind. Eng. Chem., Anal. Ed.*, **18**, 349 (1946).

(23) The author is indebted to Dr. Roger Herriott for the use of this instrument.

traction of the virus, show that a significant portion of the S^{35} supplied to the plants was taken up and utilized. One can, therefore, conclude that if CV4 had contained S, even in the smallest amount shown by the analytical data, this would have been manifested by appreciable radioactivity in the isolated and highly purified CV4. Confirmation of this conclusion appears to be provided by the outcome of the TMV experiment where, as shown in Table I, 55% of the expected S^{35} activity was found in the highly purified TMV. The author was assisted in these experiments by Miss Jessie Mason McNeil.

Discussion and Summary

The fact that a highly purified preparation of cucumber virus 4 obtained from cucumber plants which had received a nutrient solution containing S^{35}, possessed much less than 1% of the potential, calculated radioactivity of a compound containing 0.6% sulfur, indicates that no sulfur is present in CV4. This conclusion is supported by the finding that 55% of the calculated radioactivity was present in a similar preparation of tobacco mosaic virus, which is known to contain 0.2% of sulfur.[24]

The sulfur values obtained by two different laboratories on portions of the CV4 of the S^{35} experiment illustrate the confusing results which made the isotope experiment imperative, for the analyst who had previously obtained high values for most preparations, reported essentially no sulfur present (0.07%), whereas a second analyst found an amount comparable to that present in TMV, *i. e.*, about 0.2%. The nature of this pseudo-sulfur, found in 90% of the analyses of CV4 thus far, remains to be solved. It seems clear, however, that it is an artifact.

As an incidental point, the S^{35} experiment demonstrated in a graphic manner how a virus can be separated from normal plant materials in a stepwise fashion by the technique of differential centrifugation. The clarified plant sap, from which the virus was separated by an initial high-speed centrifugation, possessed over 2 million units of S^{35} activity. After 3 cycles of centrifugation, the total S^{35} activity of the viral preparation was about 1500 units, and after 5 cycles, 31 units. It seems reasonable in view of these facts, to assign the relatively minute amount of radioactivity in the highly purified CV4 to a residual trace of impurity.

The demonstration that CV4 contains no sulfur constitutes a striking difference between this virus and the other strains of TMV which have been studied chemically thus far, for the latter all contain sulfur, mainly in the form of cysteine.

(24) A. F. Ross, *J. Biol. Chem.*, **136**, 119 (1940).

BERKELEY 4, CALIFORNIA RECEIVED FEBRUARY 15, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF PENNSYLVANIA]

The Effects of Substituents on the Dissociation Constants of Substituted Phenols. I. Experimental Measurements in Aqueous Solutions[1]

BY CHARLES M. JUDSON[2,3] AND MARTIN KILPATRICK[4]

The Sarmousakis modification[5] of the Kirkwood–Westheimer[6] electrostatic theory of the effects of substituents on the dissociation constants of benzenoid acids was originally tested by a comparison with the experimentally observed constants for the benzoic acids in several different pure solvents. To assist in providing a further test of the Sarmousakis treatment, the dissociation constants of a number of substituted phenols have been measured using a stepwise colorimetric method similar to that used previously in this Laboratory.[7] Complete data for the substituted phenols measured by a consistent method have been reported in the literature only for certain alcohol–water mixtures.[8] Values in a pure solvent are preferred for comparison with the electrostatic theory. The data obtained in the present investigation along with the previously available data have provided a satisfactory set of values for the substituted phenols in aqueous solution. These values have been compared with values calculated by the electrostatic theory and have been used to provide additional support for the theory.[9]

The ratio of the dissociation constant of an indicator A_i to that of an uncolored acid A may be defined by the equation

$$K_{A_iB} = c_{B_i}c_A/c_{A_i}c_B \qquad (1)$$

where B_i and B refer to the corresponding conjugate bases. By placing a small measured amount of the indicator in a buffer solution of known concentration of the uncolored acid with its sodium salt, the ratio of the dissociation constants can be determined from a colorimetric measurement of the concentration of one form of

(1) Taken from the dissertation presented by Charles M. Judson to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosphy, August, 1947. Presented before the 112th meeting of the American Chemical Society held in New York, N. Y., September, 1947.

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(4) Present address: Department of Chemistry, Illinois Institute of Technology, Chicago, Ill.

(5) Sarmousakis, *J. Chem. Phys.*, **12**, 277 (1944).

(6) Kirkwood and Westheimer, *ibid.*, **6**, 506 (1938); Westheimer and Kirkwood, *ibid.*, **6**, 513 (1938); Westheimer and Shookhoff, THIS JOURNAL, **61**, 555 (1939); Westheimer, *ibid.*, **61**, 1977 (1939).

(7) Mason and Kilpatrick, *ibid.*, **59**, 572 (1937); Minnick and Kilpatrick, *J. Phys. Chem.*, **43**, 259 (1939); Kilpatrick and Mears, THIS JOURNAL, **62**, 3047, 3051 (1940)

(8) Schwarzenbach and Egli, *Helv. Chim. Acta*, **17**, 1176 (1934); Schwarzenbach and Rudin, *ibid.*, **22**, 360 (1939).

(9) Judson and Kilpatrick, THIS JOURNAL, **71**, 3115 (1949)

the indicator. By making a series of such measurements of relative dissociation constants and including in this series one compound, acetic acid, for which the dissociation constant in water had been previously established, the dissociation constants were measured for a series of nitrophenol indicators and uncolored substituted phenols. This procedure was particularly suitable for measurement of phenols with nitrophenol indicators because the extrapolation to zero concentration is simplified when the buffer acid and the indicator have the same charge type, the ratio of the dissociation constants being to a first approximation independent of concentration.

Experimental

Apparatus.—Preliminary measurements were made with a Rubicon photoelectric colorimeter (number 4600) using a galvanometer and a 4400 Å. filter supplied by the manufacturer.

With the object of increasing the precision of the measurements, another colorimeter was constructed by modifying the instrument used by Minnick and Mears.[7] The modified instrument consisted of a projection bulb source, a regulated power supply for the source, a Hilger spectroscope used as a monochromator, a light-tight box within which four absorption cells could be brought successively into the light path, and a 931 multiplier phototube circuit to measure the intensity of the transmitted light.[10]

The optical system was essentially that used by Minnick and Mears. The absorption cells were plane-window, cylindrical glass cells with a path of 25 mm., obtained from the Phoenix Precision Instrument Co. The cells were found to have identical effective solution depths as determined by extinction measurements. The monochromator was calibrated by reference to a mercury arc. All measurements were made at 4450 Å. with a half-width of 24 Å.

The electrical circuits were modified because of the difficulties reported by previous workers. The voltage regulators used for the light source supply was similar to one described by Terman.[11] A three-phase full-wave rectifier circuit with 1120 volt center-tapped transformers supplied the power to the regulator. Using twenty-one 6L6 tubes in parallel in the regulator, an output of one ampere was obtained. The 200 volt output was dropped through a resistance to obtain a 100 volt potential for the source. The resulting potential was constant to 0.002 v. which was shown to be sufficient to ensure regulation of light intensity to 0.01%. The 110 v. projection bulb was operated at 100 v. increasing its life at some expense of intensity.

Two separate filtered half-wave power supply circuits were provided for the dynode and anode potentials of the multiplier phototube. A Sola constant-voltage transformer was used to regulate the input to both supply circuits. The output of the dynode supply was further controlled by an electronic voltage regulator similar to one designed for a Geiger counter supply.[12] This regulator was found more convenient than regulation based on the control characteristics[13] of the tube in which the voltage step at one dynode is made unequal to that at the other dynodes. The potential supplied to the anode was 280 v. The potential supplied to the dynodes was 560 v., constant to 0.1 v. This potential was divided into nine equal portions by a 180,000 ohm divider. The limit of accuracy of the transmittance measurements was apparently set by the regulation of the dynode potentials. Because this regulator was drawing more current than it was designed for, the precision of the transmittance measurements was limited to 0.2%.

The output of the phototube was measured by passing the photocurrent through a high resistance decade (R1 in Fig. 1) and measuring the potential developed across the decade with a type K potentiometer (R2). A second potentiometer (R3) was used to compensate for the dark current of the phototube which generally amounted to about 0.3% of the photocurrent. The balance of the potentiometer was measured with a Rubicon galvanometer (0.0012 μa/mm.) used in conjunction with an Ayrton shunt (not shown in Fig. 1).

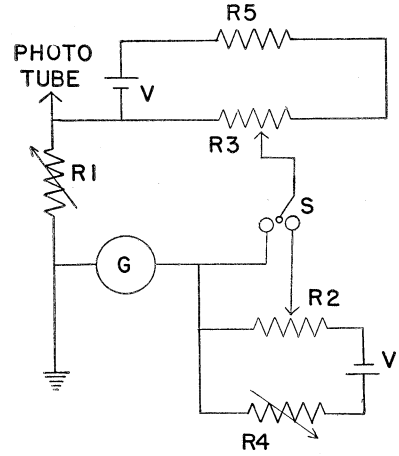

Fig. 1.—Circuit for measuring photocurrent: R1, 100,000ω decade; R2, type K potentiometer; R3, 30ω slide wire; R4, 1000ω decade, R5, 7000ω; V, 1.5 volt batteries; G, galvanometer.

Instead of using a standard cell, the photocurrent for the measured transmittances was always compared with the photocurrent obtained with a cell containing pure water. As the type K potentiometer used was not designed for direct reading of potentials compared to a standard of unity, it was necessary to use the standard cell position, 1.018 v., for the measurement of the reference solution, the ratio of the two photocurrents then being 1.018 times the reading of the potentiometer.

The optical system was placed in a transite air-bath lagged with rock wool. Water cooled to 5° by a mechanical refrigerating unit was circulated through a radiator inside the air-bath. A thyratron relay controlled by a bimetallic regulator operated a nichrome wire heater and simultaneously a mercury switch relay which in turn controlled an impeller pump in the cooling system. Three fans were used to circulate the air. The temperature inside the absorption cell box was 25.0 ± 0.1°. The temperature was measured with a Beckmann thermometer calibrated by comparison with a Bureau of Standards platinum resistance thermometer.

Solutions measured with the Rubicon colorimeter were brought to 25° in a water-bath and were then quickly transferred to the test-tube absorption cells and the transmittance measured immediately. The temperature could be controlled in this way to ±0.5°.

Procedure.—At the beginning of each series of measurements with the photomultiplier instrument, the four absorption cells were cleaned and filled with water and the windows were polished. Using one cell as a reference, the relative transmittances of the other three cells were measured to obtain a calibration of the cells. Three of the cells were then removed, rinsed with the solutions to be measured, filled and replaced without touching the cell

(10) We are indebted to J. P. Hervey of the Johnson Foundation for Research in Medical Physics of the University of Pennsylvania and to J. Presper Eckert of the Moore School of Electrical Engineering of the University of Pennsylvania for suggestions in the design of the electrical circuits used.

(11) Terman, "Radio Engineers' Handbook," McGraw-Hill Book Co., Inc., New York, N. Y., 1943, p. 615, Fig. 19.

(12) Strong, "Procedures in Experimental Physics," Prentice-Hall, New York, N. Y., 1939, p. 296, Fig. 28.

(13) Rajchman and Snyder, *Electronics*, **13**, 20 (1940)

window. The transmittances of the three solutions were then measured by comparison with the reference cell containing pure water. The cells were then filled with another set of solutions in the same way. At the end of the group of measurements the cells were again filled with water and the cell calibration checked. In filling the cells an air bubble was left just below the stopper to prevent the formation of small bubbles on the window. The light source and the thermostat were allowed two hours to come to equilibrium for each measurement. The fans and cooling system were turned off momentarily during the measurements to avoid vibration.

The dark current compensation was adjusted with the light beam interrupted just before each measurement and was checked after the measurement. The comparison of the cell transmittances was repeated several times in quick succession, balancing the potentiometer in the standard cell position for the reference absorption cell by varying R4, and then balancing the potentiometer slide wire for the photocurrent from the unknown solution. The repeated comparison was carried out in a systematic way so that the effects of photocell fatigue would be reproducible.

In using the Rubicon colorimeter, the light intensity was first adjusted with no absorption cell in place to an arbitrary value so that a reading of 0.99 would be obtained with a cell containing pure solvent. Two cells were selected which showed identical transmittances with water and with absorbing solutions and duplicate measurements of the solvent and of each solution were made in these cells. Dark current readings were made before and after each series of measurements by turning off the light source. A correction was made using the average of the two dark current readings.

A blank correction was made for the absorption of the buffer solution whenever applicable. This blank was determined either by adding a small amount of hydrochloric acid to the buffer solution immediately after measuring the transmittance or by measuring a buffer solution made up without any indicator. In the former case a small correction was made in the blank for the transmittance of the acid form of the indicator present in the acidified solution.

Preliminary measurements were made of the transmittances of solutions of the complete acid form and the complete basic form of each indicator used. It was found that a single wave length could be used which was suitable for all of the nitrophenols used.

Solutions on the basic and acid forms of each indicator were then measured as a function of concentration. In each case a quantity of sodium hydroxide or hydrochloric acid was added sufficient to ensure a negligible contribution to the absorption from the opposite form of the indicator. Blanks were subtracted for the apparent absorption of the added acid or base where required. In some cases a slight variation of the transmittance with the amount of added base or acid was observed and the value required was obtained by extrapolation to dilute solution, the concentration always being kept high enough to keep the indicator completely in the acid or basic form.

The extinction constant k defined by Beer's law

$$-\log T = kc \qquad (2)$$

was calculated from the measured transmittance T and the concentration c for each indicator in the basic and in the acid form. The extinction constant generally showed small variations with indicator concentration. The measured values of k were plotted against c or against $-\log T$.

The transmittances of buffer solutions of the acids with suitable indicators were then measured for two different buffer ratios differing by a factor of about two and for several different concentrations for each pair of compounds being compared. Each solution contained an amount of indicator sufficient to make the transmittance around 40% which is near to the transmittance at which maximum precision is obtained. The buffer solutions were prepared by adding measured volumes of stock solutions of the indicator and buffer acids and of standard 0.08 N carbonate-free sodium hydroxide.

The calculation of the concentration of the basic and acid forms of the indicator was made by a series of approximations. The absorption of the acid form was first neglected and the approximate concentration of the basic form calculated from the measured transmittance and the previously determined extinction constant for the basic form. The concentration of the acid form was then estimated from the known total concentration and the approximate concentration of the basic form. A correction was then made for the absorption by the acid form and a second approximation for the basic form calculated, etc. The amounts of the basic and acid forms of the buffer acid were calculated from the amount of acid and base added, the amount of indicator converted to the basic form and the amount of hydroxyl or hydrogen ion formed. The hydrogen ion concentration was calculated from the value of the dissociation constant of either the buffer or the indicator acid since one of these constants was known in each case. In calculating the hydrogen ion concentration the activity coefficient was estimated from the Debye-Hückel approximation.

Materials.—The 2,5-dinitrophenol and the 3,4-dinitrophenol were separated from the mixture obtained by the nitration of Eastman Kodak *m*-nitrophenol.[14] The 2,5-dinitrophenol was recrystallized several times from alcohol (m. p. 105.8–106.2°). The 3,4-dinitrophenol was purified by dissolving in aqueous sodium hydroxide solution and precipitating with dilute acid. After two purifications in this manner the product could be recrystallized from dry benzene without forming an oil and was then recrystallized from an alcohol–water mixture (m. p. 134.6–135.1°). No 2,3-dinitrophenol could be isolated from this nitration mixture.

m-Nitromesitol was prepared from mesitylene.[15] Dinitromesitylene prepared from Eastman Kodak Co. mesitylene[16] was reduced with ammonium acid sulfide in a bomb,[17] and the resulting nitromesidine was diazotized and nitromesitol obtained by boiling the diazonium sulfate solution with sulfuric acid solution.[17,18] The product was precipitated from sodium carbonate solution with acid, recrystallized from alcohol and finally purified by vacuum sublimation (m. p. 63.4–63.9°). Attempts to prepare *m*-nitromesitol by nitration of mesitol were unsuccessful.

The *o*-nitrophenol (m. p. 44.9–45.3°) and *m*-nitrophenol (m. p. 96.6–96.8°) were Eastman Kodak Co. products recrystallized several times from alcohol–water mixtures. The *o*-nitrophenol was first steam distilled. The *p*-nitrophenol was a Kahlbaum product recrystallized from water (m. p. 113.1–113.8°).

The phenol was a J. T. Baker product purified by fractional distillation (b. p. 182.0–182.5°; m. p. 39.8–39.9°). The *p*-chlorophenol was a Paragon Testing Laboratory product, purified by fractional distillation (b. p. 219–220°; m. p. 43.2–43.7°). The *m*-chlorophenol (b. p. 216.7°, m. p. 33.2–33.5°), *o*-chlorophenol (b. p. 176°) and *o*-bromophenol (b. p. 194–195°) were Eastman Kodak Co. products fractionally distilled. The 2,4-dichlorophenol was an Eastman Kodak Co. product purified by fractional sublimation (m. p. 42.0–42.8°).

The *p*-fluorophenol was prepared from Eastman Kodak Co. *p*-fluoroanisole by treatment with aluminum chloride following the procedure described for the preparation of *o*-fluorophenol.[19] The product was purified by fractional distillation (b. p. 185.0–185.5°).

The acetic and benzoic acids were Kahlbaum products used without further purification.

Fractional distillations were carried out in an eleven-ball, lagged, electrically-heated Snyder column at a 10:1 reflux ratio except for the distillations of *m*-chlorophenol

(14) Holleman and Wilhelmy, *Rec. trav. chim.*, **21**, 432 (1902).

(15) We are indebted to Walter Brooks for the preparation of the *m*-nitromesitol.

(16) Kuster and Stallberg, *Ann.*, **278**, 213 (1894).

(17) Knecht, *ibid.*, **215**, 98 (1882).

(18) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 404.

(19) Bennett, Brooks and Glasstone, *J. Chem. Soc.*, 1821 (1935).

and *p*-fluorophenol which were carried out in a smaller six-ball column. Melting points and boiling points were measured with calibrated thermometers and stem corrections were made throughout. All products were dried over phosphorus pentoxide before use.

The melting points found for *m*-chlorophenol and *p*-chlorophenol are about 5° higher than those listed in Landolt–Börnstein but are in agreement with those recently reported by the Dow Co.[20]

Standard carbonate-free sodium hydroxide was used to make up the buffer solutions. The sodium hydroxide was standardized by comparison with Bureau of Standards benzoic acid and was kept in a bottle coated with Vulcalock cement.[21] All solutions were made up in water which had been redistilled from alkaline permanganate, fractionally condensed and freed of carbon dioxide by long bubbling with nitrogen gas.

The volumetric glassware and the balance weights used had been calibrated according to standard procedures.

Results

A preliminary measurement of each dissociation constant ratio was made with the Rubicon colorimeter in order that optimum values of the buffer ratio could be selected for the final measurements. Because of the length of time required for a set of measurements with the photomultiplier colorimeter, measurements were made with this instrument only for the first six comparisons in Table I which constituted the main series of comparisons relating phenol to acetic acid. The other comparisons, which involved a ratio with one of the compounds in the main series, were made with the Rubicon colorimeter because the accuracy required was not so high in these measurements. The error in the determination of the dissociation constant of an acid, which was ultimately compared to benzoic acid or to phenol, involved the error in each of several of the main series of comparisons but involved not more than one of the comparisons which were made with the Rubicon colorimeter.

TABLE I

MEASURED VALUES OF LOG $K_{AiB}°$

p-Nitrophenol, acetic acid	$\bar{3}.617 \pm 0.001$
p-Nitrophenol, 2,4-dichlorophenol	$0.710 \pm .005$
m-Nitrophenol, 2,4-dichlorophenol	$\bar{1}.504 \pm .004$
m-Nitrophenol, *p*-chlorophenol	$1.032 \pm .004$
m-Nitromesitol, *p*-chlorophenol	$0.394 \pm .004$
m-Nitromesitol, phenol	$0.967 \pm .001$
2,5-Dinitrophenol, acetic acid	$\bar{1}.541 \pm .003$
3,4-Dinitrophenol, acetic acid	$\bar{1}.333 \pm .002$
m-Nitrophenol, *o*-chlorophenol	$0.131 \pm .002$
m-Nitrophenol, *o*-bromophenol	$0.079 \pm .004$
m-Nitrophenol, *m*-chlorophenol	$0.678 \pm .002$
m-Nitromesitol, *p*-fluorophenol	$0.826 \pm .013$
o-Nitrophenol, 2,4-dichlorophenol	$0.616 \pm .006$

The measured value of K_{AiB} was plotted against the ionic strength and the thermodynamic constant $K_{AiB}°$ was determined by extrapolation to zero concentration using the method of least squares. Where the plot showed no distinct trend the data were averaged without extrapolation. $K_{AiB}°$ was calculated separately for the two different buffer ratios used and the two values were averaged.

The accepted values of log $K_{AiB}°$ are shown in Table I with the calculated probable error. The dissociation constants of the various acids were calculated from these data using the value 1.751×10^{-5} for the dissociation constant of acetic acid, calculated on a molarity basis from the average of the electromotive force[22] and conductance[23] values. In Table II the logarithm of the dissociation constant $K_c°$ and the logarithm of the ratio of the dissociation constant to that of phenol, K_{AxB_0}, are shown for each acid measured. The constant K_{AxB_0} is the quantity to be used in the study of the effects of substituents. Values which have been reported in the literature for these compounds are shown in Table III for comparison purposes. These values have been corrected to

TABLE II

MEASURED DISSOCIATION CONSTANTS

Compound	log $K_c°$	log K_{AxB_0}
Acetic acid	$\bar{5}.243 \pm 0.000$	5.194 ± 0.009
2,5-Dinitrophenol	$\bar{6}.784 \pm .003$	$4.735 \pm .009$
3,4-Dinitrophenol	$\bar{6}.576 \pm .002$	$4.527 \pm .009$
p-Nitrophenol	$\bar{8}.860 \pm .001$	$2.811 \pm .009$
o-Nitrophenol	$\bar{8}.766 \pm .008$	$2.717 \pm .008$
2,4-Dichlorophenol	$\bar{8}.150 \pm .005$	$2.101 \pm .007$
m-Nitrophenol	$\bar{9}.654 \pm .006$	$1.605 \pm .006$
o-Bromophenol	$\bar{9}.575 \pm .007$	$1.526 \pm .007$
o-Chlorophenol	$\bar{9}.523 \pm .006$	$1.474 \pm .006$
m-Nitromesitol	$\bar{9}.016 \pm .008$	$0.967 \pm .001$
m-Chlorophenol	$\bar{10}.977 \pm .006$	$.928 \pm .006$
p-Chlorophenol	$\bar{10}.622 \pm .007$	$.573 \pm .004$
p-Fluorophenol	$\bar{10}.190 \pm .015$	$.141 \pm .013$
Phenol	$\bar{10}.049 \pm .008$	$.000 \pm .000$

TABLE III

DISSOCIATION CONSTANTS FROM LITERATURE

Compound	$-\log K_c°$					
Phenol	9.95[a]	9.81[b]	9.83[c]	9.90[d]	9.94[e]	10.01
o-Nitrophenol	7.23[a]	7.17[g]	7.23[h]			
m-Nitrophenol	8.35[a]	8.00[g]	8.28[f]	8.17[i]	8.25[j]	8.41[m]
p-Nitrophenol	7.14[a]	6.91[i]	7.09[k]	7.15[m]	7.16[l,h]	7.19[g]
2,5-Dinitrophenol	5.22[a]	5.10[i]	5.11[j]	5.15[n]		
3,4-Dinitrophenol	5.42[a]	5.35[j]	5.37[g]	5.43[n]		
o-Chlorophenol	8.48[a]	8.11[d]	8.50[b]			
m-Chlorophenol	9.02[a]	8.79[d]	8.85[b]	9.07[o]		
p-Chlorophenol	9.38[a]	9.18[b]	9.20[d]	9.43[c]		
2,4-Dichlorophenol	7.85[a]	7.75[b]	7.89[p]			
o-Bromophenol	8.42[a]	8.39[d]				
p-Fluorophenol	9.81[a]	9.95[q]				

[a] This investigation. [b] Murray and Gordon, THIS JOURNAL, **57**, 110 (1935). [c] Mizutani, *Z. physik. Chem.*, **118**, 318, 327 (1925). [d] Ref. 28. [e] Boyd, *J. Chem. Soc.*, **107**, 1538 (1915). [f] Ref. 24a. [g] Ref. 14. [h] Euler and Bolin, *Z. physik. Chem.*, **66**, 71 (1909). [i] Kolthoff, *Pharm. Weekblad*, **60**, 949 (1923). [j] Ref. 24c. [k] Ref. 24d. [l] Ref. 24b. [m] Brönsted and Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929). [n] Ref. 27. [o] Hodgson and Smith, *J. Chem. Soc.*, 263 (1929). [p] Ref. 24e. [q] Ref. 29.

(20) Stull, *Ind. Eng. Chem.*, **39**, 523 (1947).

(21) Soule, *Ind. Eng. Chem., Anal. Ed.*, **1**, 109 (1929).

(22) Harned and Ehlers, THIS JOURNAL, **54**, 1350 (1932).

(23) MacInnes and Shedlovsky, *ibid.*, **54**, 1429 (1932).

25° using temperature coefficients from the literature.[24]

Discussion

Extrapolation.—Reasonably good extrapolation lines were obtained by plotting log K_{A_iB} against the ionic strength u. Actually it was found that, over the small range of concentrations involved, the extrapolation could just as well be made by plotting K_{A_iB} instead of log K_{A_iB}. The extrapolation against the ionic strength is based on the equation[25] for the variation in the activity coefficient with ionic strength.

In two different experiments it was found, unexpectedly, that the data for the different buffer ratios formed distinctly separate lines extrapolating to the same value of $K_{A_iB}°$. That is, the extrapolation depended on c_A as well as on c_B which is nearly equal to μ.

Kortüm[26] has studied the variation in the extinction coefficient of nitrophenols with varying concentration of electrolyte and non-electrolyte. He found particularly marked changes in the extinction of 2,4-dinitrophenolate caused by the addition of phenol. With these experiments by Kortüm in mind an equation was developed for the extrapolation of the measured K_{A_iB} assuming that the major effect was a change in extinction constant which was linear with c_A. The equation obtained was

$$K_{A_iB}° = K_{A_iB} + \frac{K_{A_iB}c_A(c_{B_i} + c_{A_i})\delta}{kc_{A_i}} \qquad (3)$$

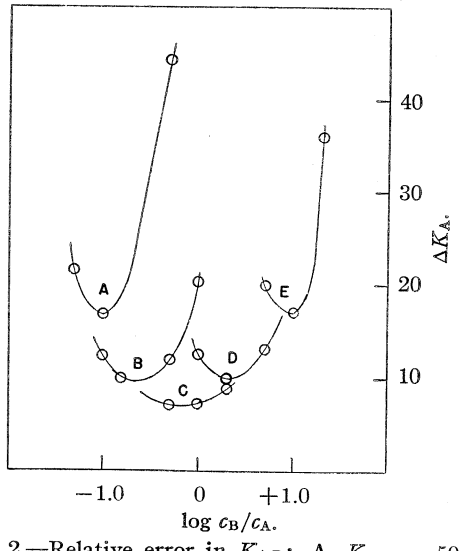

Fig. 2.—Relative error in K_{A_iB}: A, K_{A_iB} = 50; B, K_{A_iB} = 10; C, K_{A_iB} = 1; D, K_{A_iB} = 0.1; E, K_{A_iB} = 0.01: horizontal axis, log c_B/c_A; vertical axis, $(\Delta K_{A_iB}/K_{A_iB})/(\Delta c/c)$.

(24) (a) Lunden, *Z. physik. Chem.*, **70**, 249 (1910); (b) Lunden, *J. chem. phys.*, **5**, 574 (1907); (c) Michaelis and Kruger, *Biochem. Z.*, **119**, 307 (1921); (d) Michaelis and Gyemant, *ibid.*, **109**, 165 (1920); (e) Hantzsch, *Ber.*, **32**, 3066 (1899).

(25) Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943, p. 387, eq. 12-6-3.

(26) Kortüm, *Z. physik. Chem.*, **30**, 317 (1935).

where δ is a proportionality constant for the change of k with c_A. It can be shown that the last term on the right is approximately proportional to c_B for relatively large values of c_{B_i}/c_{A_i} so that an extrapolation according to equation (3) will differ appreciably from an extrapolation against μ or c_B only for experiments using relatively low values of c_{B_i}/c_{A_i}. In all of the experiments involving low values of the indicator ratio it happened that K_{A_iB} was nearly independent of concentration so that the fit of the data to equation (3) was no better and no worse than an extrapolation against μ. Further consideration of the problem suggested that if the extinction coefficient varied markedly with c_A the activity coefficient might also vary with c_A as well as with μ. In any case if the activity or extinction coefficient depends on c_A the extrapolation against concentration will give separate lines for different values of the buffer ratio.

Precision.—The relative error in measuring indicator concentrations colorimetrically can be calculated by differentiating equation (2). With the Rubicon colorimeter, having a constant absolute error in the transmittance, the error in measuring concentration is lowest at about 37% transmittance. With the photomultiplier colorimeter the relative error in transmittance can be kept constant over a considerable concentration range and the error of the measurement continues to decrease slightly at transmittances below 37%. As it was not convenient to use high indicator concentrations, all measurements were made with concentrations selected to give a transmittance of about 40%.

The selection of the buffer ratio to be used was more complicated. Using rather arbitrary assumptions about the sources of error the curves shown in Fig. 2 were obtained for the relative error in the measured K_{A_iB} as a function of K_{A_iB} and c_B/c_A. In any case it can be shown that the error in measuring a given value of K_{A_iB} will have a minimum value at some intermediate buffer ratio and will increase at very high and very low values of c_B/c_A and that the optimum point will be at lower buffer ratios for high values of K_{A_iB}. The buffer ratios used were selected from the curves of Fig. 2 to give approximately the minimum errors.

Measurements were made at two different buffer ratios for each experiment in order to reduce the possibility of errors. Although it is not immediately obvious, a detailed examination shows that it is possible for a mixture of two indicators with different dissociation constants but with comparable extinction constants to give rise to an intermediate K_{A_iB} value which appears to be nearly constant over a range of buffer ratios. The evidence for the purity of the indicators must then rest on other grounds than the constancy of K_{A_iB} with changing buffer ratio.

If significant quantities of carbon dioxide were present in the solutions, an error would be caused

in the buffer ratio. If the amount of carbon dioxide can be assumed constant in solutions with decreasing buffer concentration, a distinct curvature would be introduced into the extrapolation line. The absence of such curvature in the data obtained was taken as evidence that the precautions taken to keep out carbon dioxide were sufficient.

Some measurements were made at temperatures other than 25° to estimate the temperature coefficients of the dissociation constants and of the extinction constants. It was concluded that 0.1° regulation was satisfactory for an accuracy of 0.2% in the measured K_{AiB}.

Comparison with Literature.—The dissociation constant of *m*-nitromesitol has not been measured previously. The values measured for the other nitrophenols are in reasonably good agreement with the values given in Table III except for the value given by Holleman and Wilhelmy for *m*-nitrophenol which is apparently in error. The visual colorimetric values of Kolthoff and of Michaelis seem also to be consistently lower than the values obtained in other ways. The values reported by Bader[27] for the mononitrophenols are not shown in Table III as they are entirely out of line with all later measurements.

The agreement for the chlorophenols is only fair. Abichandani and Jatkar[28] measured the complete set of chloro-, bromo- and iodophenols and reported that the dissociation constants of the bromo- and iodophenols were somewhat lower than those for the chlorophenols, particularly for the ortho compounds. The measurement of *o*-bromophenol in the present investigation was made to check this point, failing to show a difference comparable with the 0.28 log unit difference reported by Abichandani and Jatkar. Bennett, Brooks and Glasstone[29] also reported from measurements in ethanol–water mixtures that the fluorophenols were distinctly weaker than the chlorophenols, the largest difference being observed for the para isomer. The present measurement of *p*-fluorophenol verifies the marked difference between this compound and *p*-chlorophenol.

(27) Bader, *Z. physik. Chem.*, **6**, 289 (1890).

(28) Abichandani and Jatkar, *J. Ind. Inst. Sci.*, **3**, 99 (1940).

Summary

A photoelectric colorimeter has been constructed and used for precise measurements of the ratio K_{AiB} between the dissociation constant in aqueous solution at 25° for a nitrophenol indicator and the constant for another substituted phenol. A detailed study has been given to the sources of error in measurements by this method. The thermodynamic dissociation constant and the ratio K_{AxB_0} between the dissociation constant of the substituted phenol and the constant for phenol have been calculated from these data for twelve substituted phenols. The values obtained have been compared with the results of previous measurements.

(29) Bennett, Brooks and Glasstone, *J. Chem. Soc.*, 1821 (1935).

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The Effects of Substituents on the Dissociation Constants of Substituted Phenols. II. Calculations from the Electrostatic Theory[1]

BY CHARLES M. JUDSON[2,3] AND MARTIN KILPATRICK[4]

Measurement of the dissociation constants of some substituted phenols have been described in the preceding paper.[5] The equation developed by Sarmousakis[6] using electrostatic theory to calculate the ratio K_{AxB_0} between the dissociation constant for a substituted acid and the constant for the unsubstituted acid has been applied in this paper to the substituted phenols. The conventions used to determine the variable parameters in the equation were changed slightly from those used by Sarmousakis. The calculated values have been compared with the observed values from the previous paper and from the literature. The test of the agreement between the calculated and observed values was made more rigorous by making the comparison for both the phenols and the benzoic acids using a consistent method of calculation.

The equation developed by Sarmousakis is a modification of the equation used by Kirkwood and Westheimer[7] for the electrostatic interaction between a substituent dipole and a dissociating proton. It can be readily shown from a simple treatment that this equation should have the general form

$$-2.3 \log K_{AxB_0} = \frac{e\mu \cos \theta}{r^2 D_E kT} \qquad (1)$$

(1) Taken from the dissertation presented by Charles M. Judson to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Philosophy, August, 1947. Presented before the 112th meeting of the American Chemical Society held in New York, N. Y., September, 1947.

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(5) Judson and Kilpatrick, THIS JOURNAL, **71**, 3110 (1949).

(6) Sarmousakis, *J. Chem. Phys.*, **12**, 277 (1944).

(7) Kirkwood and Westheimer, *ibid.*, **6**, 506 (1938); Westheimer and Kirkwood, *ibid.*, **6**, 513 (1938); Westheimer and Shookhoff, THIS JOURNAL, **61**, 555 (1939); Westheimer, *ibid.*, **61**, 1977 (1939).

where μ is the dipole moment of the substituent, r is the distance from the center of the dipole to the dissociating proton, θ is the angle between the vector representing the dipole and the vector corresponding to r, e is the charge on the electron, k is the Boltzmann constant, T is the absolute temperature and D_E is an effective dielectric constant. Kirkwood and Westheimer first showed how the term D_E could be estimated for certain cases. They calculated D_E for the para-substituted benzenoid acids by considering the molecule to be a prolate spheroidal cavity of low internal dielectric constant D_i embedded in a medium of higher dielectric constant D which is the dielectric constant of the solvent.

Sarmousakis set up as a model for the para-substituted acid an oblate rather than prolate spheroid with the proton and the center of the dipole located on the focal circle of the speroid, obtaining the equation

$$-\log K_{A_xB_0} = \frac{1}{2.3kT}\left[\frac{e\mu_\xi \cos(/\mu_\xi/i_1,r)}{r^2 D_\xi} + \frac{e\mu_\phi \cos(/\mu_\phi/i_2,r)}{r^2 D_\phi}\right] \quad (2)$$

The terms of this equation have been defined by Sarmousakis. It is sufficient to note that the equation is similar in form to equation (1) but is expressed in vector form with two quantities D_ξ and D_ϕ representing the effective dielectric constant. Sarmousakis showed how to calculate the quantities D_ξ and D_ϕ in terms of D and D_i and a parameter ξ_0 defining the shape of the molecule. The solution was expressed in terms of certain Legendre polynominals which were tabulated in Sarmousakis' paper. The quantity ξ_0 can be calculated in a simple manner from the molecular volume τ and the focal radius c which define the spheroidal cavity. It was possible using equation (2) to make calculations for the metasubstituted acids as well as the parasubstituted acids.

Sarmousakis recognized that there was a certain arbitrariness in the selection of numerical values for some of the parameters in equation (2). Instead of calculating the focal radius c from the distance between the dipole and the proton in the parasubstituted acid, he adjusted the focal radius c arbitrarily for each metasubstituted benzoic acid so as to give agreement between the calculated and observed values for the dissociation constant in aqueous solution. Using the same value for c in the parasubstituted acid, the difference between the calculated and observed values for the parasubstituted acid was then attributed to a resonance effect.

There are two possible positions which may be assumed for the proton in a substituted benzoic acid, a free rotation position permitting rotation about both the C–C bond and the C–O bond, and an extended position in which the C–O–H bond is frozen with the proton away from the dipole. The arbitrary values of c selected were found to lie between the values of c calculated for these two positions.

Calculations of $K_{A_xB_0}$.—The conventions used in carrying out the calculations for the present paper were, with a few exceptions, the same as those used by Sarmousakis. An attempt was made, however, to carry out the calculations without any arbitrary adjustment of parameters such as was used by Sarmousakis. The focal radius c calculated from structural considerations was used instead of the arbitrarily adjusted focal radius used by Sarmousakis. In calculating the focal radius the position of the proton was taken for the phenols as an average position with free rotation about the C–O bond and the position for the benzoic acids was taken to be the average extended position described above. The distance r was calculated trigonometrically instead of using the value $\sqrt{3c}$ for the value of r. The location of the center of the dipole was taken for all cases at the mid-point of the line from the benzene ring to the projection of the outermost atom on the axis of the ring, instead of locating the dipole for polyatomic substituents at the position of the iodo group dipole.

The dipole moments for the halogenobenzenes were taken from Hurdis and Smyth,[8] for nitro-

TABLE I

log $K_{A_xB_0}$

m-Phenols	Obsd.	Calcd. 1[a]	Calcd. 2[b]
F	0.82	0.78	1.01
Cl	1.02	.80	1.03
Br	0.96	.77	0.99
I	.92	.71	.91
CH_3	− .07	− .18	− .14
NO_2	1.61	1.71	1.81
p-Phenols			
F	0.14	0.56	0.73
Cl	.64	.56	.72
Br	.59	.54	.70
I	.64	.50	.64
CH_3	− .23	− .13	− .10
NO_2	2.81	1.20	1.20
m-PhCOOH			
F	0.34	0.29	0.36
Cl	.38	.29	.37
Br	.39	.29	.36
I	.35	.26	.34
CH_3	− .06	− .06	− .05
NO_2	.72	.70	.63
p-PhCOOH			
F	.06	.21	.26
Cl	.22	.21	.26
Br	.23	.20	.25
I	[c]	.18	.23
CH_3	− .17	− .05	− .03
NO_2	.78	.53	.40

[a] Preliminary calculations. [b] Final calculations. [c] Not measured, low solubility.

(8) Hurdis and Smyth, THIS JOURNAL, **64**, 2212 (1942).

benzene from Smyth[9] and for toluene from Baker and Groves.[10] The bond distances and angles and the atomic radii were selected from the values given by Pauling,[11] Branch and Calvin[12] Maxwell.[13] The dielectric constant of water was taken as 78.5[14] and the value 2.00 used by Kirkwood and Westheimer and by Sarmousakis was again used for D_i. $K_{A_xB_0}$ values calculated in this way are shown in the third column of Table I.

Experimental Values of $K_{A_xB_0}$.—In order to compare the calculated and experimental values of log $K_{A_xB_0}$ it was necessary to select with as much consistency as possible a single set of values for the dissociation constants of the meta- and parasubstituted phenols and benzoic acids in aqueous solution. The values selected by Elliott and Kilpatrick[15] for comparison with their data in alcohol solution were used for the benzoic acids. The values reported in the previous paper were used for the nitrophenols, and the data given by Boyd[16] were used to calculate $K_{A_xB_0}$ for the cresols. The values for the chlorophenols were calculated from an average of the values in the previous paper and the values of Abichandani and Jatkar.[17] Except for *p*-fluorophenol, the values for the other halogenophenols, which differed only slightly from the values for the corresponding chlorophenols, were calculated from the average difference between the reported constants for the halogenophenols and the constants reported by the same investigator for the corresponding chlorophenol. The data of Hodgson and Smith[18] were used for the halogenophenols in addition to the sources cited for the chlorophenols. The measured value for *p*-fluorophenol, which was quite different from the value for *p*-chlorophenol, was taken directly from the previous paper. The accepted experimental values are listed in the second column of Table I.

Calculations with Adjusted Parameters.—The calculated values in the third column of Table I are consistently lower than the observed values. An arbitrary adjustment of parameters was therefore required. Instead of changing the focal radius c, the internal dielectric constant D_i was arbitrarily adjusted to provide the best possible agreement between the calculated and observed values for the metasubstituted halogenophenols and halogenobenzoic acids. The revised calculated values shown in the fourth column were obtained with D_i equal to 1.54. It was found that the same value of D_i selected to give agreement for the *m*-chloro, *m*-bromo and *m*-iodophenol also gave the best agreement for the corresponding *m*-halogenobenzoic acids.

The increase in the absolute value of $K_{A_xB_0}$ obtained by changing D_i from 2.00 to 1.54 clearly would not improve the agreement with the observed values for the metasubstituted nitro and methyl derivatives. Since the true location of the dipole in these polyatomic substituents was not known, it was possible to adjust this position so as to bring about better agreement between the observed and calculated values for the metasubstituted phenols and benzoic acids. In these cases it was not possible to bring about exact agreement for both the phenols and the benzoic acids so a compromise adjustment was made. The position selected for the dipole in the nitro group was at a distance of 1.26 Å. from the ring, compared to a distance of 1.46 Å. from the ring to the nitrogen atom and a distance of 1.99 Å. to the projection of the oxygen atom on the line of the C–N bond. For the methyl group the dipole was located 1.35 Å. from the ring, compared to a distance of 1.50 Å. to the methyl carbon atom and 1.83 Å. to the projection of the methyl hydrogen atom.

Resonance Contributions.—Sarmousakis calculated values of Δ log $K_{A_xB_0}$ for the parasubstituted benzoic acids from the difference between the observed and calculated values. This term Δ log $K_{A_xB_0}$ was considered to be a measure of the resonance contribution to the acid strength of the parasubstituted acid. In the present calculations the treatment is slightly more complicated because the calculated values have not been adjusted to bring exact agreement with the observed values for each individual acid. For this reason Δ log $K_{A_xB_0}$ was calculated by subtracting the difference between the observed and calculated values for the meta acid from the difference between the observed and calculated values for the para acid.

These methods of calculating resonance contributions are based on the assumption that there is no resonance in the metasubstituted acid. Actually it can be seen that in Table I there is a larger difference between the observed and calculated values for *m*-fluorophenol than for the other *m*-halogenophenols. This appears to be due to a resonance effect whose magnitude can be estimated by subtracting the average difference between the observed and calculated values for the remaining *m*-halogenophenols from the difference for *m*-fluorophenol. The resonance contributions estimated similarly for the other *m*-halogen acids were very small.

While the *m*-halogen acids can be considered from the point of view of the differences from one halogen to another, it is not so easy to tell from the measured $K_{A_xB_0}$ values whether there is any resonance in the acids with nitro and methyl substituents in the meta position. The differences

(9) Smyth, *J. Phys. Chem.*, **41**, 209 (1937).
(10) Baker and Groves, *J. Chem. Soc.*, 1147 (1939).
(11) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940.
(12) Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941.
(13) Maxwell, *J. Optical Soc. Am.*, **30**, 374 (1940).
(14) Akerlof, THIS JOURNAL, **54**, 4125 (1932).
(15) Elliott and Kilpatrick, *J. Phys. Chem.*, **45**, 472 (1941).
(16) Boyd, *J. Chem. Soc.*, **107**, 1538 (1915).
(17) Abichandani and Jatkar, *J. Ind. Inst. Sci.*, **3**, 99 (1940).
(18) Hodgson and Smith, *J. Chem. Soc.*, 263 (1939).

between the observed and calculated values for these metasubstituted acids may also be due in part to resonance effects.

The calculated values of the resonance contribution term are shown in Table II. While the general ideas involved in predicting the effects of resonance on the strength of acids have been presented in several places[19] and the effects for aromatic acids have been studied in particular detail,[19a] the resonance structures required to explain the effects in the acids considered here do not appear to have been formulated explicitly in any one place.

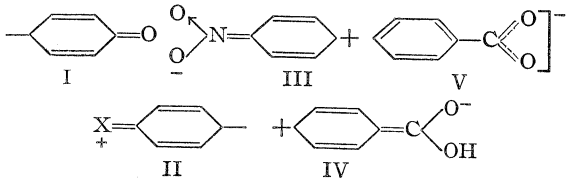
TABLE II

$\Delta \log K_{A_xB_0}$

	Phenols		Benzoic acids	
	m	*p*	*m*	*p*
F	−0.18	−0.40	−0.04	−0.18
Cl	.00	− .07	− .01	− .05
Br	− .02	− .08	.01	− .05
I	.02	− .01	− .01	....
CH_3	....	− .20		− .13
NO_2	....	1.81		.29

The resonance in phenol between the aromatic ring and the anion of the acidic group (I) is more important than the resonance involving the corresponding form of the free acid. This leads to an acid strengthening resonance effect in phenol. The resonance between the ring and an alkyl or halogen group in the para position (II) tends to weaken the resonance of the acidic group (I) and thereby weaken the acid. The resonance between the ring and the para nitro group (III) enhances the resonance (I) and is acid strengthening.

The resonance between the carbonyl group and the ring in benzoic acid (IV) tends to weaken the resonance between the carbonyl group and the anion of the acidic group (V) and is acid weakening. The resonance of the para nitro group (III) with the ring decreases the resonance (IV) and is acid strengthening while the resonance of the methyl or halogen group (II) increases (IV) and is acid weakening.



I III V

II IV

The resonance in the halogen-substituted acids is observed to increase in magnitude from the iodo to the fluoro group. The increase for the *p*-fluoro acid over the value for the *p*-chloro acid is particularly marked and shows that the magnitude of the resonance term cannot be predicted from the mesomeric moment[20] alone, since the mesomeric moments of the halogenobenzenes increase more or less uniformly from one halogen group to the next.

While resonance effects are not usually encountered in metasubstituted acids, the resonance effect in *m*-fluoro acids has been observed previously and explanations have been offered to account for it.[21]

Specific Ortho Effects.—The Legendre polynomials required for the calculation of D_ξ and D_ϕ for orthosubstituted acids have not been evaluated because the series converge too slowly. Some other method of treatment must be used to find out whether the experimental data can be interpreted to show the presence or absence of specific ortho effects.

Jenkins[22] has reported that for the halogeno- and nitrobenzoic acids the logarithm of the dissociation constant for three isomeric substituted benzoic acids and the unsubstituted acid is proportional to a function F which represents the field strength which would exist at the number one carbon atom of the ring due to the substituent dipole if the dielectric constant were unity. The function F is calculated from the equation

$$F = \mu\sqrt{1 + 3\cos^2\theta}/r^3 \qquad (3)$$

where r, μ and θ have the same meaning as in equation (1). According to this treatment log $K_{A_xB_0}$ should be a constant for the three isomeric acids if the effects are entirely inductive. The values of this ratio are shown in Table III for the substituted benzoic acids.

TABLE III

$\log K_{A_xB_0}/F$ FOR BENZOIC ACIDS

Subst.	Ortho	Meta	Para
F	2.2	3.2	0.8
Cl	3.3	3.7	3.1
Br	3.8	4.0	3.3
I	4.1	3.9	....
CH_3	6.0	−4	−15
NO_2	3.3	4.0	6.1

The dissociation constants were taken from the same sources as those used for Table I and the field strength was calculated using the same conventions and the same physical constants as were used to calculate log $K_{A_xB_0}$ from the Sarmousakis treatment. The function F was considered positive in all cases so that an increase in the algebraic value of the ratio in the table always corresponds to an acid strengthening.

The assumption involved in this treatment is that the acid group may be regarded more or less as a perfect conductor so that the ring carbon atom is the center determining the free energy of ionization. Since the resonance effect in the metasubstituted acids is relatively small, deviations of the ratios in Table III from the value for

(19) (a) Ref. 12, Chapter VI; (b) Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944.

(20) Groves and Sugden, *J. Chem. Soc.*, 1992 (1937).

(21) Dippy and Lewis, *ibid.*, 644 (1936).

(22) Jenkins, *ibid.*, 640 (1939).

the corresponding metasubstituted acid may be considered to indicate the presence of effects other than inductive.

The resonance effects of the parasubstituted acids indicated by the variations in Table III are in qualitative agreement with the resonance effects which were measured quantitatively by the Sarmousakis treatment. An acid strengthening resonance effect is shown for *p*-nitrobenzoic acid and an acid weakening resonance for *p*-toluic acid and the *p*-halogenobenzoic acids. The *o*-nitrobenzoic and *o*-toluic acids show deviations from the meta-substituted acids in the opposite direction from the deviations shown by the para-substituted acids. This may be considered evidence of a specific ortho effect, acid strengthening for *o*-toluic acid and acid weakening for *o*-nitrobenzoic acid. The *o*-halogenobenzoic acids have ratios between those of the meta- and the parasubstituted acids. In this case the presence or absence of specific ortho effects is not clearly demonstrated.

Jenkins had concluded that the absence of specific ortho effects was proven by the approximate agreement in these ratios for the three corresponding acids, except for the toluic acids in which case he admitted that a specific ortho effect was indicated. It must be admitted that if the values of log $K_{A_xB_0}$ are plotted against F, as was done by Jenkins, the discrepancies are not quite so obvious as when the ratios are calculated as in Table III. As an example the data for the nitrobenzoic acids are shown in Fig. 1. Since the theoretical basis of the treatment is not clearly established, there is certainly a question how large a deviation is required to be significant. Since the differences between the ratios in Table III for the meta- and parasubstituted acids can be interpreted satisfactorily in terms of resonance effects in the parasubstituted acid, the interpretation of the deviations for the orthosubstituted acids in terms of chelation or of resonance of a different type from that found in the parasubstituted acid seems justified.

Jenkins also plotted the logarithm of the dissociation constant against the electric potential at the number one carbon atom.[23] In a plot of the potential ψ against log $K_{A_xB_0}$ for a set of isomeric substituted benzoic acids, a line is obtained quite similar to that obtained in plotting against the field strength, but this line does not pass through the origin. In treating the phenols Jenkins plotted against the potential and found that the data for the ortho- and para-substituted halogenophenols in alcohol–water mixtures formed a line passing through the origin, that is, the point representing the unsubstituted acid. He then argued that the relative magnitude of resonance and inductive effects should be the same in the ortho- and para-substituted acids and that this linear relationship therefore indicated the

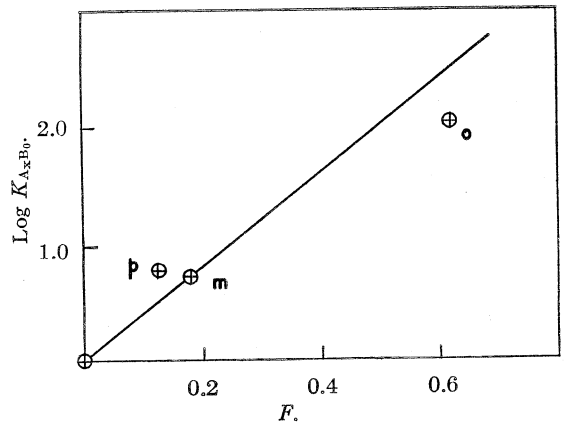


Fig. 1.—Dissociation constants of nitrobenzoic acids.

absence of specific ortho effects in the halogenophenols. There are three objections which can be taken to Jenkins' treatment of the halogenophenols. First, no reason was given to explain why the plot against potential should necessarily go through the origin when it had been shown that the plot for the halogenobenzoic acids did not go through the origin. Without the origin as a fixed point there is no obvious significance to a line through the points for two of the isomeric acids. Second, no proof has been given that the relative effects of resonance are the same in the ortho- and parasubstituted acids although this is probably acceptable as an approximation. Third, the value used in Jenkins' paper for *p*-fluorophenol in alcohol–water solution does not agree with the value in the paper of Bennett, Brooks and Glasstone[24] from which it was reported to have been taken. Using the value from the original paper the data for the fluorophenols does not fit the relationship proposed by Jenkins.

Abichandani and Jatkar[17] returned to the use of the field strength as a measure of the inductive effect in the phenols and used the method of Jenkins' first paper. They plotted the data for the halogenophenols in water and in alcohol–water mixtures against the field strength to show the existence of specific ortho effects in the halogenophenols. Using this same treatment, the ratio log $K_{A_xB_0}/F$ has been calculated for the halogen-, nitro- and methyl-substituted phenols in aqueous solutions using the same sources of data used in the application of the Sarmousakis treatment, with the

TABLE IV

log $K_{A_xB_0}/F$ OF PHENOLS

Subst.	Ortho	Meta	Para
F	2.7	7.7	1.8
Cl	4.2	10.0	8.9
Br	4.1	9.9	8.6
I	4.6	10.1	10.1
CH_3	−5.2	−5	−21
NO_2	4.4	8.9	22

(23) Jenkins, *J. Chem. Soc.*, 1137 (1939).

(24) Bennett, Brooks and Glasstone, *ibid.*, 1821 (1935).

addition of the dissociation constant for *o*-fluorophenol from Bennett, Brooks and Glasstone. The large acid weakening effects in *p*-cresol and *p*-fluorophenol, the less marked weakening in the other *p*-halogenophenols and the large acid strengthening in *p*-nitrophenol are clearly shown just as for the comparable treatment of the benzoic acids and as for the more quantitative treatment by the Sarmousakis method. There is further a marked acid weakening effect in *o*-chloro-, *o*-bromo- and *o*-iodophenol. This effect is distinctly different from the resonance effect in the *p*-halogenophenol which is small except for the fluorophenol. There is also an acid weakening effect in *o*-nitrophenol shown and, in the case of *o*-cresol, there is an acid strengthening which at least compensates for the acid weakening resonance which appears in *p*-cresol.

The theoretical weakness of the treatment based on the field strength at the number one carbon atom is recognized. The basis for suggesting the further use of this treatment for the study of deviations from the normal inductive effects is that the effects indicated by this treatment for the phenols and benzoic acids can all be accounted for in terms of resonance forms which are reasonable in the light of our present knowledge.[19] Except for the effects in *o*-halogenophenols and in *o*-nitrobenzoic acid, these deviations from the inductive effect have been previously accepted. The effect in *o*-nitrobenzoic acid is small and therefore not definitely established. The effect in the *o*-halogenophenols is clearly established if this method of treatment is valid.

Summary

The Sarmousakis modification of the Kirkwood–Westheimer method of calculating the ratio of the dissocation constant of a substituted acid to that of the unsubstituted acid has been used to calculate values for the meta- and parasubstituted phenols and benzoic acids. Using a consistent set of assumptions it has been possible to adjust the parameters so that agreement could be obtained between the calculated and the observed values for aqueous solutions for both the metasubstituted phenols and the metasubstituted benzoic acids. The differences between the calculated and observed values for the parasubstituted acids have been calculated as a measure of resonance effects.

Following a suggestion made by Jenkins, values of log $K_{A_xB_0}/F$ were calculated relating the ratio between the dissociation constants to the field strength at the ring carbon atom due to the dipole. Differences in this ratio for the corresponding ortho-, meta- and parasubstituted acids have been interpreted qualitatively in terms of resonance and chelation effects.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Preparation and Polymerization of Unsaturated Quaternary Ammonium Compounds[1,2]

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The absence of information in the literature concerning the polymerization of unsaturated quaternary ammonium compounds prompted us to study the preparation and polymerization of compounds of this type as a possible source of water insoluble polymers containing strongly basic groups. Products of this nature should be capable of absorbing negative ions from neutral salt solutions.

Since the presence of nitrogen in organic compounds quite often exhibits an inhibitory effect on peroxide catalyzed polymerization, there was some doubt that polymerization of these compounds could be accomplished. However, since quaternary ammonium halides are salts of strong bases and strong acids, it appeared likely that polymerization of these neutral salts would occur under the proper conditions. This was found to be the case as described in detail below.

In order for a cross-linked polymer to result from vinyl type polymerization of a pure unsaturated quaternary ammonium salt, the presence of at least two unsaturated groups in the molecule is essential. Therefore, all of the compounds studied have contained at least two unsaturated groups, while some have contained three or four. The compounds were prepared by reaction of unsaturated tertiary amines, several of which had not been prepared previously with the appropriate alkyl halides. The majority of the compounds were prepared as the bromides, and were found to have rather high melting points. Introduction, however, of relatively high molecular weight radicals such as benzyl usually lowered the melting point. Most of the salts were found to be rather hygroscopic and are very soluble in water, low molecular weight alcohols, and formamide, fairly soluble in hot ketones, but insoluble in most other organic solvents.

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(2) This material was presented in part before the Organic Division of the American Chemical Society, St. Louis, Missouri, Sept., 1948.

TABLE I

UNSATURATED TERTIARY AMINES

Compound	Formula	B. p. °C.	Mm.	d^{25}_{25}	$n^{25}D$	Nitrogen analyses, % Calcd.	Found	Yield, %
N-Allylmorpholine[a]	$C_7H_{13}NO$	156–8	768	0.9267	1.4569	11.02	10.98	60
N,N'-Diallylpiperazine[b]	$C_{10}H_{18}N_2$	213	761	.8865	1.4761	16.88	16.80	31
Diallylbenzylamine[c]	$C_{13}H_{17}N$	89	4	.9109	1.5122	7.48	7.39	73
N-β-Methylallylpiperidine	$C_9H_{17}N$	165	760	.8351	1.4559	10.06	9.88	42
N-β-Methylallylmorpholine	$C_8H_{15}NO$	171	760	.9120	1.4555	9.91	9.74	61
Diallylbutylamine[d]	$C_{10}H_{19}N$	170	760	.7863	1.4389	9.14	9.11	53
N,N'-Di-β-methylallylpiperazine	$C_{12}H_{22}N_2$	235	760	.8692	1.4710	14.42	14.11	52

[a] Picrate, m. p. 118°; chloroplatinate, m. p., 183.5°; picrolonate, m. p. 213°. N-Allylmorpholine was prepared by (1) reaction of morpholine and allyl bromide and (2) reaction of allylamine and β,β'-dichloroethyl ether. [b] Picrate, m. p. 254° (d); chloroplatinate, m. p. 280°. [c] Prepared from organic halide and diallylamine. [d] Previously reported without physical constants Brauchli and Cloetta [*Chem. Zentr.*, 99, I, 2732 (1928)].

The high melting points of these compounds made it necessary to attempt polymerization either in solution, or by addition of some component to lower the melting points. Their solubility in water suggested the use of water soluble catalysts such as hydrogen peroxide, ammonium or potassium persulfate. However, attempts to obtain polymerization of aqueous solutions of these compounds using these catalysts were unsuccessful. Attempted polymerizations using benzoyl peroxide and di-*t*-butyl peroxide as catalysts were also unsuccessful.

Addition of suitable components for lowering the melting point to a desirable range proved to be quite valuable in some cases. Equal quantities of triallylbenzylammonium bromide, which melts at 132°, and several of the higher melting compounds when thoroughly mixed resulted in solids which fused to clear liquids in the range of 85–95°. Addition of a small quantity of *t*-butyl hydroperoxide to these fused masses resulted in copolymerization of the mixture.

Further polymerization studies revealed the fact that fusion temperatures of these compounds could be lowered tremendously by the addition of extremely small amounts of water or formamide. Examples illustrating these methods of polymerization are given under the experimental section.

The polymers and copolymers of these compounds have been found to undergo the ion exchange reactions as predicted. The complete cycle is illustrated in the following series of reactions

$$n\mathrm{R_4NBr} \xrightarrow[\text{hydroperoxide}]{t\text{-Butyl}} (\mathrm{R_4NBr})_n$$

(R groups may be equal or different. At least two groups are unsaturated.) Cross-linked, water insoluble polymer. (Washed free of soluble bromides)

$$(\mathrm{R_4NBr})_n + n\mathrm{KOH} \longrightarrow (\mathrm{R_4NOH})_n + n\mathrm{KBr}$$

Continued until no halogen present in filtrate. Resin washed until neutral filtrate obtained.

$$(\mathrm{R_4NOH})_n + n\mathrm{KCl} \longrightarrow (\mathrm{R_4NCl})_n + n\mathrm{KOH}$$

Filtrate was very strongly basic.

Experimental

Materials.—Piperazine hexahydrate and piperidine (practical grade) were obtained from Eastman Kodak Company and used as received. The *n*-butylamine and morpholine were obtained from Carbide and Carbon Chemical Company and used without further treatment. The diallylamine, allyl chloride, β-methylallyl chloride, and di-*t*-butyl peroxide were obtained through the courtesy of Shell Chemical Company. The allyl chloride and β-methylallyl chloride were redistilled before use. The allyl bromide was obtained from Dow Chemical Company and used without further purification. The *t*-butyl hydroperoxide was obtained as a 60% solution through the courtesy of Union Bay State Company.

Preparation of Unsaturated Tertiary Amines.—The unsaturated tertiary amines required for this work were prepared by a modification of the procedure outlined in "Organic Syntheses"[3] for preparation of benzylaniline. The secondary amine was treated with a 0.05 mole excess of the appropriate halide in presence of a 0.25 mole excess of sodium bicarbonate in aqueous solution. The amines were purified by distillation after separation from the aqueous solution and drying.

Since the number of unsaturated tertiary amines recorded in the literature is surprisingly small, many of these are new compounds. The properties, analyses and yields of these new tertiary amines are summarized in Table I.

Preparation of Quaternary Ammonium Salts.—An equimolecular quantity of the appropriate alkyl or alkenyl halide was added dropwise, with stirring, to a hot solution of the unsaturated tertiary amine in acetophenone. Stirring was continued, and the solution was refluxed gently for approximately two hours. In most cases the products were insoluble in the solvent and crystallized on cooling. Purification was accomplished by recrystallization from ketones, alcohol–ether mixtures, or formamide–acetone mixtures. The products were stored under anhydrous conditions to prevent absorption of moisture. The properties, analyses, and yields of these compounds are summarized in Table II.

Polymerization Studies.—The following experiments will serve to illustrate the methods of polymerization and the ion-exchange properties of the polymers:

(1) One-half gram of triallylbenzylammonium bromide and 0.5 g. of tetraallylammonium bromide were mixed well and placed in a bath at 110°. Fusion of the mixture began at 85° and was complete at 95°, a clear solution being obtained. When the temperature of the liquid reached 108°, five drops of 60% *t*-butyl hydroperoxide was added with stirring, and the reaction vessel removed from the bath. Polymerization began immediately as was evidenced by a temperature rise to 140°. A rubbery mass having a reddish-brown color was formed. When the exothermic reaction was over, the vessel was returned to the bath and heating continued at 125° for two hours. The polymer was insoluble in water.

(2) Ten grams of tetraallylammonium bromide, 0.94 g. of formamide and 0.22 g. of 60% *t*-butyl hydroperoxide were mixed well and placed in an oven at 75°. Fusion was

(3) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 102.

TABLE II

UNSATURATED QUATERNARY AMMONIUM HALIDES

Bromide	Formula	Allyl bromide reacted with:	M. p., °C.	Bromine analyses, % Calcd.	Found	Yield, %
Ethyltriallylammonium	$C_{11}H_{20}BrN$	Ethyldiallylamine	159	32.47	32.65	77
Triallylbutylammonium	$C_{13}H_{24}BrN$	Diallylbutylamine	175	29.14	28.98	77
Diallylmorpholinium	$C_{10}H_{18}BrNO$	Allylmorpholine	213	32.21	32.30	89
Tetraallylpiperazinium di-	$C_{16}H_{28}Br_2N_2$	N,N'-Diallylpiperazine	207	39.25	39.26	67
Tetraallylammonium[a]	$C_{12}H_{20}BrN$	Triallylamine	185	30.95	31.07	69
Diallylpiperidinium	$C_{11}H_{20}BrN$	N-Allylpiperidine	190[b]	32.47	32.64	79
Triallylbenzylammonium	$C_{16}H_{22}BrN$	Diallylbenzylamine	132	25.93	25.70	71
Allyl-β-methylallylmorpholinium	$C_{11}H_{20}BrNO$	β-Methylallylmorpholine	197	30.48	30.56	53
Allyl-β-methylallylpiperidinium	$C_{12}H_{22}BrN$	β-Methylallylpiperidine	195.5	30.71	31.10	72
Diallyl di-β-methylallylpiperazinium di-	$C_{18}H_{32}Br_2N_2$	N,N'-Di-β-methylallylpiperazine	182	36.63	36.57	54
Di-β-methylallylpiperidinium	$C_{13}H_{24}BrN$	β-Methylallylpiperidine[c]	175	29.14	29.21	63
Diallylmorpholinium[d]	$C_{10}H_{18}ClNO$	Allylmorpholine	180	17.41	17.29	65

[a] Previously reported as decomposing at 80°, Grosheintz [*Bull. soc. chim.*, [2] **31**, 391 (1879)]. [b] This is a flash m. p.; no true melting point on slow heating. [c] β-Methylallyl bromide was the reacting halide in this case. [d] The compound prepared was the chloride. Allyl chloride was the reacting halide. The reported analytical values are % chlorine.

complete at this temperature. After a short time, the liquid became a dark brown, glassy solid. After twenty hours in the oven at 75°, the polymer was removed and washed with hot water, 7.6 g. of a granular, water insoluble substance being obtained.

(3) Ten grams of triallylbutylammonium bromide, 0.39 g. of distilled water and 0.11 g. of 60% *t*-butyl hydroperoxide were mixed well and placed in an oven at 100°. After twelve hours, the temperature was raised to 125° and held for twelve hours. The polymer was obtained in a 52.5% yield as a light brown, granular, water insoluble product.

(4) The copolymer obtained from triallylbenzylammonium bromide and tetraallylammonium bromide was washed with hot distilled water until the filtrate no longer gave a test for halogen. It was then treated with a 1% solution of potassium hydroxide, stirred at room temperature for several minutes and filtered. The filtrate, after acidifying with halogen-free nitric acid, gave a precipitate of silver bromide upon addition of silver nitrate, showing that the polyquaternary ammonium bromide was being converted to the polyquaternary ammonium hydroxide and releasing bromide ions. This treatment was continued until the acidified filtrate was found to be halogen-free, indicating that replacement of the halogen ion with hydroxyl ion was complete. This was shown to be correct by decomposing a sample of the dried polymer by sodium fusion and testing for halogen in the filtrate, no precipitate of silver bromide being formed. The product was washed with distilled water until a neutral filtrate was obtained. Upon treatment of the polymer with a neutral solution of potassium chloride, a strongly basic filtrate was obtained, showing that chloride ions were removed from solution by the polymer, and hydroxide ions released.

Acknowledgment.—We are indebted to Mr. A. E. Potter, Mr. J. L. Wester and Mr. R. L. Goette of this Laboratory for many of the analyses reported here, as well as for additional valuable assistance.

Summary

Several new unsaturated tertiary amines and quaternary ammonium salts have been prepared and characterized.

These unsaturated quaternary ammonium halides have been polymerized to water insoluble polymers, and it has been shown that these polymers may be converted to the polyquaternary ammonium hydroxides by an ion exchange reaction with potassium hydroxide resulting in the formation of a series of strongly basic ion exchange resins.

GAINESVILLE, FLORIDA RECEIVED[4] MARCH 23, 1949

(4) Original manuscript received October 2, 1948.

[CONTRIBUTION FROM THE DEPARTMENT OF SANITARY ENGINEERING, GRADUATE SCHOOL OF ENGINEERING, HARVARD UNIVERSITY]

Equilibrium Studies on N-Chloro Compounds. II. The Base Strength of N-Chloro Dialkylamines and of Monochloramine[1]

BY IRA WEIL AND J. CARRELL MORRIS

A knowledge of the possible basic or acidic nature of the chlorine substitution products of ammonia, monochloramine (NH_2Cl), and dichloramine ($NHCl_2$) is of great importance in analyzing the behavior of these compounds in water solution. Moreover, such information is of theoretical interest, since it would provide a knowledge of the change in acid or base strength produced by the substitution of a chlorine atom for a hydrogen on an ammonia-type molecule. This paper presents the results of an attempt to evaluate the base strength of the monosubstituted compound, NH_2Cl, and of its alkyl homologs.

In the water system, substitution of a chlorine for a hydrogen has a strong acidifying effect which is roughly comparable to that produced by substitution of an acetyl group. Thus, the acid ionization constant of HOCl is 3×10^{-8} and that of CH_3COOH is 2×10^{-5}, as compared with 2×10^{-16} for water itself. The effect of the acetyl group in this case is accentuated by the large amount of resonance in the acetate ion. In the ammonia system the acetyl group has a base-weakening effect of the same order of magnitude, for the base strength of CH_3CONH_2 is only (3×10^{-15})[2] whereas that of ammonia is 2×10^{-5}. By analogy one might predict roughly that NH_2Cl and its alkyl homologs should also be very weak bases with ionization constants in the neighborhood of 10^{-15}.

Unfortunately a direct measurement of an ionization constant of this magnitude for monochloramine appears impossible, since the basic properties would be manifested to a measurable extent only in very acid solutions, and monochloramine disproportionates very rapidly under such conditions. However, by working with the N-chlorodialkylamines it has been possible to eliminate this side reaction and to obtain a direct measurement of the base strengths of N-chlorodimethylamine and N-chlorodiethylamine. From these, reasonable estimates of the base strength of monochloramine can be made.

The method employed for the direct determinations was to measure the ultraviolet absorption spectra of the N-chlorodialkylamines in solutions of varying acid concentration. It was observed that as the acid concentration of solutions of these substances is increased above 0.01 *M* the characteristic absorption bands for the N-chlorodialkylamines are increasingly diminished in intensity. These changes in the absorption spectra are not accompanied by any changes in the oxidizing-chlorine titers, and the absorption bands can be made to appear and disappear rapidly by alternate addition of alkali and acid. Consequently, the observed spectral changes were attributed to ionization processes, and the quantitative measurements are based upon this interpretation.

Experimental

Materials.—The distilled water and the acid and base solutions used in the determinations were all made "chlorine-demand-free"[3] to insure that no reducing materials remained.

Stock chlorine solutions were obtained by bubbling gaseous chlorine into distilled water and diluting the solution until the desired strength was obtained, approximately 1.3×10^{-3} molar. The solutions were checked daily by addition of potassium iodide followed by titration with sodium thiosulfate.

Dimethylammonium chloride and diethylammonium chloride (Eastman Kodak Company) were dried and weighed to prepare stock solutions which contained 7×10^{-3} mole per liter. The concentrations of these solutions were checked by Kjeldahl nitrogen determinations, which gave values within 0.5% of those obtained from the weights of the salts.

Perchloric acid and sodium hydroxide solutions were standardized with reagent-grade potassium acid phthalate.

Procedure.—Equivalent quantities of the chlorine and amine solutions at 25° were mixed at a *p*H of 10.7 to form the N-chlorodialkylamine. At this *p*H, the time for 99% reaction is less than one minute.[4] Fifty ml. of the resulting solution, which was approximately 4×10^{-4} molar, was diluted with perchloric acid and sodium hydroxide to obtain the desired acid concentration and ionic strength and was then made up to 100 ml. in a volumetric flask. One portion of this solution was placed in the quartz cell of the spectrophotometer and a second portion was titrated to obtain the exact concentration of N-chlorodialkylamine.

The absorption data were obtained with a Beckman ultraviolet spectrophotometer, Model DU. In all the determinations 10-cm. quartz cells which had been calibrated against one another were used. In place of the conventional cell holder there was substituted a cell block which permitted the cells to be kept at a constant temperature of 25.0 ± 0.3° by the circulation of water from a constant temperature bath.

The absorption for each sample was measured from 220 to 300 mμ, against a blank which contained the same quantities of acid and base as the chloramine sample. Transmission values near the absorption maximum were measured three or four times on each sample and were found to check within an average deviation of ±0.002 in terms of optical density. Readings were taken at 5 mμ intervals with band widths varying from 0.3 to 1.4 mμ.

The absorption spectra of the N-chlorodialkylamine bases were determined on solutions prepared at *p*H 10.7. Three concentrations, 1×10^{-4}, 2×10^{-4} and 3×10^{-4} *M* were employed. Values of the molar extinction coefficients for the three concentrations, calculated from the transmission data, agreed within 2 to 3 units at practically

(1) This paper is based on work performed under Contract No. W-44-009 eng-463 for the Engineer Research and Development Laboratories.

(2) Euler and Ölander, *Z. physik. Chem.*, **131**, 107 (1928)

(3) Butterfield, Wattie, Megregian and Chambers, *Pub. Health Reports*, **58**, 1837 (1943).

(4) Weil and Morris, THIS JOURNAL, **71**, 1664 (1949)

all wave lengths. Absorption spectra of the acidified solutions were determined at a total chloramine concentration of 2×10^{-4} M.

The reliability of the dissociation constant values calculated from the spectra depends largely on the accuracy of differences in the extinction coefficient values, as shown by equation (5). On the basis of the estimated errors in the individual extinction coefficient values, the largest error in any one value of K_c is 14%, the minimum error, about 3%. The final average values of K_a are believed to be accurate to ± 5%.

Results and Discussion

Absorption Spectra.—Values of ϵ, the molar extinction coefficient, for N-chlorodimethylamine and N-chlorodiethylamine in the region 220 to 300 mμ are shown as the upper curves in Figs. 1 and 2, respectively. These were computed from the transmission data on solutions at *p*H 10.7 by means of the usual formula, $\epsilon = (1/lM) \log I_0/I$, l being in cm. and M in moles per liter. N-Chlorodimethylamine has an absorption maximum at 263 ± 2 mμ and N-chlorodiethylamine shows one at 262 ± 2 mμ. Determinations of the ionization constants were based on measurements at 265 mμ for N-chlorodimethylamine and at 260 mμ for N-chlorodiethylamine. At these wave lengths the molar extinction coefficients, which are very close to the maximum values, are 366 ± 3 and 312 ± 3, respectively.[5]

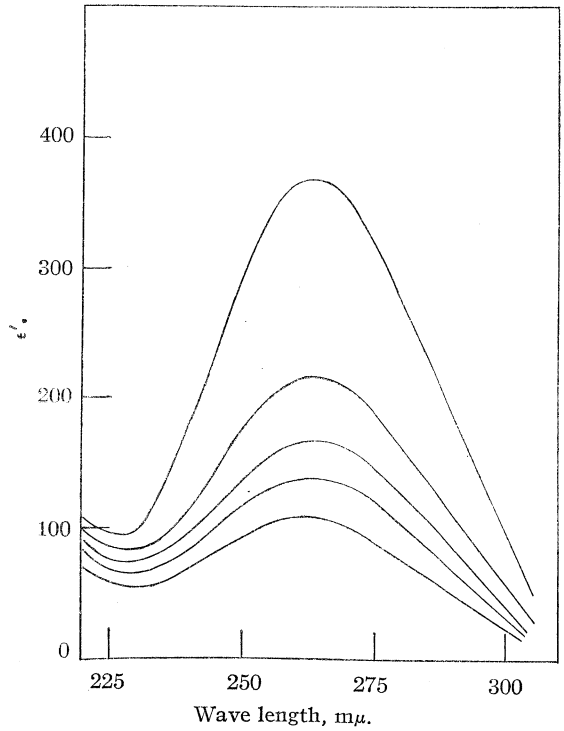

Fig. 1.—Absorption spectra of N-chlorodimethylamine at different acid concentrations. The uppermost curve is at a *p*H of 10.7. For the others in descending order, $[H^+]$ = 0.125, 0.224, 0.322, and 0.519, respectively.

(5) Metcalf, *J. Chem. Soc.*, 148 (1942), gives λ_{max} = 263 mμ and ϵ_{max} = 300 for both substances.

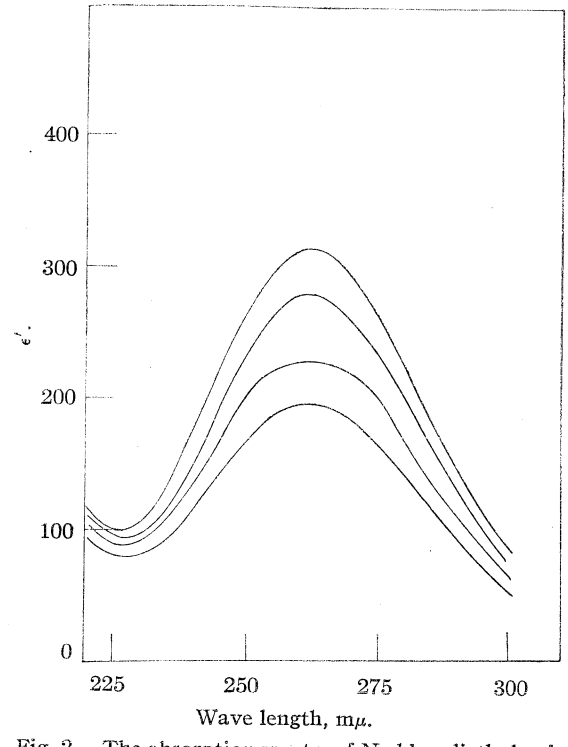

Fig. 2.—The absorption spectra of N-chlorodiethylamine at different acid concentrations. The uppermost curve is at a *p*H of 10.7. For the others in descending order, $[H^+]$ = 0.0100, 0.0298, and 0.0495, respectively.

The other curves in Figs. 1 and 2 depict typical absorption spectra for acidified solutions of these chloramines. The curves have been computed from the transmission data in terms of "apparent molar extinction coefficients," ϵ', defined as $\epsilon' = (1/lM_0) \log I_0/I$, M_0 being the total chloramine concentration, whether present as base or ion. The decreasing absorption with increasing acidity is evident.

Concentration Dissociation Constants.—For a solution containing both free base and ion the Beer–Lambert law becomes

$$(1/l) \log I_0/I = \epsilon_B [B] + \epsilon_{BH^+} [BH^+] = \epsilon' M_0 \quad (1)$$

Combination of this expression with the relation $M_0 = [B] + [BH^+]$ gives for the ratio of the molarity of chloramine to that of chlorammonium ion

$$[B]/[BH^+] = (\epsilon' - \epsilon_{BH^+})/(\epsilon_B - \epsilon') \quad (2)$$

At constant ionic strength the dissociation constant or acidity for the reaction

$$BH^+ \rightleftharpoons B + H^+ \quad (3)$$

may be expressed in terms of concentrations as

$$K_c = [H^+][B]/[BH^+] \quad (4)$$

Combination of this with equation (2) then gives

$$K_c = [H^+] (\epsilon' - \epsilon_{BH^+})/(\epsilon_B - \epsilon') \quad (5)$$

Values of ϵ_B and ϵ' for substitution in this equation were taken from the data at 265 mμ for N-

chlorodimethylamine and at 260 mμ for N-chlorodiethylamine. However, direct evaluation of the ϵ_{BH^+} terms was not practical and so an indirect technique was used. Rearrangement of equation (5) gives the expression

$$\epsilon_{BH^+} = \epsilon' - K_c(\epsilon_B - \epsilon')/[H^+] \qquad (6)$$

Consequently, evaluation of ϵ_{BH^+} may be accomplished by plotting values of ϵ' for a constant ionic strength against the function $(\epsilon_B - \epsilon')/[H^+]$ and determining the intercept of the straight line drawn through the points.

Determination of ϵ_{BH^+} in this way for both N-chlorodialkylammonium ions is shown in Fig. 3. The intercepts give $\epsilon_{BH^+} = 30 \pm 5$ for N-chlorodimethylammonium ion at 265 mμ and $\epsilon_{BH^+} = 15 \pm 5$ for N-chlorodiethylammonium ion at 260 mμ.

Tables I and II show values of K_c for N-chlorodimethylamine and N-chlorodiethylamine obtained by means of equation (5) with the preceding values for ϵ_{BH^+}. At fixed ionic strength the figures are constant within the experimental error, but vary with the ionic strength of the solutions.

TABLE I

DISSOCIATION CONSTANT DATA FOR N-CHLORODIMETHYLAMMONIUM ION

Temperature 25°; absorption measurements at 265 mμ; $\epsilon_B = 366$; $\epsilon_{BH^+} = 30$

$[H^+]$	Ionic strength, μ	$M_0 \times 10^4$, (mol/l.)	ϵ'	K_c, mole/l.
0.0380	0.039	1.96	327	0.294
.0250	.104	1.89	338	.278
.0644	.104	1.99	301	.270
.0841	.104	1.97	285	.268
.1039	.104	1.99	275	.276
.1730	.174	2.03	227	.244
.3460	.347	2.10	151	.196
.1250	.520	2.02	217	.156
.2240	.520	1.98	169	.159
.3220	.520	1.91	141	.158
.4210	.520	2.04	122	.158
.5190	.520	1.98	108	.157
.6920	.693	2.10	80	.123

TABLE II

DISSOCIATION CONSTANT DATA FOR N-CHLORODIETHYLAMMONIUM ION

Temperature 25°; absorption measurements at 260 mμ; $\epsilon_B = 312$; $\epsilon_{BH^+} = 15$

$[H^+]$	Ionic strength, μ	$M_0 \times 10^4$, mole/l.	ϵ'	K_c, mole/l.
0.0173	0.018	1.94	265	0.092
.0346	.036	1.99	227	.086
.0100	.070	1.91	278	.076
.0298	.070	2.01	229	.077
.0495	.070	2.01	196	.076
.0692	.070	2.06	171	.077
.1039	.104	2.03	139	.073
.1730	.174	2.10	98	.067

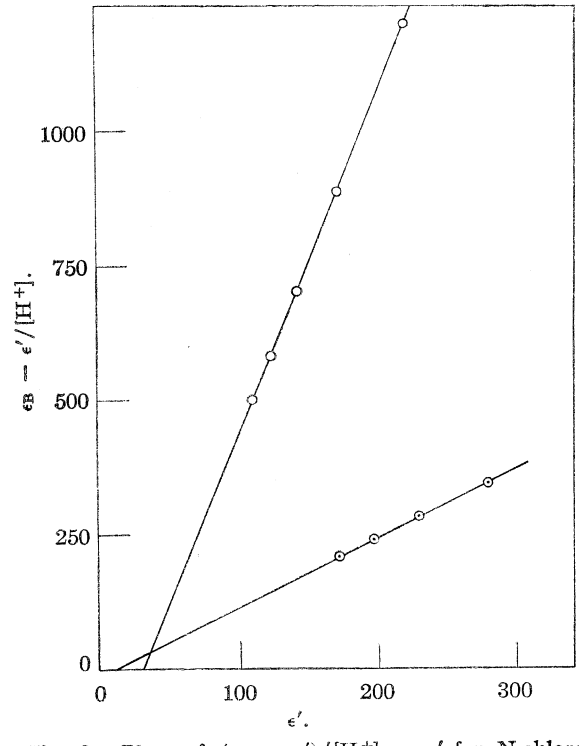

Fig. 3.—Plots of $(\epsilon_B - \epsilon')/[H^+]$ *vs.* ϵ' for N-chlorodimethylamine (O) and for N-chlorodiethylamine (⊙), at constant ionic strength.

Activity Dissociation Constants.—Evaluation of the true acidity constant defined as

$$K_a = ([H^+]f_{H^+}[B]f_B)/([BH^+]f_{BH^+}) = K_c f_B f_{H^+}/f_{BH^+} \qquad (7)$$

requires a knowledge of or method of estimation for the activity coefficient ratio, $f_B f_{H^+}/f_{BH^+}$. The high ionic concentrations make it impossible to use the Debye–Hückel limiting law. Previous investigators[6] have made the assumption that f_B/f_{BH^+} is independent of the base employed, and have made corrections on that basis, although it is readily apparent from a consideration of the extended forms of the Debye–Hückel equation that this is only an approximation. However, the assumption should have increased validity if it is applied to bases of essentially the same nature and size. Hence in the present case it was assumed that the activity coefficient ratios for the N-chlorodialkylamines are the same as those for trimethylamine, which have been determined by Harned and Robinson,[7] and their values were used in the calculation of ionic strength corrections for the chloramines.

The data reported by Harned and Robinson are in the form $(f_B/f_{BH^+}f_{OH^-})^{1/2}$. These values were squared and then multiplied by the activity coefficient product of water[8] to yield $f_B f_{H^+}/f_{BH^+}$. The values so obtained were then plotted against the ionic strength and correction factors for the

(6) Hammett and Deyrup, THIS JOURNAL, **54**, 2721 (1932).
(7) Harned and Robinson, *ibid.*, **50**, 3157 (1928).
(8) Harned and Mannweiler, *ibid.*, **57**, 1873 (1935).

desired ionic strengths were read from the smooth curve drawn through the points.

Table III shows the application of these corrections to the K_c data to obtain values for K_a. The consistency of the figures indicates that the procedure employed is a suitable one. A weighted average, which takes into account the number of determinations and the estimated error at each ionic strength, gives for N-chlorodimethylammonium ion, $K_a(25°) = 0.345$, and for N-chlorodiethylammonium ion, $K_a(25°) = 0.095$ mole/liter.

TABLE III

ACTIVITY DISSOCIATION CONSTANTS FOR N-CHLORODIALKYLAMMONIUM IONS AT 25°

Ionic strength, μ	K_c, mole/l.	$f_B f_{H^+}/f_{BH^+}$	K_a, mole/l.
A. N-Chlorodimethylammonium ion			
0.039	0.294	1.14	0.335
.104	.273	1.29	.352
.174	.244	1.44	.351
.347	.196	1.81	.355
.520	.158	2.13	.336
.693	.123	2.52	.310
		Weighted average	0.345 ± 0.015
B. N-Chlorodiethylammonium ion			
0.018	0.092	1.07	0.098
.036	.086	1.13	.097
.070	.077	1.22	.095
.104	.073	1.29	.094
.174	.067	1.44	.096
		Weighted average	0.095 ± 0.003

Basic Ionization Constants.—The basic ionization constants, K_b, corresponding to the process

$$B + H_2O \rightleftarrows BH^+ + OH^- \qquad (8)$$

are related to K_a by the equation $K_b = K_w/K_a$, in which K_w is the activity product for water. Application of this expression gives for N-chlorodimethylamine, $K_b(25°) = 2.9 \times 10^{-14}$ and for N-chlorodiethylamine, $K_b(25°) = 1.06 \times 10^{-13}$.

By comparison of the basic ionization constants of the dialkylamines with those of the N-chlorodialkylamines, an estimate of the decrease in basicity resulting from substitution of a chlorine on a nitrogen atom can be obtained. The change in ionization constant produced by chlorine substitution for dimethylamine is from 6.0×10^{-4}[9] to 2.9×10^{-14} or a factor of 5×10^{-11}; for diethylamine it is from 1.3×10^{-3}[10] to 1.06×10^{-13} or a factor of 8×10^{-11}. It may reasonably be assumed that the basic ionization constant of NH_2Cl is smaller than that of ammonia by a similar factor. Since K_b for ammonia is 1.8×10^{-5}, the basic ionization constant for monochloramine should be approximately 1×10^{-15}.

Acknowledgment.—The authors wish to express their appreciation for the help of Miss Frances R. Tibbetts and Miss Alice E. Ozanian in obtaining the data for this paper.

Summary

Basic ionization constants for N-chlorodimethylamine, $(CH_3)_2NCl$, and N-chlorodiethylamine, $(C_2H_5)_2NCl$, have been determined from measurements of the ultraviolet absorption spectra of acidified solutions of these compounds. The values obtained for the activity ionization constants at 25° are $K_b = 2.9 \times 10^{-14}$ for N-chlorodimethylamine and $K_b = 1.06 \times 10^{-13}$ for N-chlorodiethylamine.

On the assumption that substitution of a chlorine for a hydrogen on the nitrogen atom has the same effect on base strength for ammonia as for the N-chlorodialkylamines, it has been estimated that $K_b = 1 \times 10^{-15}$ for monochloramine, NH_2Cl.

The ultraviolet absorption spectrum of N-chlorodimethylamine has a maximum at 263 mμ with a molar extinction coefficient, $\epsilon = 370$; that for N-chlorodiethylamine has a maximum at 262 mμ with $\epsilon = 315$.

CAMBRIDGE, MASS. RECEIVED APRIL 4, 1949

(9) Everett and Wynne-Jones, *Proc. Roy. Soc.* (*London*), **A177**, 499 (1941).

(10) Hall and Sprinkle, THIS JOURNAL, **54**, 3469 (1932).

[CONTRIBUTION FROM THE UNIVERSITY OF OREGON]

A New Apparatus for Measuring Diffusion in Solutions*

BY ROBERT B. DEAN

When a solute diffuses into a solvent the concentration will vary with time and distance in a unique manner depending on the boundary conditions and the diffusion coefficient. If either the concentration, c, or the gradient of concentration, dc/dh, is known as an empirical function of the time, t, and distance, h, the diffusion coefficient D, can be calculated.[1,2] When c is known as a function of h and t for free diffusion, D can be calculated directly from Boltzmann's equation[1,3]

$$D = -\frac{1}{2}\, dy/dc \int_0^c y\, dc \qquad (1)$$

where $y = h/\sqrt{t}$ (see also ref.[4]).

Any method for measuring c as a function of t and h should preferably do so without disturbing the diffusing system. This logically suggests optical methods. When the solute absorbs light its diffusion can be followed by obvious colorimetric methods.[5-7] Colorless solutes can be followed by observing the refractive index of the diffusion column. Nakamura[8] was apparently the first to measure the concentration by the critical angle of reflection at one face of the diffusion cell. He used a cell which was 1 cm. thick and formed the initial boundary by flowing the solution under the pure solvent. His initial boundary cannot have been sharp and convection currents would be hard to eliminate in such a thick cell. Furth and his co-workers[6,9,10,11] pioneered in the use of thin chambers which minimize convection but they formed the initial boundary by withdrawing a sliding partition. Any sliding surface inevitably produces mixing and the results from Furth's school show fluctuations of more than 10% in the estimation of D. Zuber's optical arrangement[9] was furthermore limited by the precision of his goniometer. Instead of recording the entire refractive index–height curve he measured the angle of extinction at a number of selected heights. The short optical path of his apparatus also limits the possible precision of his method.

The apparatus described in this paper was designed to produce a direct record of the variation of concentration with height and at the same time eliminate convection and sliding boundaries.

The apparatus (see Fig. 1) consists of a thin chamber (approximately 4 cm. square) formed between one face of a 60° prism and a special fused glass cell.[12] The glass plate which forms the distal wall of the diffusion chamber terminates in a horizontal "knife-edge" at the top. This plate is backed up by a glass cell having a capacity one hundred times that of the diffusion chamber. The glass cell is attached to the prism face with stopcock grease and pressed on to a tight fit. The central portion of the chamber is parallel to the prism to within one wave length of sodium light in a vertical direction. It is inclined to the prism face about six wave lengths (3×10^{-4} cm.) per cm. in the central region. The cell is 0.03 cm. thick and parallel walled to 0.1% in the direction of diffusion. A mask on the exit face of the prism limits the effective object to the central portion of the diffusion cell. At the edges of the cell the departures from parallel walls are two to three times greater than in the center.

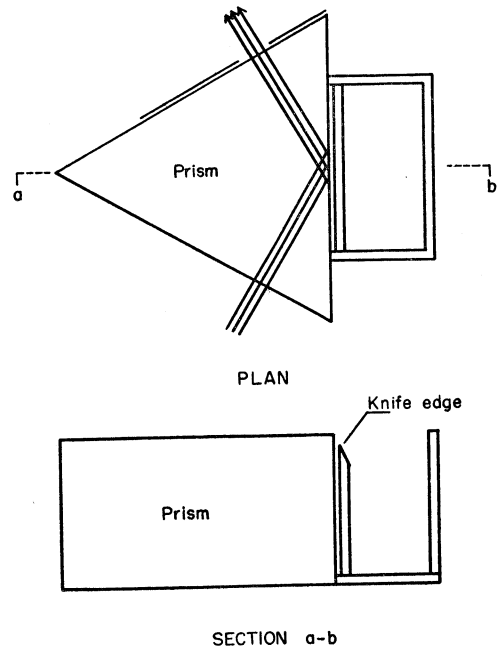

Fig. 1.—Diagram of diffusion cell and prism.

To start a diffusion run the chamber is filled with the 0.4 ml. of the more concentrated solution. The cell is then filled with 40 ml. of the more dilute solution, frequently water, at 25° and the time at which the top of the "knife-edge" floods is taken as zero time. As the solute in the chamber diffuses up to the "knife-edge" it falls over and sinks to the bottom of the large chamber. Approximately 20% of the contents of the chamber will have diffused into the outer cell when the concentration at the bottom falls to 99% of its original value. When this happens the boundary conditions no longer correspond to free diffusion in a semi-infinite prism and the run is ordinarily stopped. This quantity of solute will produce a

(*) The material in this paper was presented to the Division of Physical and Inorganic Chemistry of the American Chemical Society at the 114th meeting in Portland, Sept. 14, 1948.

(1) L. G. Longsworth, *Ann. N. Y. Acad. Sci.*, **46**, 211 (1945).
(2) C. O. Beckman and J. L. Rosenberg, *ibid.*, **46**, 329 (1945).
(3) L. Boltzmann, *Wied. Ann.*, **53**, 959 (1894).
(4) W. G. Eversole, J. D. Peterson and H. M. Kindsvater, *J. Phys. Chem.*, **45**, 1398 (1941).
(5) W. G. Eversole and E. W. Doughty, *ibid.*, **39**, 289 (1935), and **41**, 663 (1937).
(6) R. Furth, *Physik. Z.*, **26**, 719 (1925).
(7) R. Furth, *J. Sci. Instruments*, **22**, 61 (1945).
(8) S. Na amura, *J. College Sci., Tokyo Imperial Univ.*, **19**, 8 (1903).
(9) R. Zuber, *Z. Physik*, **79**, 280 (1932).
(10) E. Ullman, *ibid.*, **41**, 301 (1927).
(11) R. Furth, *et al.*, *Kolloid Z.*, **41**, 300 (1927).

(12) Made by Central Scientific Co.

maximum change of 0.02% in the concentration of the outer chamber if mixing is perfect. It is likely that mixing will not be perfect in the outer chamber and the concentration change will be correspondingly less. Convection cannot occur in the actual diffusion chamber because the walls are close together (0.3 mm.). Furthermore the density of the solution in the lower part of the cell is about 4% greater than at the top for 1 *N* potassium chloride. A temperature difference of 1° produces a density difference of only 0.02% so the possibility of thermal convection in the diffusion column can be ruled out for aqueous salt systems.

The lens system (see Fig. 2) consists of a plano cylindrical plus 2 diopter eyeglass lens (f = 50 cm.) and a plano spherical plus 2 diopter lens. The plane sides of the lenses face out and they are approximately 1 cm. apart. The focal line of the cylindrical lens is in the center of diffusion chamber and its axis is horizontal. The focal point of the spherical lens is on the photographic plate. There is a 0.6 cm. vertical slit mask on the exposed prism face and a 0.6 cm. horizontal slit mask between the lenses. The prism is illuminated through its third unpolished face by light from a mercury sun-lamp filtered through glass filters to isolate the green line at 5461 Å.

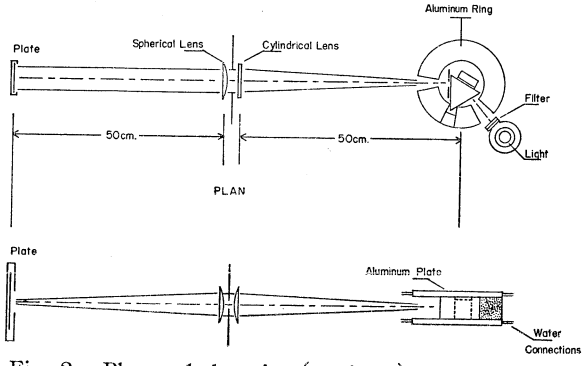

Fig. 2.—Plan and elevation (sectional) of optical bench.

Light entering the prism through the fine-ground face is scattered to produce even illumination over the entire diffusion chamber. Light striking the chamber at less than the critical angle is partially reflected and partially transmitted into the chamber where it is lost. Light striking at the critical angle or greater is totally reflected. In the horizontal plane the cylindrical lens is inoperative and the spherical lens focusses the parallel ray reflected at the critical angle, or any other angle, to a point on the plate corresponding to the angle of reflection. In the vertical plane light arising from any level in the diffusion cell is rendered parallel by the cylindrical lens and focussed to a corresponding level by the spherical lens.

The image thus consists of two fields differing in illumination. The location of the boundary between these fields depends upon the angle of total reflection in the prism which in turn depends upon the ratio of the refractive indices of the glass prism and the solution in the diffusion chamber. The critical angle for pure water against crown glass, n = 1.51, is 61° 59′. Light reflected at the critical angle reaches the exit face of the prism virtually perpendicular and undergoes only slight deviation at that face. For organic liquids a flint prism would be preferable. The variation in the critical angle is practically linear with the refractive index of the solutions in contact with the glass for the range of concentrations available. A 10% solution of most solutes produces a deviation of about 2 cm. on the photographic plate.

The aperture width of 0.6 cm. was chosen as the best compromise between diffraction and lack of focus. Since the object plane is necessarily inclined at 60° to the optical axis it is impossible to focus light from the cell exactly on a plane. The requirements of horizontal focussing are incompatible with those of vertical focussing and a sharp focus can only be obtained by narrow apertures which, however, introduce diffraction errors. For the dimensions chosen the optimum aperture is about 0.6 cm. which limits the theoretical resolution to 13″ of arc or approximately 0.003% salt solution. The observed resolution is not yet as good as this; it is possible to locate a boundary to within 0.02 mm. corresponding to 0.01% salt solution. Various Eastman Kodak Co. photographic plates have been used successfully including IVG and VG spectroscopic plates and Wratten Metallographic plates all used with Eastman D-19 developer to produce maximum contrast. Figure 3 shows a contact print of one of the plates.

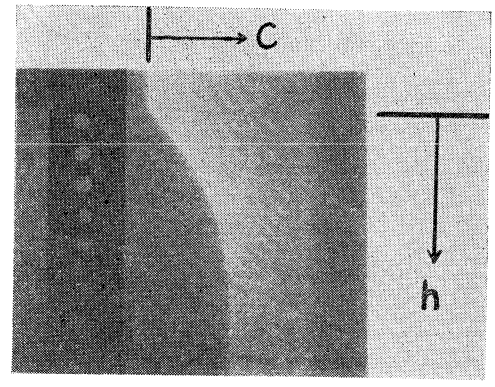

Fig. 3.—Print of a negative showing the variation of concentration with height in the diffusion cell.

The apparatus is mounted at one end of an optical bench which rests on a concrete pier. The prism and cell sit on a copper carrying plate which in turn sits on a hollow aluminum plate 8 in. in diameter. The prism and cell are surrounded by sections of a square cross section aluminum ring which is cut away to permit light to enter and leave the prism. Another hollow aluminum plate sits on top of the ring. Water is circulated by a centrifugal pump, from a tank containing heating and cooling coils, through the top plate of the prism, then through a glass tube containing a mercury thermoregulator and back through the lower plate to the tank. The heater is regulated by a thyratron controlled by the thermoregulator and operated from a 6-v. transformer. This thermostat maintains the temperature of the solution in the cell to within 0.02° or better. Care is taken not to let the mercury light shine on the cell except when a picture is being taken. Except for the mercury lamp the entire apparatus is housed in a plywood box with removable walls.

The image developed on the photographic plate should be measured with a coördinate comparator. Not all the parts for such a comparator have been received yet and the pictures obtained so far have been measured with a travelling microscope and eye-piece micrometer using a low magnification objective. This method is subject to errors caused by distortion of the image field and is furthermore very inconvenient. The results obtained are therefore of a preliminary nature and no attempt has been made to calculate D by Boltzman's equation, 1.

An estimate of D on the assumption that D is independent of c can be made conveniently by using probability paper. Since the concentration at the "knife-edge" is maintained essentially constant the boundary conditions in the initial stages correspond to diffusion into a semi-infinite prism. This is identical with one half of the case of diffusion from an initially sharp boundary into an infinite prism. The relation between c, h and t is given by the following equation for these

conditions (1)

$$\frac{c}{c_0} = \frac{1}{\sqrt{4\pi D_0 t}} \int_{\infty}^{h} e^{-\frac{h^2}{4D_0 t}} \, dh \qquad (2)$$

This is identical in form with the equation for the probability integral

$$Z = \frac{1}{\sqrt{2\pi\sigma^2}} \int_{\infty}^{h} e^{-\frac{h^2}{2\sigma^2}} \, dh \qquad (3)$$

where z varies from zero to 1. From equations 2 and 3 it is evident that

$$\sigma^2 = 2D_0 t \text{ or } D_0 = \frac{\sigma^2}{2t} \qquad (4)$$

Values of z as a function of h are readily available in tables and it is also possible to purchase probability graph paper[13] ruled from 0 to 100% in such a way that a plot of z *vs.* h is a straight line. The value of σ is equal to the difference in the h intercepts at 50% and either 15.87 or 84.13%. D_0 can of course be estimated from the 15.87 or the 84.13% intercept alone but it has been found safer to plot the values of c *vs.* h on probability paper and draw the best straight line through the points to obtain the h intercepts. To do this the c values are converted to C' values from 50 to 100 by the relation

$$C' = (50c/c_0) + 50 \qquad (5)$$

or the equivalent reaction for values from 0 to 50

$$C' = 50 - (50c/c) \qquad (6)$$

Figure 4 shows data from two photographs of one run with 1 N potassium chloride. The D values obtained, 1.8 and 1.9 $\times 10^{-5}$, show satisfactory agreement with the integral value of 1.85 $\times 10^{-5}$, calculated from the data given by Vinograd and McBain[14] corrected according to Gordon.[15] This

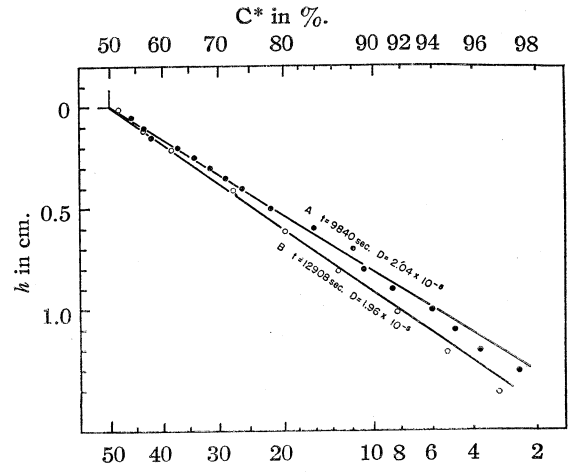

Fig. 4.—Diffusion of 1 N KCl at 25° plotted on probability paper.

agreement is partially fortuitous since D for potassium chloride varies by 10% over the range from 0 to 1 N. The probability integral method is essentially equivalent to the height and area method for analysing curves of dc/dh obtained by the scale method.[16]

Summary

1. An apparatus is described in which diffusion takes place in a narrow chamber along one face of a prism into an effectively infinite volume of solvent.

2. The initial boundary is formed by flooding the top of the thin chamber.

3. The concentration of diffusing material is determined from the angle of total reflection which is recorded photographically.

4. The apparatus is suitable for solutions containing of the order of 1% solute.

(13) From Keuffel and Esser.

(14) J. R. Vinograd and J. W. McBain, THIS JOURNAL, **63**, 2008 (1941).

(15) A. R. Gordon, *Ann. N. Y. Acad. Sci.*, **46**, 285 (1945).

(16) E. M. Bevilacqua, *et al.*, *ibid.*, **46**, 309 (1945).

EUGENE, OREGON RECEIVED MAY 7, 1949

[CONTRIBUTION FROM THE STANFORD RESEARCH INSTITUTE, STANFORD UNIVERSITY]

Studies of Protein Foams Obtained by Bubbling[1]

BY WILLIAM C. THUMAN,[2] A. G. BROWN[2] AND J. W. MCBAIN

Introduction

The foaming of protein solutions is of theoretical interest, and also has wide applications in the baking industry and in fire fighting practice. It is known to be greatly dependent upon pH and the presence of salts, though but little systematic work has been published in this field.

Recently it was shown by Perri and Hazel[3] that a soybean protein solution exhibited a maximum foaming capacity in the neighborhood of the isoelectric point. Barmore[4] in studying the properties of egg white foams as a problem of the baking industry reported that organic acids and acid salts considerably increase foam stability. Peter and Bell[5] found the stability of foams from the protein of whey to be increased by addition of

(1) (a) This investigation was conducted under Contract N-7onr 321 between The Stanford Research Institute and the Office of Naval Research, supervised by Professor J. W. McBain; (b) presented at the 115th meeting of the American Chemical Society, San Francisco March, 1948.

(2) Present address: Stanford Research Institute, Stanford, California.

(3) J. M. Perri and F. Hazel, *J. Phys. Colloid Chem.*, **51**, 661 (1947).

(4) M. A. Barmore, Colorado Agricultural College Technical Bulletin, 9, 1934.

(5) P. N. Peter and R. W. Bell, *Ind. Eng. Chem.*, **22**, 1124 (1930).

alkali, sodium sulfite, or a mixture of calcium chloride with calcium hydroxide. In the results of Clark[6] with hydrolyzates of blood protein the maximum foam volume was obtained from a solution near the isoelectric point.

Most of the work on the foaming capacity of protein solutions has been carried out with protein materials of uncertain composition or consisting of obvious mixtures. Thus, it seemed desirable to extend the work of Perri and Hazel employing other pure proteins. For the present study purified egg albumin and salmine sulfate were selected. With the egg albumin, previous work could be greatly extended. Salmine sulfate was chosen because its isoelectric point is at a *p*H of 12, in sharp contrast to both α-soybean protein and egg albumin with isoelectric points respectively 4.1 and 4.6 to 4.8.

Preliminary experiments were carried out by Irving M. Abrams,[7] who found that single bubbles on salmine sulfate solutions show a sharp maximum in lifetime at about *p*H 10. We have found that the foaming capacity of 0.5% salmine solutions is a maximum around this same *p*H and that solutions of egg albumin also show a maximum in foaming capacity slightly on the acid side of the isoelectric point.

The effects of *p*H and of added electrolytes have been examined in some detail for the purified egg albumin.

Materials.—The two proteins used in these experiments were a protamine sulfate (salmine sulfate) supplied by Eli Lilly and Company and a sample of hen egg albumin from the laboratories of the Harvard Medical School. As we received it, the latter sample had been recrystallized three times and dialyzed against water and dried. Freshly prepared solutions of protein were used each day. The concentrations in these experiments were 0.05% for the albumin and 0.5% for the protamine. This concentration of egg albumin approximates in nitrogen value the soybean solution used by Perri and Hazel.[3] The higher concentration of the protamine was necessary due to its poor foaming characteristics.

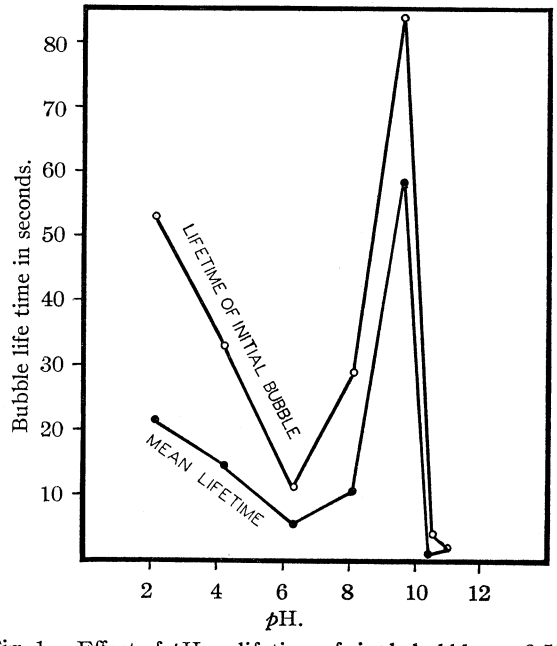

Fig. 1.—Effect of *p*H on lifetime of single bubbles on 0.5% salmine sulfate.

Method.—For determinations of foaming capacity, 1.0 cc. of liquid was transferred to the porous plate of a modified Stiepel type foam meter[8] by means of a Blodgett pipet. During foam formation the rate of air flow through the porous plate was maintained at 16 cc. per minute until there was no further increase in the volume of the foam. This maximum volume was recorded. While individual values for foaming capacity are probably subject to an error, in the extreme, of 2 cc., most curves were obtained as the result of several independent determinations in order to minimize errors in foam volume and also errors in *p*H caused by fouling of the glass electrode by the protein.

Except where otherwise indicated, the protein was dispersed in distilled water and made up to volume with the required solution of electrolyte. For some experiments, clear solutions of the protein were obtained by dissolving the protein in a minimum volume of 10^{-3} *M* hydroxide and making it to volume with sufficient solution of electrolyte to give the required electrolyte concentration.

When a range of *p*H values was desired, the first *p*H of a solution to be tested was that of the solution as prepared. Subsequent determinations on the acid side of this first value were made after stepwise additions of hydrochloric acid; on the alkaline side by additions of potassium hydroxide. Determination of *p*H was made with a Model G Beckman glass electrode *p*H meter employing standard or blue glass electrodes in the appropriate ranges.

In those experiments requiring conditions free from carbon dioxide, boiled distilled water was used in preparation of the solutions. Access of carbon dioxide to the solution during the experiment was prevented by a current of air free from carbon dioxide flowing into and out of the container in which the solution was enclosed. Air flow, adjustment of *p*H, and removal of the sample by means of the Blodgett pipet was made possible by an opening in the top of the container. In those experiments requiring saturated solution of carbon dioxide, the solution was enclosed in the above container, and carbon dioxide from dry ice was allowed to flow into and out of the vessel during the experiment.

Experiments on Life of Single Bubbles by I. M. Abrams.—Preliminary experiments were carried out on the life-time of single bubbles released from an orifice and floating to the surface of 0.5% protamine solutions at different *p*H values. These experiments were carried out in closed vessels to exclude dust and minimize evaporation.

The effect of *p*H on bubble lifetime as indicated by the lifetime of initial bubbles at different *p*H values and by the average lifetime at these values is shown in Fig. 1 for 0.5% protamine solutions. While the variation of bubble life at any observed *p*H was very great, a sharp maximum in stability was observed somewhat on the acid side of the isoelectric point. Stability was at a minimum at about *p*H 6 and increased again at low *p*H values.

Foams with Salmine Sulfate.—The results with single bubbles suggested the desirability of extending the investigation to actual foams, both of the protamine and of albumin. The results for the foaming capacity of 0.5% protamine solutions at different *p*H values are shown in Fig. 2. At the concentration used (0.5%) the foams obtained were weak and poorly characterized. However, a broad maximum in foaming capacity does appear somewhat on the acid side of the isoelectric point.

(6) N. O. Clark, "A Study of Mechanically Produced Foam for Conbatting Petrol Fires," His Majesty's Stationery Office, London, 1947.

(7) Present address: Chemical Process Co., Redwood City, California.

(8) S. Ross, *Ind. Eng. Chem., Anal. Ed.*, **15**, 329 (1943).

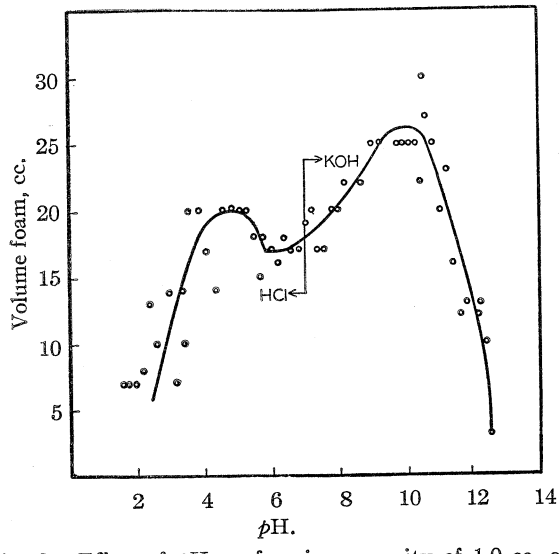

Fig. 2.—Effect of *p*H on foaming capacity of 1.0 cc. of 0.05% protamine sulfate.

Foams with Egg Albumin

Standard Foaming Capacity Curve.—Well-defined foams were obtained using a 0.05% aqueous solution of albumin at different *p*H values, especially in the region of maximum foaming capacity. Greatest foaming occurs on the acid side (*p*H 3.7 to 4.0) of the normal isoelectric point of albumin (*p*H 4.6 to 4.8), and at very high and very low *p*H values, as shown in Fig. 3. The absence of foam between *p*H's 6 and 11 is very striking. Figure 3 will appear dotted for reference in all later figures.

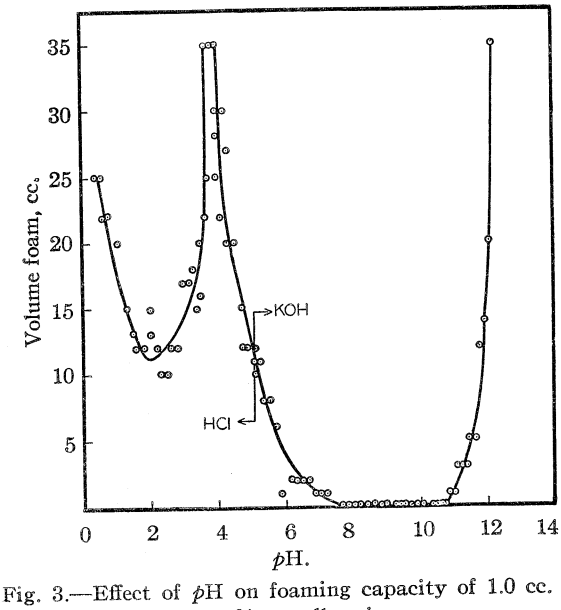

Fig. 3.—Effect of *p*H on foaming capacity of 1.0 cc. of 0.05% egg albumin.

These solutions were exposed to air and therefore contained carbon dioxide. However, determinations of foaming capacity in the *absence* of carbon dioxide give values which, within experimental error, appear to fall on the same standard curve. Saturating the solutions with carbon dioxide slightly decreases the amount of foam produced near the isoelectric point. These results are shown in Fig. 3a.

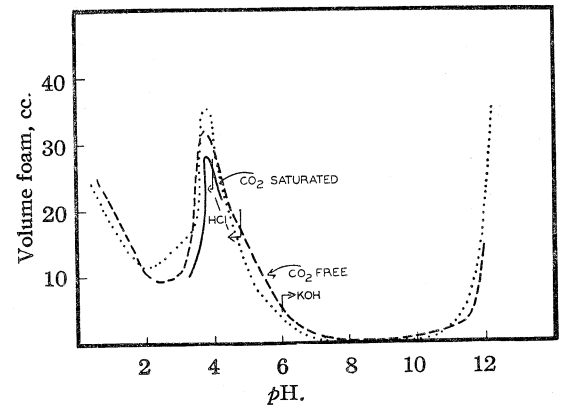

Fig. 3a.—Effect of *p*H on foaming capacity of 1.0 cc. of 0.05% egg albumin in absence of carbon dioxide. Effect of saturating the solution with carbon dioxide.

Effect of Added Weak Acids at Various *p*H's Adjusted with Potassium Hydroxide or Hydrochloric Acid.—The effect of anions on the maximum foaming capacity was investigated in the region of the isoleectric point by foaming 1.0 cc. of 0.05% albumin in 10^{-3} *M* salt solutions, adding hydrochloric acid or potassium hydroxide as required. Arrows on the accompanying figures indicate initial *p*H values. It is to be noted that the characteristics of albumin in the region of the isoelectric point are of interest to the baking industries. The effects of adding acetic acid, potassium acid tartrate, citric acid and phosphoric acid are shown in Figs. 4 and 5. The curve for a saturated solution of carbon dioxide has been mentioned previously (Fig. 3a).

Effect of Added Salts.—The effect of cation valence at different salt molarities is shown in Table I. The results

TABLE I

EFFECT OF CATIONS ON FOAM CAPACITY OF 0.05% EGG ALBUMIN

Molarity of added salt	KCl		$CaCl_2$		$Ca(NO_3)_2$		$Th(NO_3)_4$	
	*p*H	Foam, cc.	*p*H	Foam, cc.	*p*H	Foam, cc.	*p*H	Foam, cc.
0	5.09	10	5.09	10	5.2	12	5.2	12
10^{-1}	5.45	12	5.85	12	5.0	14	2.3	25
10^{-2}	5.1	14	6.0	12	4.9	14	2.9	50
10^{-3}	5.2	12	5.8	10	4.9	11	3.3	45
10^{-4}	5.1	12	5.0	10	4.8	12	4.0	6
10^{-5}							4.2	6
10^{-6}							5.0	17
10^{-7}							5.2	14

were not at all similar to those which might have been expected from the work of Perri and Hazel, and it became obvious that salt effects should be investigated over a range of *p*H values for each concentration of salt. Such studies are shown in Fig. 6 for 10^{-2}, 10^{-3} and 10^{-4} *M* potassium chloride and for 10^{-3} *M* calcium chloride. The curve for the calcium chloride–potassium hydroxide system (Fig. 6) was obtained later and will be discussed in connection with Fig. 9.

Effect of Degree or Kind of Dispersion of the Albumin.—Albumin "solutions" as ordinarily made up, and as used in all the above experiments, were obtained by simply dissolving the albumin in distilled water. These solutions had a *p*H of 5.05 to 5.1 and were slightly turbid. *Clear* solutions were obtained by dissolving the protein in 10^{-3} *M* potassium hydroxide. Foaming capacities of such solutions were determined over a range of *p*H values obtained by additions of hydrochloric acid or further potassium hydroxide and are shown in Fig. 7. Access of carbon dioxide

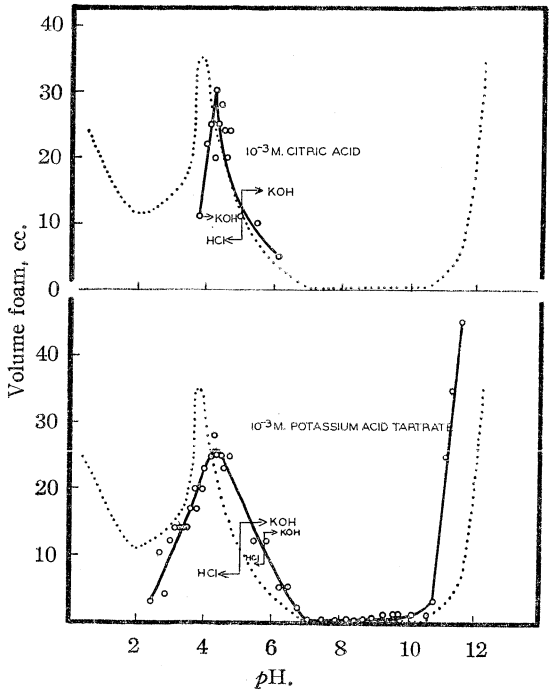

Fig. 4.—Effect of 10^{-3} M potassium acid tartrate or 10^{-3} M citric acid on foaming capacity of 1.0 cc. of 0.05% egg albumin at different pH values.

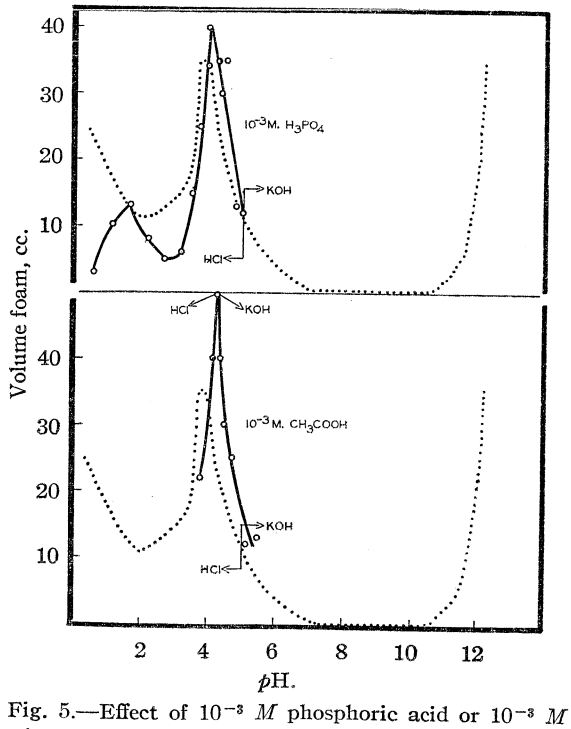

Fig. 5.—Effect of 10^{-3} M phosphoric acid or 10^{-3} M acetic acid on foaming capacity of 1.0 cc. of 0.05% egg albumin at different pH values.

to these solutions was prevented. For comparison, results are shown also in Fig. 7 for the foaming capacity of a *clear* solution of albumin dissolved in 5×10^{-4} M potas-

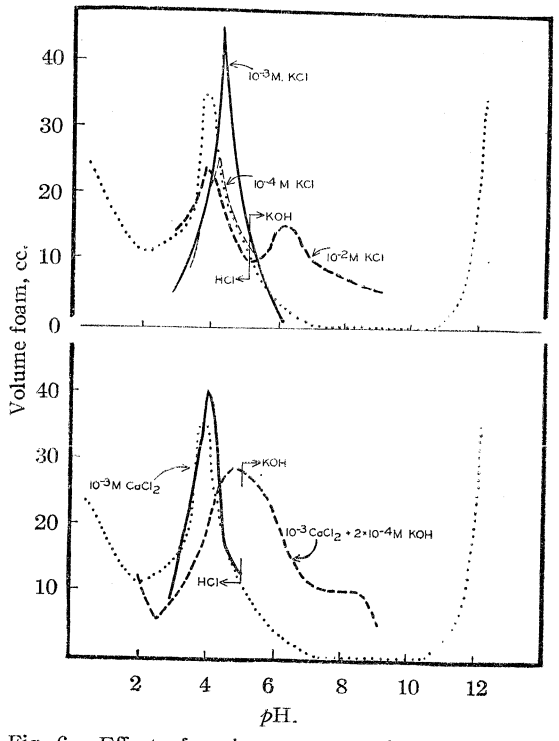

Fig. 6.—Effect of various concentrations of potassium chloride on foaming capacity of 1.0 cc. of 0.05% egg albumin at different pH values. Effect of 10^{-3} M calcium chloride on the foaming capacity of 1.0 cc. of 0.05% albumin solution at various pH values; comparison of the foaming of egg albumin originally dispersed in 10^{-3} M calcium chloride solution at pH 5.95 with the foaming of egg albumin originally *dissolved* in 10^{-3} M potassium hydroxide and then made 2×10^{-4} M in potassium hydroxide and 10^{-3} M in calcium chloride.

sium carbonate, to which hydrochloric acid or potassium hydroxide was then added to adjust the pH.

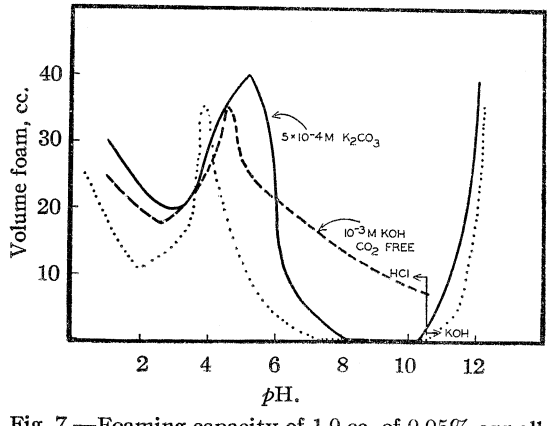

Fig. 7.—Foaming capacity of 1.0 cc. of 0.05% egg albumin showing effect of *dissolving* the albumin in 10^{-3} M potassium hydroxide or in 5×10^{-4} M potassium carbonate, access of carbon dioxide from the air prevented at all times.

It is apparent that much more foam is produced in the alkaline region when the protein is first dissolved in alkali.

The lesser foaming in potassium carbonate solution as compared to potassium hydroxide solution may be due to a depressing effect of carbonate or bicarbonate ion or it may be due to an effect of the slightly lower initial *p*H of the potassium carbonate solution.

Experiments with Dissolved Egg Albumin in Presence of Barium Ion.—After showing the importance of first *dissolving* the egg albumin in 10^{-3} *M* potassium hydroxide, a series of experiments was carried out with egg albumin *dissolved* in a minimum volume of 10^{-3} *M* barium hydroxide (50 mg. albumin in 20 cc.) and then adjusted to various concentrations of barium ion by adding water or concentrated barium hydroxide, making the albumin 0.05%. Access of carbon dioxide was prevented. Adjustment of *p*H was made with hydrochloric acid. The five curves are presented in Fig. 8. The very great increase in foaming caused by the barium ion in the alkaline range is strikingly evident. Near *p*H 4, on the contrary, foaming decreases regularly with increasing concentrations of barium salt.

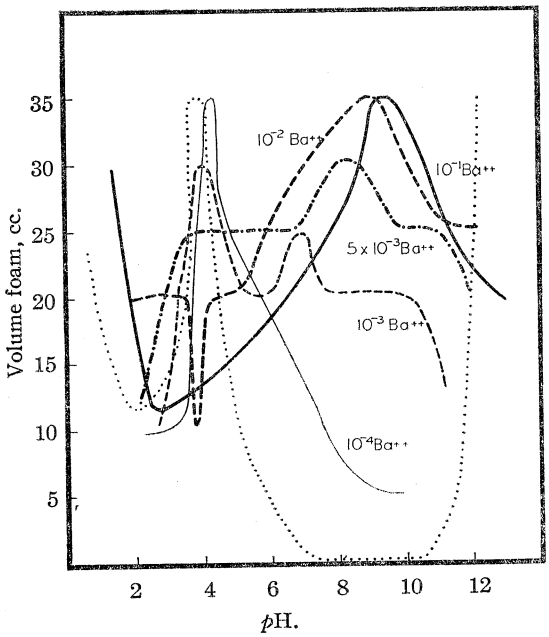

Fig. 8.—Foaming of 0.05% egg albumin *dissolved* originally in barium hydroxide and kept carbonate free, with *p*H adjusted by adding hydrochloric acid, showing decrease in foaming at *p*H 4 caused by barium salt and great increase at *p*H's 7 to 10.

Dispersed and Dissolved Egg Albumin in Presence of Barium Chloride.—Figure 9 shows the results of further experiments in which on the one hand, 0.05% egg albumin was initially *dispersed* in 10^{-3} *M* barium chloride at *p*H 5.4, and *p*H's adjusted with potassium hydroxide or hydrochloric acid; and, on the other, initially *dissolved* in a minimum of 10^{-3} *M* potassium hydroxide, then adjusted to 2×10^{-4} *M* potassium hydroxide and 10^{-3} *M* barium chloride, with further adjustments of *p*H by adding hydrochloric acid. The initial point of each series is indicated by a cross on the curve in Fig. 9. A similar effect for calcium chloride is shown in Fig. 6. It is seen that the degree or kind of dispersion of the protein and the presence of alkaline earth ion are both important in promoting foaming in the alkaline range.

Effect of Sea Water.—Ability of a material to foam in sea water is of importance in certain special foam applications. In this connection the egg albumin, dissolved at a concentration of 0.05 % in synthetic sea water (*p*H 8.2), gave 15 cc. of foam by the bubbling method; whereas, after adjusting the *p*H by small additions of hydrochloric acid or potassium hydroxide, the following foam volumes were obtained: *p*H 7.2, 17 cc.; *p*H 9.0, 32 cc.; *p*H 10.0, 20 cc. In distilled water at these *p*H values the foaming capacity of the pure albumin is negligible (Fig. 3). It is interesting that the sea water causes a maximum in foaming in about the same *p*H region as does barium ion at a concentration equivalent to the total alkaline earth concentration of the sea water (Fig. 8).

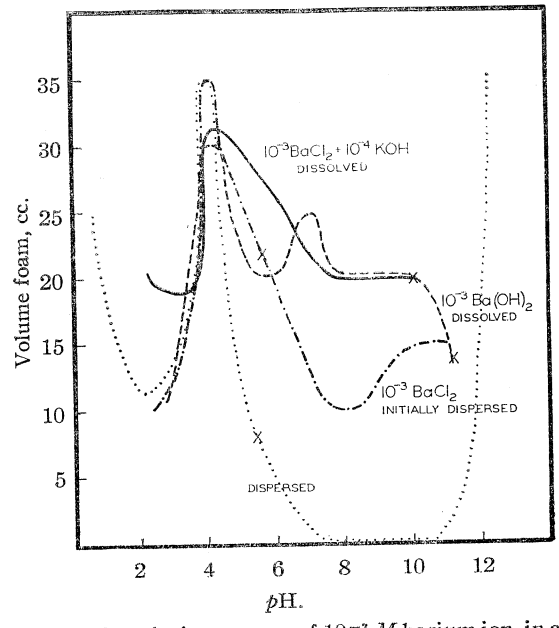

Fig. 9.—Results in presence of 10^{-3} *M* barium ion, in absence of carbon dioxide. Comparison of effect of barium ion on egg albumin initially *dispersed* at *p*H 5.4 (marked by cross) with effect of egg albumin initially *dissolved* at *p*H 10.1 (marked by cross) and with the effect of barium ion on egg albumin originally dissolved at *p*H 11.2 (marked by cross) in 10^{-3} *M* barium hydroxide. The dashed line as in Fig. 8 represents solutions made in barium hydroxide with *p*H's adjusted by adding hydrochloric acid; the full line, solutions made in 10^{-3} *M* potassium hydroxide diluted to 2×10^{-4} *M* potassium hydroxide and kept 10^{-3} *M* barium chloride with *p*H's adjusted by hydrochloric acid; the heavy dot-dash line refers to a dispersion containing 10^{-3} *M* barium chloride with *p*H's adjusted by potassium hydroxide or hydrochloric acid.

Discussion

It is seen that the foaming properties of proteins are complex and necessitate isolating the various factors by obtaining series of experiments over the whole *p*H range while studying one factor at a time. This is illustrated by the different curves in our figures.

The first point noticed is the pronounced maximum in the foaming of the albumin and protamine solutions at a *p*H slightly on the acid side of the isoelectric point. The albumin solutions also showed high foaming capacity at very high and very low *p*H values. The foaming capacity at this maximum appears to be the same whether the albumin was originally dispersed at *p*H 5 or originally dissolved at *p*H 10 (in 10^{-3} *M* potassium

hydroxide or 10^{-4} *M* barium hydroxide) although the position of the maximum is slightly shifted.

In the alkaline ranges albumin originally *dissolved* in potassium or barium hydroxide froths freely; whereas, if the albumin is first merely dispersed in water at *p*H 5–5.4 and the *p*H increased by adding potassium hydroxide, the albumin does not froth at all between *p*H's 7 and 11.

If sufficient barium ion is added to albumin dissolved in 10^{-3} *M* hydroxide, the frothing at *p*H 9 equals the maximum normally observed near the isoelectric point, but additional barium salt did not improve the foaming further. However, at *p*H 4, barium salt has the opposite effect, and lessens the foaming, as is seen in Fig. 8. Barium is seen to be much more effective than calcium or potassium in promoting foaming in the alkaline range. With increasing amounts of barium ion, maximum foaming occurs at increasingly higher *p*H values.

There appears to be a significant correlation between denaturation and maximum foaming. When foaming was a maximum, either at *p*H 4 for the "standard" curve or at *p*H 9 through the influence of barium ion, a residue which could not be redissolved was observed after collapse of the foam; when foaming was weak, no such denatured residue was found. Adam[9] has discussed denaturation in connection with protein films obtained either by spreading the protein on the surface of water or by adsorption of the protein at the air–protein solution interface, and has associated the effect with the "unfoldment" of the protein molecule in the surface film. It would appear from our results that only under conditions of optimum foaming is the protein adsorbed at the air–solution interface in the form of a fully extended coherent film.

Some further insight as to the nature of the adsorbed albumin film in the foam may be gained from the fact that, under conditions of optimum foaming, the air–liquid surface area produced was estimated by bubble size measurements to be of the order of magnitude of one square meter for each 5 mg. of albumin present in the original solution (surface tension 62 dynes/cm.). Comparisons with the results of Hughes[10] for the spreading of albumin at the air–water interface suggest that, under conditions of maximum foaming, the adsorbed surface film is of the "gel" type.

It therefore appears that the essential condition for maximum foaming is that the protein solution be capable of yielding readily a fully extended, semi-rigid, coherent protein film adsorbed at the air–solution interface. It would seem to be suggested that this condition is fulfilled when there is a minimum net charge on the protein complex—at very high and very low *p*H values due to suppression of ionization of the protein, at the isoelectric point due to "self-neutralization," and at intermediate values due to neutralization of free COO^- or NH_3^+ groups by cations or anions, respectively. Our results actually depart from this idealized concept in two respects. Maximum foaming actually appeared on the acid side of the isoelectric point and anion effects were not apparent. It is possible that the isoelectric point of albumin in an "unfolded" or extended condition at the air–water interface may be slightly different from that of the protein in solution although the possibility of a shift due to the presence of electrolytes is not completely eliminated. The reason the expected anion effect did not appear in our results may be that in this *p*H range (below *p*H4 for albumin) the weak acids involved were almost completely undissociated.

It is interesting to note that Gorter and coworkers[9] have found that the rate of spreading of proteins at the air–water interface is a maximum at the isoelectric point and at very high and very low *p*H values. They showed that in the alkaline range cations improve spreading according to a typical lyotropic series and also that anions had similar effects on the acid side of the isoelectric point.

Zhukov and Bushmakin[11] observed a maximum stability of benzene emulsions stabilized with gelatin at the iso-electric point, *i. e.*, where the surface tension and viscosity are at a minimum. Two minimum stability points were observed at *p*H 2.5 and 9.5 coinciding with maximum viscosities. They concluded that non-hydrated and undissociated gelatin molecules serve best for emulsification.

Our results appear to amplify and extend those of Perri and Hazel[3] and offer possible explanations for those of others. Thus Barmore observed a maximum foaming capacity of fresh whole egg white at *p*H 8, which may be due to inorganic cations, although globulins are of course also present. In so far as whey proteins may be compared with egg albumin, the results of Peter and Bell[5] correlate satisfactorily with ours.

It appears from this work that in any study of the foaming properties of proteins it is important to be aware of electrolytes, either added or originally present in the protein, to consider the degree or kind of dispersion of the protein and to observe the foaming characteristics over a wide range of *p*H values for each concentration of electrolyte used.

Summary

1. Proteins produce maximum foam somewhat on the acid side of the isoelectric point. This is shown by single bubbles and by frothing for egg albumin (*p*H 4) and protamine (*p*H 10).

2. This maximum is enhanced by dissolving the egg albumin in 10^{-3} *M* acetic acid.

3. If egg albumin is merely dispersed to a somewhat turbid "solution" at *p*H 5, it does not foam in the range *p*H 7 to 11.

(9) N. K. Adam, "The Physics and Chemistry of Surfaces," 3rd ed., 1941, pp. 87–92.

(10) A. H. Hughes, *Trans. Faraday Soc.*, **29**, 214 (1933).

(11) I. I. Zhukov and I. N. Bushmakin, *J. Russ. Phys.-Chem. Soc.*, **59**, 1061 (1927).

4. If first dissolved in 10^{-3} *M* alkali (potassium hydroxide or barium hydroxide) it foams freely in the alkaline range.

5. Alkaline earth ion or salt greatly promotes foaming in the alkaline range, but may minimize it on the acid side.

6. The data presented, considered in the light of previous knowledge, indicate that different proteins follow a general pattern in their foaming behavior and that this pattern is similar to that exhibited by other properties of proteins.

STANFORD, CALIFORNIA RECEIVED JANUARY 17, 1949

[CONTRIBUTION NO. 1240 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

The Preparation and Properties of Vanadium Nitrosyl Chlorides

BY ARTHUR GREENVILLE WHITTAKER[1] AND DON M. YOST

In connection with an investigation of vanadium tetrachloride, VCl_4, it was observed that a beautiful, dark purple, coarsely crystalline substance forms readily when dry nitric oxide is passed through a solution of vanadium tetrachloride in carbon tetrachloride. Similar crystalline materials result when dry nitric oxide reacts with pure vanadium tetrachloride in either the liquid or vapor state. Although compounds containing the NO group have been previously studied,[2] the reaction products herein described do not appear to have been mentioned in the literature and are therefore new.

Experimental

The vanadium tetrachloride was prepared as described in a previous paper.[3] Nitric oxide was prepared by slowly adding 50% sulfuric acid to a solution which was four formal in potassium nitrite and one formal in potassium iodide.[4] The gas was purified and dried by passing it through successive tubes containing potassium hydroxide, calcium chloride and magnesium perchlorate.

In preparing these new compounds, three different sets of conditions were tried, yielding three different sets of principal reaction products. In all cases a number of products were formed, but the principal ones were the dark purple crystals and vanadium trichloride. Small amounts of nitrosyl chloride and vanadium oxytrichloride were always produced, however. The three sets of reaction conditions and principal products are: (1) Nitric oxide reacting with vanadium tetrachloride in the vapor phase gave the solid $V_2Cl_3(NO)_5$, and a large fraction of vanadium trichloride; (2) Nitric oxide passed into liquid vanadium tetrachloride resulted in the precipitation of the compound V_2Cl_7NO; (3) The insoluble solid VCl_4NO was formed when nitric oxide was passed into a dilute (say 10%) carbon tetrachloride solution.

All reactions were started at room temperature, but as considerable heat is evolved the exact temperatures during reaction cannot be specified. No attempt was made to estimate the heat of reaction. The compounds were purified by subliming them from one end of a pyrex tube (50 cm. × 2.5 cm.), which was filled with dry air or carbon dioxide at one atmosphere, to the other. Although sublimation begins at about 45°, the hot end of the tube was maintained at 135° and the cold end at room temperature. The residue at the hot end of the tube was always vanadium trichloride. Before the crystals were removed from the tube the collection end was placed in a furnace at 50° overnight to distill any liquid away from the crystals

Densities were determined pycnometrically; carbon tetrachloride served as the liquid. Magnetic susceptibility measurements were made by the Gouy method.

Extensive analyses of the various preparations were made using the following methods: (1) Vanadium was determined, in sulfuric acid solution, with standardized permanganate. (2) Chlorine was precipitated as silver chloride and weighed. (3) Nitrogen was determined by first oxidizing to nitrate with alkaline permanganate the nitric oxide or nitrous acid formed when the purple crystals react with water. The excess permanganate was reduced with hydrogen peroxide and the manganese dioxide filtered off. Nitrogen in the filtrate was determined by the Kjeldahl method, using aluminum metal in sodium carbonate solution as a reducing agent.

Results and Properties of the Compounds.—The average values of the results of the analyses and of the measurements of the densities and magnetic susceptibilites are presented in Table I. As indicated there the results of the analyses were best satisfied by compounds with the empirical formulas VCl_4NO, V_2Cl_7NO and $V_2Cl_8(NO)_5$.

All the compounds gave off a colorless gas and ultimately yielded a blue solution when placed in water. The blue solution was due to vanadyl ion, VO^{++}, and the gas was identified as nitric oxide. The amount of nitric oxide liberated by each compound is indicated in Table I. In the case of V_2Cl_7NO the rate of solution was slower and it was possible to observe a brown solution in the immediate vicinity of the crystals as they reacted with water. The brown color was much like that due to VO^+ which one gets on dissolving vanadium trichloride in water.

Long, dark purple, opaque crystals were formed by each of the compounds. Microscopic examination revealed that dark purple light was transmitted by small crystals. Also, the crystals were birefringent, and they show parallel extinction. The crystals of VCl_4NO and $V_2Cl_8(NO)_5$ were needle-like, and had a tendency to form penetration twins. The crystals of V_2Cl_7NO were shorter prisms that tended to form hemispherical tufts of the prisms like pins in a pin cushion.

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(1) du Pont Fellow in Chemistry at the California Institute of Technology.

(2) (a) L. Malatesta, *Gazz. chim. ital.*, **71**, 615 (1941); (b) Blanchard, *Chem. Rev.*, **21**, 3 (1937); **26**, 409 (1940).

(3) A. G. Whittaker and Don M. Yost, *J. Chem. Phys.*, **17**, 176 (1949).

(4) H. Johnston and W. F. Giauque, THIS JOURNAL, **51**, 3194 (1929); D. M. Yost and H. Russell, Jr., "Systematic Inorganic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1944, p. 14.

TABLE I

SOME PROPERTIES OF THE VANADIUM NITROSYL CHLORIDES

Compound	Percentage composition						NO lib. by H_2O, %	Density at 28°	χ_m[a] ($\times 10^6$) 25.3°
	V	Obsd. Cl	NO	V	Theory Cl	NO			
VCl_4NO	23.1	62.5	11.9[b]	22.9	63.6	13.5	13.5	2.32	2340
V_2Cl_7NO	26.8	65.8	7.8	22.6	65.6	7.8	2.5	2.50	4180
$V_2Cl_8(NO)_5$	19.0	52.6	23.9[b]	19.0	53.0	28.0	3.0	2.15	2470

[a] χ_m is the molal susceptibility. [b] These results are known to be low.

Moisture in the air reacts readily with all of the preparations to give nitric oxide and vanadyl chloride. Subjected to pressure of about 0.1 mm. at room temperature, the compounds simply sublimed from a retort tube to a cold trap. Such experiments gave a rough measure of the relative volatility of the compounds. Listed in order of increasing volatility they are: V_2Cl_7NO, VCl_4NO and $V_2Cl_8(NO)_5$.

Efforts were made to decompose the compounds by heating them rather suddenly to 400 to 500° in an apparatus consisting of a reaction tube, a cold trap at −78°, and a pneumatic trough to catch gases that did not condense in the cold trap. The compound VCl_4NO did not appear to decompose since it could be sublimed repeatedly from one end of the reaction tube to the other without leaving a residue. The compound V_2Cl_7NO showed some decomposition in that the cold trap caught a small amount of nitrosyl chloride, and a small residue of vanadium trichloride remained. In the case of $V_2Cl_8(NO)_5$ decomposition took place to some extent giving NOCl and perhaps NO, some of which reacted with oxygen in the apparatus and condensed in the cold trap as a mixture of NO_2 and N_2O_3. A residue of V_2O_5 appeared to be formed. In all cases the pneumatic trough caught no significant amount of gas other than that due to expansion of the air on heating. At the elevated temperature all the compounds appeared to react slowly with oxygen in the air to give vanadium oxytrichloride.

The compounds were found to be insoluble in the dried liquids, carbon tetrachloride, *n*-butyl alcohol, ether, dioxane and nitrobenzene. All were soluble to the extent of a few per cent. in carbon tetrachloride at 100° while enclosed in a sublimation tube. Efforts to dissolve the compounds in boiling carbon tetrachloride at atmospheric pressure in a test-tube resulted in the decomposition of the compounds.

Discussion.—Unfortunately, the various preparation methods do not produce results which were clear cut. With all three some of the preparations turned out to be mixtures of two or more of the compounds. In some, but not all, cases the properties of the mixtures could be resolved into those of the components by using a simple additivity relation based on the chemical analysis and the probable pure components. As the procedure did not always yield sensible results, the existence of a fourth compound in the group is not precluded. At any rate one or more pure samples of the above described compounds were independently produced.

The results of the magnetic susceptibility measurements deserve further mention. It is interesting that two of these compounds, namely, VCl_4NO and V_2Cl_6NO are examples of "even molecules" which are paramagnetic. For example, in the case of VCl_4NO the odd electron of the vanadium does not appear to couple with that of the NO group. Complete coupling would produce a diamagnetic substance, which is certainly not the case here.

If it is assumed that this compound obeys the Curie–Weiss law for the odd electrons per molecule, then the Curie temperature turns out to be −99°. This is not an unreasonable value. The other compounds are too complicated to make a reasonable guess as to how their paramagnetism arises.

Since these compounds are not reported elsewhere in the literature, the following names are proposed: VCl_4NO can be named vanadium nitrosyl tetrachloride, V_2Cl_7NO can be named divanadium nitrosyl heptachloride, and $V_2Cl_8(NO)_5$ can be named divanadium pentanitrosyl octachloride.

We are greatly indebted to Mr. David L. Douglas for helpful discussion and careful study of the results of the experiments. The work was kindly supported by a grant from the Research Corporation.

Summary

1. Three new compounds are reported as resulting from reactions between vanadium tetrachloride and nitric oxide. These compounds have the empirical formulas VCl_4NO, V_2Cl_7NO and $V_2Cl_8(NO)_5$; they have been named vanadium nitrosyl tetrachloride, divanadium nitrosyl heptachloride, and divanadium pentanitrosyl octachloride, respectively.

2. Various properties of the compounds are reported. These include reaction with water, qualitative solubilities where no reaction takes place with the solvent, and their behavior at reduced pressure and when suddenly heated to about 450°. All the compounds have very nearly the same general appearance, and all sublime readily.

3. The density of each compound was measured, and found to be 2.32, 2.50 and 2.15 g./cc. for VCl_4NO, V_2Cl_7NO and $V_2Cl_8(NO)_5$, respectively.

4. The magnetic susceptibility of each compound was measured at 25.3° and found to be 2340×10^{-6}, 4180×10^{-6} and 2470×10^{-6} per mole for VCl_4NO, V_2Cl_7NO and $V_2Cl_8(NO)_5$, respectively.

PASADENA, CALIFORNIA RECEIVED MAY 10, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WASHINGTON UNIVERSITY]

The Kinetics of the Thallium(I)–Thallium(III) Exchange Reaction

BY RENÉ J. PRESTWOOD[1] AND ARTHUR C. WAHL

Harbottle and Dodson[2] and the authors[3] have previously reported that the rate of the exchange reaction between thallium(I) and thallium(III) in acid solution is measurable. Harbottle and Dodson found that in perchloric acid the rate was proportional to the first power of the concentration of each reactant. They also found that the rate increased when lithium perchlorate was added, varied when the acid concentration was varied, being a maximum at about 1 f., and was greater in hydrochloric acid than in perchloric acid. The authors found the rate was greater in nitric acid than in perchloric acid, increased with increasing nitric acid concentration (1.0–1.5 f.) and decreased with increasing perchloric acid concentration (1.5–3.5 f.). This paper describes our studies of the kinetics of the thallium(I)–thallium(III) exchange reaction.

Experimental

Radioactivity.—The 3.5-year Tl^{204} was used as tracer in all experiments. Part of the Tl^{204} was produced by the n,γ reaction and was obtained from the Clinton Laboratories on allocation from the U. S. Atomic Energy Commission; part was produced by the d,p reaction in the Washington University cyclotron. The activity produced in the cyclotron was purified by solution of the bombarded metal in dilute nitric acid, oxidation with aqua regia, ether extraction of thallium(III) chloride from 6 f. hydrochloric acid containing lead(II) carrier, precipitation of thallium(III) hydroxide from copper(II) and zinc(II) carriers with ammonium hydroxide, solution of the hydroxide in nitric acid, reduction with sulfite, precipitation of added iron(III) carrier with ammonium hydroxide, oxidation of the supernatant with aqua regia, and reprecipitation and solution of thallium(III) hydroxide. Thallium(III) oxide was purified prior to irradiation in the Oak Ridge pile by solution of thallium metal in dilute nitric acid, precipitation of thallium(I) chloride, oxidation with aqua regia, ether extraction of thallium(III) chloride from 6 f. hydrochloric acid, and precipitation and reprecipitation of thallium(III) hydroxide with ammonium hydroxide. The hydroxide was dried at 150–200°. The irradiated thallium(III) oxide was dissolved in nitric acid, the solution oxidized with aqua regia to be certain all the Tl^{204} was in the plus three oxidation state, and thallium(III) hydroxide precipitated and dissolved in the appropriate acid. The specific activity of this thallium was the same as that of an aliquot further purified from added lead and mercury carrier. Aluminum absorption curves of the radiation from either n,γ or d,p produced Tl^{204} agreed with the curve reported by Fajans and Voight.[4] The initial half-thickness was 30 mg. per cm.^{2}, the range 310 mg. per cm.^{2}, the beta to gamma ratio about 10^4.

Chemicals.—With the exception of the materials used in the preliminary studies of separation methods, all reaction mixtures were made up from the following solutions.

0.100 f. thallium(I) perchlorate (inactive)
0.100 f. thallium(III) perchlorate (radioactive) in 2.50 f. perchloric acid
5.00 f. perchloric acid
5.00 f. sodium perchlorate
5.00 f. sodium nitrate

Thallium(I) perchlorate was prepared by evaporation of a perchloric acid solution of Fisher pure thallium(I) nitrate and recrystallization of thallium(I) perchlorate three times from water. The thallium(III) perchlorate solution was prepared by solution of a mixture of active and inactive thallium(III) oxide in 9.3 f. perchloric acid and dilution. The inactive thallium(III) oxide was prepared by the method used to purify the oxide prior to neutron irradiation. Both thallium perchlorate solutions were assayed for thallium gravimetrically by precipitation of thallium (I) hexachloroplatinate(IV). The excess acid in the thallium(III) perchlorate solution was assayed by addition of excess standard sodium hydroxide, centrifugation of thallium(III) hydroxide, and back-titration with standard acid. Mallinckrodt "Analytical Reagent Grade" 60 or 71% perchloric acid and dried sodium nitrate and G. Frederick Smith anhydrous sodium perchlorate were used to prepare the remaining solutions. Mallinckrodt "Analytical Reagent Grade" ammonium hydroxide, sodium bromide, sodium chromate, sodium cyanide, and hexachloroplatinic acid (10% solution) were used in various solutions employed in the separation of the reactants.

Measurement of Radioactivity.—All precipitates were mounted by filtration on a tared, 18-mm. diameter piece of Whatman No. 42 filter paper, dried at 110°, weighed, mounted on a 2 × 2.5 in. cardboard card with scotch tape placed directly over the sample, and counted on a Geiger–Müller counter. During the filtration the filter paper was clamped between a glass chimney, 2.5 in. high and 14 mm. inside diameter, and a Hirsch funnel, without sides and with its surface ground flat. In order to obtain uniform deposits, the precipitate was allowed to settle on the filter paper before suction was applied. The Geiger counter[5] had an 8 mg./cm.^{2} dural side window, 1.0 in. in diameter. The sample was placed directly below and 0.5 cm. from the window. The counter pulses were fed directly into the discriminator of an Instrument Development Laboratories' Model 161 scaler (scale of 256). The counter was stable, had a 100 v. plateau which was flat within 1% statistical error, and had a background of 50 counts per minute inside a lead shield. The response of the counter was linear to within about 2% up to the maximum counting rate measured (3000 counts per minute).

Since samples of the same weight, composition and

(1) (a) This paper is a portion of the dissertation presented by René J. Prestwood in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Washington University, June, 1948; (b) Monsanto Fellow, 1948; (c) present address: Los Alamos Scientific Laboratory, Los Alamos, New Mexico.

(2) G. Harbottle and R. W. Dodson, THIS JOURNAL, **70**, 880 (1948).

(3) R. J. Prestwood and A. C. Wahl, *ibid.*, **70**, 880 (1948).

(4) K. Fajans and A. F. Voight, *Phys. Rev.*, **60**, 619 (1941).

(5) The details of the construction and operation of the Geiger counter will be reported in a later publication.

thickness were always compared, and since the scotch tape was of uniform thickness (9 mg./cm.^{2}), no absorption or scattering corrections were made. This procedure appears to be justified because good agreement between duplicate samples was always obtained. For example the average deviation between the measured specific activities (counts per min./mg. Tl_2CrO_4) of duplicate samples, prepared for the determination of the equilibrium specific activities of twenty-five reaction mixtures, was 0.9%, a deviation consistent with known counting and weighing errors.

Procedure.—All components of a reaction mixture except the active thallium(III) solution (*ca.* 10% of the total volume) were mixed, the solution allowed to reach temperature equilibrium in a constant temperature (±0.1°) water-bath, and the thallium(III) solution added at room temperature. Less than fifteen minutes was required for the reaction mixture to regain temperature equilibrium, a time short compared to the exchange half-times (five to twelve hundred hours). Aliquots were removed at known time intervals, the reactants separated, and specific activity measurements made. Two aliquots were removed immediately after the solutions were mixed for measurement of the apparent zero-time exchange (see Separation-Induced Exchange and Coprecipitation Effects under Results), and six aliquots were removed at time intervals chosen so that 20–60% exchange had occurred in the solution. Concentrations were calculated on the volumes of the solutions at 25°. (Corrections for volume changes would be less than 1%.)

Four procedures for the separation of thallium(I) from thallium(III) were studied.

(1) Hydroxide Separation.—Thallium(III) hydroxide was precipitated with 15 f. ammonium hydroxide. Thallium(I) chromate was precipitated from the supernatant, washed, and mounted for the specific activity determination of the thallium(I) fraction. Thallium(III) hydroxide was converted to thallium(I) chromate by solution in acid, reduction with sulfurous acid, and precipitation with sodium chromate from an ammoniacal solution. This latter thallium(I) chromate precipitate was mounted for the specific activity determination of the thallium(III) fraction. Since the hydroxide separation was used only when the concentrations of thallium(I) and thallium(III) were equal, the equilibrium specific activity, S_∞, was taken as the average specific activity of each pair of samples.

(2) Bromide Separation.—Thallium(I) bromide was precipitated with 2 f. sodium bromide and mounted for the specific activity determination of the thallium(I) fraction. Thallium(III) remaining in the supernatant was converted to thallium(I) bromide by precipitation of thallium(III) hydroxide, solution in acid, reduction with sulfurous acid and precipitation with sodium bromide. The latter thallium(I) bromide was mounted for the specific activity determination of the thallium(III) fraction. The equilibrium specific activity was taken as the average specific activity of each pair of samples.

(3) Chromate Separation.—Thallium(I) chromate was precipitated and thallium(III) complexed with cyanide by addition of an aliquot of the reaction mixture to a solution 0.5 f. in sodium chromate, 1.0 f. in sodium cyanide, and 7.0 f. in ammonium hydroxide.[6] Since thallium(I) chromate can be filtered more readily if allowed to remain in contact with its supernatant for some time, it was allowed to stand fifteen minutes, then filtered and mounted for the specific activity determination of the thallium(I) fraction. The equilibrium specific activity, S_∞, was taken as the average specific activity of all the thallium in the reaction mixture. The average specific activity measurements were made on duplicate thallium(I) chromate samples prepared by the above procedure after thallium(III) had been reduced with sulfurous acid. The sizes of the aliquots were chosen so that in any run all thallium(I) chromate samples had the same weight. The equivalence of the average and equilibrium specific activities was checked in several runs by measurement of the specific activity of the thallium(I) fraction at a time when radioactive atoms were randomly distributed. An indirect check on the amount of thallium(III) coprecipitated with thallium(I) chromate was made by preparation of fourteen thallium(I) chromate samples by the same procedure. Seven were precipitated in the presence of thallium(III) ([Tl(I)] = [Tl(III)] = 10 mf.) and seven in the absence of thallium(III). The average weight of the samples precipitated in the presence of thallium(III) was 12.5 ± 0.1 mg. compared to 12.4 ± 0.1 mg. for those precipitated in the absence of thallium(III). Therefore little if any coprecipitation occurred.

(4) Hexachloroplatinate Separation.—Thallium(I) hexachloroplatinate was precipitated with hexachloroplatinic acid and mounted for the specific activity determination of the thallium(I) fraction. The equilibrium specific activity was taken as the average specific activity of all the thallium in the reaction mixture.

Errors.—The principal sources of error were the statistical fluctuations in the counting rate (± *ca.* 1%), uncertainty in the weight of the counted samples (± *ca.* 1%), and uncertainty in the concentrations of the solutions (± *ca.* 1%). The error in specific activities due to nonuniform distribution of the samples has been discussed and was considered negligible. We believe the probable error in the rates is not over 3%. The internal consistency of the data indicate the precision may be somewhat higher than 3%.

Results

Separation-Induced Exchange and Coprecipitation Effects.—The exponential exchange law[7,8] expressed in its logarithmic form for the thallium(I)–thallium(III) exchange is

$$Rt = -\frac{[Tl(I)][Tl(III)]}{[Tl(I)] + [Tl(III)]} \ln (1 - F) \qquad (1)$$

The exchange rate, R, is the rate at which thallium(I) becomes thallium(III) and at which thallium(III) becomes thallium(I). R is a constant when thallium(I) and thallium(III) are uniformly dispersed in the same phase and all conditions, except the distribution of the radioactive atoms, are constant. Square bracketed quantities indicate concentrations in gram atoms per liter, and t is the time the exchange of radioactive atoms is followed (time after addition of tagged thallium(III) to the rest of the reaction mixture). The fraction exchange, F, is a measure of the extent of the exchange of radioactive atoms and approaches an equilibrium value of 1.0. Since thallium(I) was initially inactive, F may be expressed as

$$F = \frac{S_{(I)}}{S_\infty} = \frac{S_{(III)} - S_{(III)0}}{S_\infty - S_{(III)0}} \qquad (2)$$

where the specific activity, S, is defined as the ratio of radioactive to total thallium atoms in the indicated oxidation state or chemical fraction, subscripts (I) and (III) referring to the oxidation states of thallium, and subscripts 0 and ∞ referring to the time the specific activity was measured. As can be seen from equation 1, $(1 - F)$ should decrease exponentially with time so that if 50% exchange occurred in time t, 75% exchange would occur in time $2t$, etc., and a semi-logarithmic

(6) Harbottle and Dodson[2] used a similar solution containing ethanol with good results.

(7) H. A. C. McKay, *Nature*, **142**, 997 (1938).

(8) R. B. Duffield and M. Calvin, THIS JOURNAL, **68**, 557 (1946).

plot of $(1 - F)$ against time should be a straight line passing through 1.0 at zero time.

If some of the thallium(I) can be separated free of thallium(III) and if no exchange occurs during the separation, then the specific activity of the thallium(I) fraction is equal to the specific activity of the thallium(I) in the reaction mixture just prior to the separation and may be used to calculate the fraction exchange that occurred in solution. However, if the thallium(I) fraction contains some thallium(III) and if exchange occurs during the separation, the specific activity of the thallium(I) fraction will not be equal to the specific activity of the thallium(I) in solution prior to the separation but will be a function of the amounts of thallium(I) and thallium(III) in the separated chemical fraction, their specific activities prior to separation, and the extent of the separation-induced exchange. Similar statements apply to a thallium(III) fraction.

It is shown in the appendix that *when the separation-induced exchange and the incomplete separation effects are reproducible* the following simple relations are true.

$$F = \frac{S - S_0}{S_\infty - S_0} = \frac{F' - F_0'}{1 - F_0'} \qquad (3)$$

S and S_0 are the specific activities of a chemical fraction, enriched in one of the exchange reactants separated at time t and time zero, respectively. F' and F_0' are the fraction exchange observed after separation at times t and zero, respectively. Substitution for F in equation 1 gives

$$\ln (1 - F') = -\frac{[\mathrm{Tl(I)}] + [\mathrm{Tl(III)}]}{[\mathrm{Tl(I)}][\mathrm{Tl(III)}]} Rt + \ln (1 - F_0') \qquad (4)$$

$$\ln (S_\infty - S) = -\frac{[\mathrm{Tl(I)}] + [\mathrm{Tl(III)}]}{[\mathrm{Tl(I)}]\,[\mathrm{Tl(III)}]} Rt + \ln (S_\infty - S_0) \qquad (5)$$

Therefore semi-logarithmic plots of $(1 - F')$ *vs.* t and $(S_\infty - S)$ *vs.* t should be straight lines with intercepts of $(1 - F_0')$ and $(S_\infty - S_0)$, respectively, at $t = 0$. The slopes and half-values of these plots will be the same as those of a semi-logarithmic plot of $(1 - F)$ *vs.* t, and the exchange rate, R, may be calculated from the half-value, $t_{1/2}$ (half-time of the exchange reaction occurring in the solution; $t = t_{1/2}$ when $F = 0.5$), of any of these plots.

$$R = \frac{[\mathrm{Tl(I)}][\mathrm{Tl(III)}]}{[\mathrm{Tl(I)}] + [\mathrm{Tl(III)}]} \times \frac{0.693}{t_{1/2}} \qquad (6)$$

Figure 1, curves A, B and C, shows semi-logarithmic plots of $(1 - F')$ *vs.* t for three different separation procedures applied to identical reaction mixtures. Curve D is a plot of $(1 - F)$ *vs.* t, F having been calculated from the F' and F_0' values plotted in curves A, B and C.

The specific activity values used in calculations of the fraction exchange were in units of *counts per min./mg. of sample* and were not the ratio of *radioactive to total thallium atoms* as defined

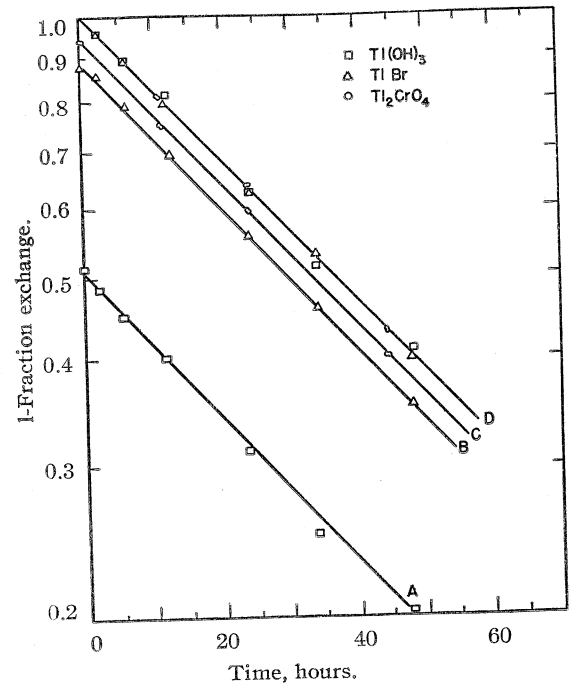

Fig. 1.—Semi-logarithmic plot of (1-fraction exchange) against time, reaction solution: 24.4 mf. $TlClO_4$, 24.4 mf. $Tl(ClO_4)_3$, 1.50 f. $HClO_4$, 24.8°. Curve A: Reactants separated by precipitation of $Tl(OH)_3$; 0.5 ml. 15 f. NH_4OH added to 2.0 ml. aliquots. Curve B: Reactants separated by precipitation of TlBr; 2.0 ml. aliquots added to 0.5 ml. 2.0 f. NaBr. Curve C: Reactants separated by precipitation of Tl_2CrO_4; 2.0 ml. aliquots added to 2.0 ml. 0.5 f. Na_2CrO_4, 1.0 f. NaCN, 7.0 f. NH_4OH. Curve D: Points of curves A, B and C corrected by equation 3.

However, since ratios of specific activities are always used in these calculations, this substitution is justified provided the counting efficiencies and compositions of all the samples from a given run are the same. The agreement of the data with the predicted exponential exchange law is a good indication that the above procedure was justified. Further justification in the case of the chromate separation procedure is given in the experimental section where it is shown that (1) the counting efficiencies of duplicate thallium(I) chromate precipitates are the same and (2) that little if any thallium(III) is coprecipitated with thallium(I) chromate. The latter is evidence that thallium(I) chromate samples have the same composition whether prepared for measurement of the specific activity of the thallium(I) fraction or the average thallium specific activity.

Several separation procedures were studied in order to find one which gave small and reproducible values of F_0'. A brief summary of the results of this study is given in Table I.

As can be seen from the data presented in Table I, only a small and reproducible apparent zero-time exchange occurred during the chromate separation. Therefore this method of separation

was used in all the kinetic studies of the homogeneous exchange. Since the thallium(I) chromate precipitate was allowed to stand for fifteen minutes in contact with its supernatant, a check was made to see if the standing increased the apparent zero-time exchange due to the heterogeneous exchange reaction between $Tl_2CrO_4(s)$ and $Tl(CN)_6^{\equiv}$. As seen from the results in Table II, the heterogeneous exchange is very slow.

The heterogeneous exchange between freshly precipitated thallium(III) hydroxide and thallium(I) ion in ammonium hydroxide solution was also measured. The fraction exchange was 22% for a ten-minute contact at room temperature.

Homogeneous Exchange—Procedure.—The general procedure has been described in the experimental section. The ionic strength (concentrations expressed in moles per liter) of all reaction mixtures was adjusted to 3.68 with sodium perchlorate. The reactants were separated by the chromate method. The measured fraction exchanges were corrected by equation 3, and the rates were calculated from the half-times obtained from semi-logarithmic plots of $(1 - F)$ *vs.* t. All points fell on straight lines passing through 1.0 at $t = 0$. A typical plot is shown in Fig. 2.

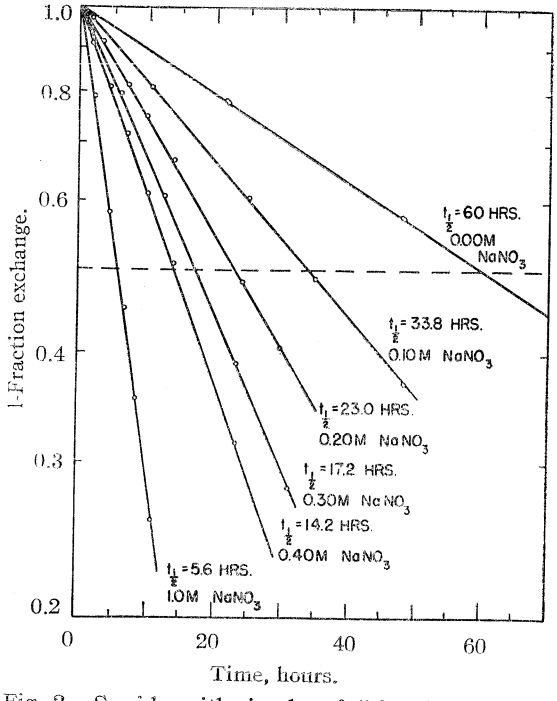

Fig. 2.—Semi-logarithmic plot of (1-fraction exchange) against time at various $NaNO_3$ concentrations (10.0 mf. $TlClO_4$, 10.0 mf. $Tl(ClO_4)_3$, 2.50 f. $HClO_4$, 37.3°, μ adjusted to 3.68 with $NaClO_4$).

Homogeneous Exchange.—[Tl(I)], [Tl(III)] Dependence.—Table III shows the dependence of the exchange half-time on the thallium(I) and thallium(III) concentrations.

TABLE I

APPARENT ZERO-TIME EXCHANGE (F_0')

Reaction mixture [Acid] (f.)	[Tl][a] (mf.)	°C.	Vol., ml.	Separations Ppt.	Vol.[b]	F_0' (%)[c]
0.3 HNO_3	48.8	~25	2.0	$Tl(OH)_3$	0.5*	66.7 ± 0.4
1.0 HNO_3	48.8	~25	2.0	TlBr	0.5*	9.0 ± 1.4
1.5 HNO_3	48.8	25	2.0	$Tl(OH)_3$	0.5	43.5 ± 0.5
				TlBr	0.5	22.5 ± 1.5
1.5 $HClO_4$	48.8	25	2.0	$Tl(OH)_3$	0.5*	51.0 ± 2.0
				TlBr	0.5	12.1 ± 0.3
				Tl_2PtCl_6	10.0*[d]	14.5 ± 0.2
				Tl_2CrO_4	2.0	6.2 ± 0.1
2.5 $HClO_4$	48.8	25	2.0	TlBr	2.0	12.9 ± 0.3
3.5 $HClO_4$	48.8	25	2.0	TlBr	2.0	12.8 ± 0.5
0.8 $HClO_4$[e]	10.0	10	10.0	Tl_2CrO_4	8.0	6.3 ± 0.0
		25	10.0	Tl_2CrO_4	8.0	5.5 ± 0.1
		37	10.0	Tl_2CrO_4	8.0	5.6 ± 0.0
		50	10.0	Tl_2CrO_4	8.0	5.7 ± 0.1
2.5 $HClO_4$[e]	20.0	10	5.0	Tl_2CrO_4	4.0	6.2 ± 0.0
		25	5.0	Tl_2CrO_4	4.0	6.1 ± 0.1
		~25	5.0	Tl_2PtCl_6	1.0	5.3 ± 0.1
		~25	5.0	Tl_2PtCl_6	1.0*	5.4 ± 0.1
		37	5.0	Tl_2CrO_4	4.0	6.0 ± 0.0
		50	5.0	Tl_2CrO_4	4.0	5.6 ± 0.0
2.5 $HClO_4$[e]	15.0[f]	25	5.0	Tl_2CrO_4	4.0	5.2 ± 0.5
	35.0[g]	25	2.0	Tl_2CrO_4	2.0	10.1 ± 0.1
	50.0	25	2.0	Tl_2CrO_4	2.0	6.4 ± 0.0
	30.0	25	5.0	Tl_2CrO_4	4.0	6.5 ± 0.0
	5.0	25	10.0	Tl_2CrO_4	8.0	5.5 ± 0.1

[a] Total thallium concentration; [Tl] = [Tl(I)] + [Tl(III)]. Unless otherwise noted [Tl(I)] = [Tl(III)] = [Tl]/2. [b] Volume of the following precipitating agents

ppt.	reagent
$Tl(OH)_3$	15 f. NH_4OH
TlBr	2 f. NaBr
Tl_2PtCl_6	0.044 f. H_2PtCl_6
Tl_2CrO_4	0.5 f. Na_2CrO_4, 1.0 f. NaCN, 7.0 f. NH_4OH

The reaction mixture was added to the precipitating agent except in runs indicated by an asterisk (*) in which the precipitating agent was added to the reaction mixture. [c] The recorded values are in general the average of two runs; a few are the average of three or four runs. The recorded errors are the average deviation of the individual runs from the average value. [d] 0.0055 f. H_2PtCl_6. [e] μ adjusted to 3.68 with $NaClO_4$. [f] 10.0 mf. Tl(I), 5.0 mf. Tl(III). [g] 10.0 mf. Tl(I), 25.0 mf. Tl(III).

TABLE II

DEPENDANCE OF APPARENT ZERO-TIME EXCHANGE ON TIME INTERVAL BETWEEN PRECIPITATION AND FILTRATION (CHROMATE SEPARATION)

Time, min.	2	10	30	90	210
F_0', %	5.5	5.6	5.8	6.0	6.2

TABLE III

(2.50 f. $HClO_4$, 24.9°, μ adjusted to 3.68 with $NaClO_4$)

$TlClO_4$, mf.	$Tl(ClO_4)_3$, mf.	$t_{1/2}$ hr.	$\frac{1}{[Tl(I)] + [Tl(III)]}$, mole^{-1}·liter
25.0	25.0	72	20.0
10.0	25.0	109	28.6
15.0	15.0	123	33.3
10.0	10.0	189	50.0
10.0	5.0	248	66.7

If the exchange reaction is bimolecular, $R = k[Tl(I)][Tl(III)]$, substitution of $k[Tl(I)][Tl(III)]$ for R in equation 6 gives

$$t_{1/2} = \frac{0.693}{[Tl(I)] + [Tl(III)]} \times \frac{1}{k} \qquad (7)$$

Figure 3, a plot of the data in Table III, shows that the half-time of the exchange is inversely proportional to the total thallium concentration, as predicted from equation 7 for a bimolecular reaction.

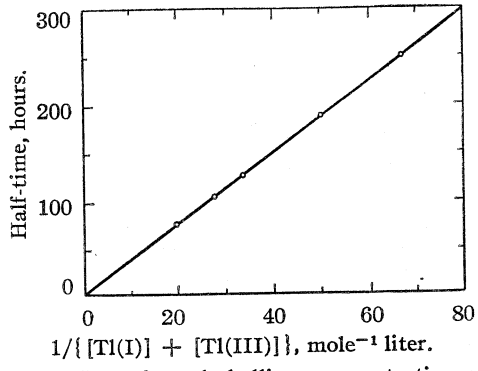

Fig. 3.—Effect of total thallium concentration on the half-time of the exchange (2.50 f. $HClO_4$, 24.9°, μ adjusted to 3.68 with $NaClO_4$).

Homogeneous Exchange—$[H^+]$ Dependence.—Table IV summarizes the data from sixteen runs made at various acid concentrations and at various temperatures. At any one temperature plots of log $R/[Tl(I)]\,[Tl(III)]$ *vs.* log $[H^+]$ resulted in curves whose slopes approached zero at high acid concentration. However, plots of $R/[Tl(I)][Tl(III)]$ against $1/[H^+]$ (see Fig. 4) resulted in straight lines. This suggests that there are two paths for the exchange, one hydrogen ion independent and one hydrogen ion dependent.

$$R = [Tl(I)][Tl(III)]\left\{k + \frac{k'}{[H^+]}\right\} \qquad (8)$$

The intercepts of the lines give the values of k at the various temperatures, and the slopes of the lines give the values of k'.

TABLE IV

(μ adjusted to 3.68 with $NaClO_4$)

$HClO_4$, f.	[Tl],[a] mf.	Temp., °C.	$t_{1/2}$ hr.	$R/[Tl(I)][Tl(III)]$, mole^{-1}·liter·hr.$^{-1}$
0.80	10.0	9.9	1160	0.0598
1.50	20.0	9.9	720	.0481
2.50	20.0	9.9	840	.0412
3.50	20.0	9.9	930	.0373
0.80	10.0	24.9	288	.241
1.50	20.0	24.9	168	.206
2.50	20.0	24.9	189	.183
3.50	20.0	24.9	198	.175
0.80	10.0	37.3	100	.694
1.50	20.0	37.3	55.5	.625
2.50	20.0	37.3	60.0	.578
3.50	20.0	37.3	63.5	.546
0.80	10.0	50.1	37.3	1.86
1.50	20.0	50.1	19.3	1.80
2.50	20.0	50.1	20.3	1.71
3.50	20.0	50.1	21.0	1.65

[a] Total thallium concentration [Tl] = [Tl(I)] + [Tl (III)]; [Tl(I)] = [Tl(III)]; perchlorate salts used.

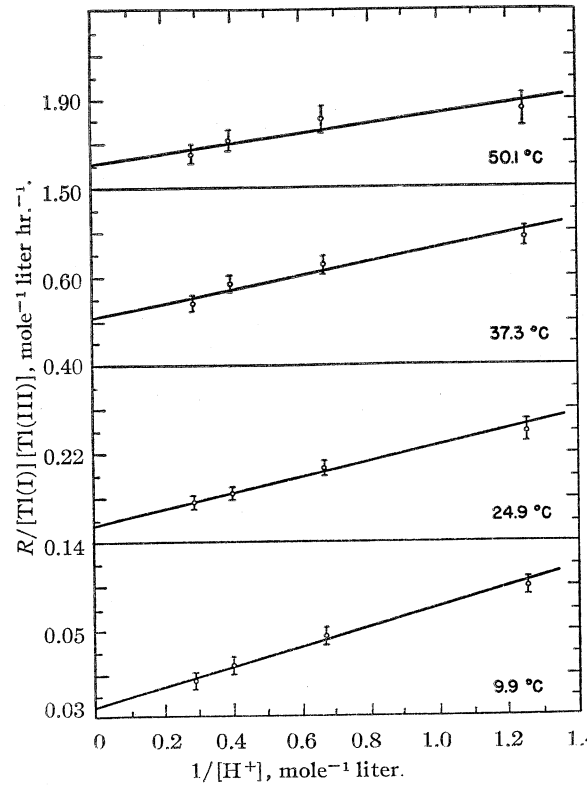

Fig. 4.—Effect of acid concentration on the exchange rate (μ adjusted to 3.68 with $NaClO_4$).

Curves A and B, Fig. 5, are semi-logarithmic plots of k and k' against the reciprocal of the absolute temperature. The experimental activation energies determined from these plots are 17,600 ± 400 cal. for the hydrogen ion independent path and 10,300 ± 1,600 cal. for the hydrogen ion dependent path. The rate constants may be expressed as

$$k = 3.8 \times 10^8\, e^{-17{,}600/RT} \text{ mole}^{-1}\text{·liter·sec.}^{-1} \qquad (9)$$

$$k' = 790\, e^{-10{,}300/RT} \text{ sec.}^{-1} \qquad (10)$$

where R is the gas constant and T is the absolute temperature.

Homogeneous Exchange—$[NO_3^-]$ Dependence.—Five runs were made at 37.3° in which the sodium nitrate concentration was varied from 0.100 to 1.00 f. and the other conditions were held constant. The experimental exchange curves obtained along with the curve for the ex-

TABLE V

(10 mf. $TlClO_4$, 10 mf. $Tl(ClO_4)_3$, 2.50 f. $HClO_4$, 37.3°, μ adjusted to 3.68 with $NaClO_4$)

$NaNO_3$, f.	$t_{1/2}$, hr.	$R/[Tl(I)][Tl(III)]$, mole^{-1}·liter·hr.$^{-1}$
0.000	60.0	0.578
.100	33.8	1.03
.200	23.0	1.51
.300	17.2	2.02
.400	14.2	2.49
1.00	5.6	6.2

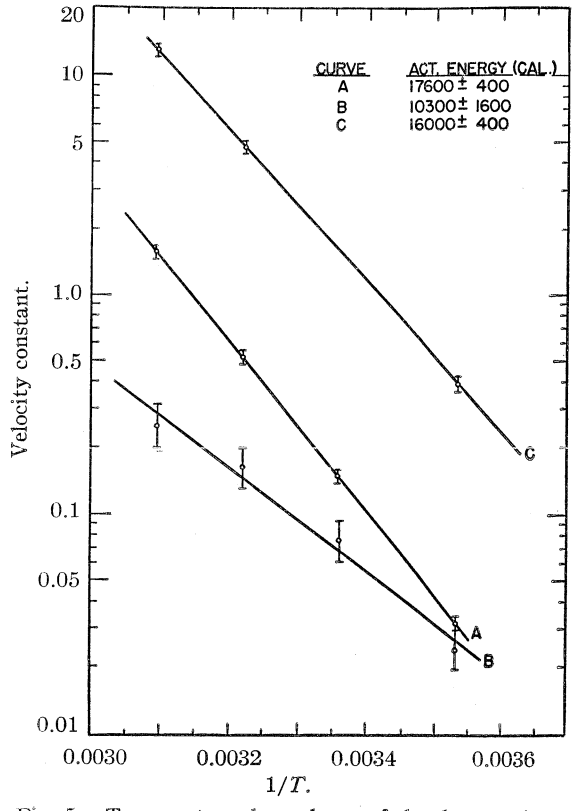

Fig. 5.—Temperature dependence of the three exchange paths. Curve A: $[H^+]$ independent path (k *vs.* $1/T$). Curve B: $[H^+]$ dependent path (k' *vs.* $1/T$). Curve C: $[NO_3^-]$ dependent path (k'' *vs.* $1/T$).

change in the absence of sodium nitrate are shown in Fig. 2. Table V is a summary of these data, and Fig. 6 is a plot of the rate against the sodium nitrate concentration.

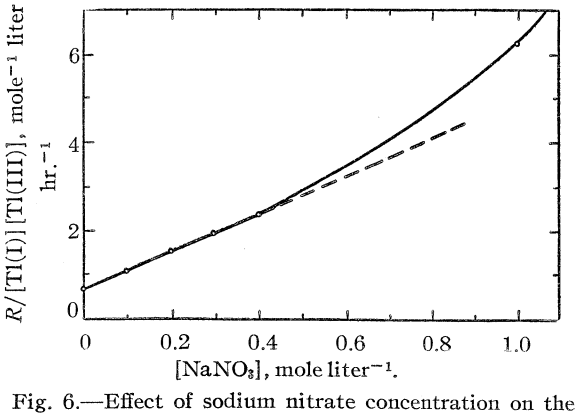

Fig. 6.—Effect of sodium nitrate concentration on the exchange rate (10.0 mf. $TlClO_4$, 10.0 mf. $Tl(ClO_4)_3$, 2.50 f. $HClO_4$, 37.3°, μ adjusted to 3.68 with $NaClO_4$).

Below 0.4 f. sodium nitrate the exchange rate is a linear function of the sodium nitrate concentration which suggests still a third path for the exchange in the presence of nitrate.

$$R = [Tl(I)][Tl(III)]\{k + (k'/[H^+]) + k''[NO_3^-]\} \quad (11)$$

The temperature dependence of k'' was investigated by measurement of the exchange rates at 9.9 and 50.1° (10 mf. $TlClO_4$, 10 mf. $Tl(ClO_4)_3$, 2.50 f. $HClO_4$, 0.400 f. $NaNO_3$, μ adjusted to 3.68 with $NaClO_4$). The half-time at 9.9° was 179 hours and at 50.1°, 5.03 hours. From the previously determined values of k and k', values of k'' were calculated at the various temperatures. A plot of k'' *vs.* $1/T$ is shown in Fig. 5, curve C. The experimental activation energy of the nitrate dependent path is 16,000 ± 400 cal. The rate constant may be represented as

$$k'' = 2.5 \times 10^8\, e^{-16{,}000/RT}\ \text{mole}^{-2}\cdot\text{liter}^2\cdot\text{sec.}^{-1} \quad (12)$$

A summary of the experimentally determined rate constants is given in Table VI.

TABLE VI

SUMMARY OF EXPERIMENTAL RATE CONSTANTS

(10.0–25.0 mf. $TlClO_4$, 5.0–25.0 mf. $Tl(ClO_4)_3$, 0.80–3.50. f. $HClO_4$, 0.00–0.40 f. $NaNO_3$, μ adjusted to 3.68 with $NaClO_4$)

Temp., °C.	k, mole^{-1}· liter·hr.$^{-1}$	k', hr.$^{-1}$	k'', mole^{-2}· liter^2·hr.$^{-1}$
9.9 ± 0.1	0.032 ± 0.002	0.023 ± 0.004	0.38 ± 0.02
24.9 ± .1	.154 ± .008	.07 ± .01	(1.60)[a]
37.3 ± .1	.510 ± .025	.15 ± .03	4.7 ± 0.2
50.1 ± .1	1.61 ± .08	.24 ± .05	13.0 ± .5

[a] Calculated from equation 12.

Heterogeneous Catalysis.—The exchange reaction at 37.3° (solution 10.0 mf. $TlClO_4$, 10.0 mf. $Tl(ClO_4)_3$, 2.50 f. $HClO_4$, μ adjusted to 3.68 with $NaClO_4$) was run in the presence of a three inch length of 0.01 inch platinized platinum wire. A similar experiment was run in the presence of five grams of pulverized silica gel. The solutions in both experiments were stirred during the runs. The half-time of the exchange in the presence of the platinum black was 1.6 hours and in the presence of silica gel 61.5 hours. These values may be compared with the half-time of 60.0 hours obtained under the same conditions in the absence of solid catalysts. The small increase in half-time in the presence of silica gel is probably not real and may be due to inaccuracies in the calculated specific activities caused by contamination of the thallium(I) chromate with silica. As the run progressed the silica became increasingly difficult to separate from the solution, and the thallium(I) chromate samples became increasingly heavy. The large decrease in the half-time of the exchange in the presence of platinum black is real and indicates the exchange may occur more rapidly in the presence of a conductor.

Discussion

Separation-Induced Exchange and Coprecipitation Effects.—It is of interest to know what proportion of the apparent zero-time exchange is due to separation-induced exchange and what proportion to incomplete separation. The large, *ca.* 50%, apparent zero-time exchange caused by precipitation of thallium(III) hydroxide is dif-

ficult to explain purely on the basis of incomplete separation. For such an explanation it would be necessary to postulate *ca.* 25% cross contamination of the thallium(I) and thallium(III) fractions. Such a figure appears at least an order of magnitude too large in view of the very low solubility of thallium(III) hydroxide in ammonium hydroxide and the clear and colorless appearance of the supernatant and wash resulting from centrifugation of the hydroxide. Also the color of thallium(I) chromate prepared for counting directly from the ammoniacal supernatant and wash was very sensitive to small amounts of thallium(III) impurity; we estimate a few per cent. of thallium(III) gave the chromate a distinctly brown color. Therefore we believe that most (> 90%) of the apparent zero-time exchange caused by the hydroxide separation was due to separation-induced exchange.

The coprecipitation of thallium(III) with thallium(I) chromate in the chromate separation was discussed in the experimental section, and it was concluded that little if any coprecipitation occurred. Therefore separation-induced exchange again seems to be the important factor in the apparent zero-time exchange.

In the bromide and hexachloroplatinate separations no attempt was made to resolve the separation-induced exchange and coprecipitation effects.

The rates of heterogeneous exchange between freshly precipitated thallium(III) hydroxide and thallium(I) ion and between freshly precipitated Tl_2CrO_4 and $Tl(CN)_6^{\equiv}$ were not sufficiently large to account for the observed separation-induced exchanges. Therefore it seems likely that most of the separation-induced exchange occurred while the precipitates were forming.

Separation-induced exchange may be an important factor in many isotopic exchange studies. At the present time there seems to be no reason to believe it need be zero or measurable. When chemical methods of separation are used and when the apparent zero-time exchange is 100%, there is no way of telling whether the rapid exchange occurred in solution prior to the separation or whether it occurred during the separation. Therefore unless physical methods of separation were used, reports of instantaneous complete exchange should be interpreted with caution.

Homogeneous Exchange.—Thallium(I) perchlorate and thallium(I) hydroxide are strong, soluble electrolytes, so essentially all thallium(I) in perchloric acid solution must exist as Tl^+. Sherrill and Haas[9] found that the solubility of thallium(III) hydroxide in perchloric acid was proportional to the cube of the hydrogen ion concentration, indicating that most thallium(III) present in perchloric acid solution exists as Tl^{+++}.

(9) M. S. Sherrill and A. J. Haas, Jr., THIS JOURNAL, **58**, 953 (1936).

The kinetic data, which are well represented by the rate law given in equation 11, indicate that in perchloric acid solution containing sodium nitrate the exchange between thallium(I) and thallium(III) proceeds via three independent paths. The following simple mechanism is consistent with the experimental rate law.

Path (1).—Two electrons are transferred directly from Tl^+ to Tl^{+++}

$$Tl^+ + Tl^{*+++} \underset{k}{\overset{k}{\rightleftharpoons}} Tl^{+++} + Tl^{*+} \qquad (13)$$

Path (2).—A small fraction[10] of one of the reactants (probably Tl^{+++}) is hydrolyzed, and two electrons are transferred between the hydrolysis product and the other reactant (the OH^- may or may not be transferred when the transition state decomposes)

$$Tl^{*+++} + H_2O = Tl^*OH^{++} + H^+ \quad K_h \text{ (rapid, reversible)} \qquad (14)$$

$$\left.\begin{aligned} &Tl^+ + Tl^*OH^{++} \xrightarrow{k_1} Tl^{+++} + Tl^*OH \text{ (rate determining)} \\ &Tl^*OH + H^+ \longrightarrow Tl^{*+} + H_2O \text{ (rapid follow reaction)} \end{aligned}\right\} \qquad (15a)$$

or

$$Tl^+ + Tl^*OH^{++} \underset{k_1}{\overset{k_1}{\rightleftharpoons}} TlOH^{++} + Tl^{*+} \text{ (rate determining)} \qquad (15b)$$

$$k' = K_h k_1 \qquad (16)$$

Path (3).—A small fraction[11] of one of the reactants (probably Tl^{+++}) is complexed with nitrate ion, and two electrons are transferred between the nitrate complex and the other reactant (the NO_3^- may or may not be transferred when the transition state decomposes)

$$Tl^{*+++} + NO_3^- = Tl^*NO_3^{++} \quad K \text{ (rapid, reversible)} \qquad (17)$$

$$\left.\begin{aligned} &Tl^+ + Tl^*NO_3^{++} \xrightarrow{k_2} Tl^{+++} + Tl^*NO_3 \text{ (rate determining)} \\ &Tl^*NO_3 \longrightarrow Tl^{*+} + NO_3^- \text{ (rapid follow reaction)} \end{aligned}\right\} \qquad 18)a)$$

or

$$Tl^+ + Tl^*NO_3^{++} \underset{k_2}{\overset{k_2}{\rightleftharpoons}} TlNO_3^{++} + Tl^{*+} \text{ (rate determining)} \qquad (18b)$$

$$k'' = Kk_2 \qquad (19)$$

The large increase in the exchange rate caused by the presence of platinum black indicates that

(10) If a large fraction of one of the reactants (Tl(III)) were hydrolyzed, the concentration of the unhydrolyzed reactant (Tl^{+++}) would decrease with decreasing hydrogen ion concentration and the curves in Fig. 4 would bend downward. The experimental points may indicate some deviation in this direction, but the deviation is within the experimental error.

(11) If a large fraction of one of the reactants (Tl(III)) were complexed by nitrate ion, the concentration of the uncomplexed reactant (Tl^{+++}) would decrease with increasing nitrate ion concentration and the curve in Fig. 6 would bend downward. The high point at 1 f. $NaNO_3$ in Fig. 6 may indicate that paths involving two or more nitrate ions may be becoming important (*e. g.*, reaction between $Tl^*(NO_3)_2^+$ and Tl^+).

in the presence of a conductor the transfer of electrons may be accomplished by still a fourth path, the electrons presumably being transferred through the conductor.

The entropy of activation for reaction 13, calculated from the experimental rate constants by use of the absolute rate theory,[12] in a solution of ionic strength 3.68 is −20 E. U. That predicted[12] for a reaction between +1 and +3 ions at zero ionic strength is about −30 E. U. The predicted entropy of activation will increase as the ionic strength of the solution increases, but no quantitative calculation has been attempted because of the known large deviations from the Debye–Hückel limiting law at high ionic strengths. (The velocity constants and heats and entropies of activation for reactions 15 and 18 cannot be calculated because the unknown equilibrium constants and heats of reactions 14 and 17 are included in the measured quantities.)

The mechanisms of electron transfer reactions and the relative importance of factors which determine the rates of such reactions are not well understood.[13] Although our study of the thallium(I)–thallium(III) exchange does little to clarify this important subject, it does point out certain inadequacies in some of the current theories.

The "equi-valence change" hypothesis proposed by Shaffer[14] and modified by Remick[15] predicts, among other things, that oxidizing and reducing agents which gain or lose the same number of electrons will react rapidly. The slow thallium(I)–thallium(III) exchange reaction is not consistent with this portion of the theory. Perhaps the theory should be modified to require a reasonable free energy decrease if a two electron transfer reaction is to be rapid.

The "coulombic-repulsion" hypothesis of Gorin[16] and Weiss[17] predicts that reactions between ions with charges of like sign will be slow. The slowness of the thallium exchange reaction and the catalytic effect of a conductor in the solution are consistent with this theory. However, the rapid oxidation[18] of tin(II) by thallium(III) in 3 f. perchloric acid appears to be inconsistent with the theory, unless it is assumed that Sn^{++} was in equilibrium with small but appreciable amounts of neutral molecules such as $Sn(OH)_2$ or that an undetected trace of catalytic impurity was present. An obvious difference between the thallium(I)–thallium(III) exchange reaction and the tin(II)–thallium(III) reaction is the over-all free energy change involved. Although there is no general correlation between the rate and the over-all free energy change of a reaction, this factor may be of importance in electron transfer reactions.

(12) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 434.

(13) A. E. Remick, *Record Chem. Progress*, **9**, 95 (1948).

(14) P. A. Shaffer, *Cold Spring Harbor Symposia Quant. Biol.*, Vol. **VII**, 50 (1939).

(15) A. R. Remick, THIS JOURNAL, **69**, 94 (1947).

(16) M. H. Gorin, *ibid.*, **58**, 1787 (1936).

(17) J. Weiss, *J. Chem. Soc.*, 309 (1944).

(18) A. C. Wahl, unpublished work.

Appendix

Correction for Incomplete Separation of Reactants and Separation-Induced Exchange.—Consider an exchange reaction between the molecular species A and B in which atoms of element X, which is common to both species, are exchanged. Define specific activity as the ratio of radioactive X atoms to the total number of X atoms in the same molecular species or chemical fraction. Let

S_A = Specific activity of reactant A at time t and prior to the separation

S_{A_0} = Specific activity of reactant A at time zero and prior to the separation

S_B = Specific activity of reactant B at time t and prior to the separation

S_{B_0} = Specific activity of reactant B at time zero and prior to the separation

S_∞ = Equilibrium specific activity of A and B

S = Specific activity of the chemical fraction enriched in A and separated from the reaction mixture at time t

S_0 = Specific activity of the chemical fraction enriched in A and separated from the reaction mixture at time zero

a = Atoms of element X that were contained in species A prior to the separation and that appear in the chemical fraction enriched in A

b = Atoms of element X that were contained in species B prior to the separation and that appear in the chemical fraction enriched in A

F = Fraction exchange at time t prior to the separation

$$= \frac{S_A - S_{A_0}}{S_\infty - S_{A_0}} = \frac{S_B - S_{B_0}}{S_\infty - S_{B_0}}$$

F' = Fraction exchange observed after separation at time t

$$= \frac{S - S_{A_0}}{S_\infty - S_{A_0}}$$

F_0' = Fraction exchange observed after separation at time zero

$$= \frac{S_0 - S_{A_0}}{S_\infty - S_{A_0}}$$

Assume that under a given set of exchange and separation conditions a and b are independent of the time of separation, *i. e.*, that the separation-induced exchange and the degree of separation of the reactants are reproducible.

$$S = \frac{aS_A + bS_B}{a + b} \quad (1)$$

$$S_0 = \frac{aS_{A_0} + bS_{B_0}}{a + b} \quad (2)$$

$$S_\infty - S = \frac{aS_\infty + bS_\infty - aS_A - bS_B}{a + b} = \frac{a(S_\infty - S_A) + b(S_\infty - S_B)}{a + b} \quad (3)$$

$$S_\infty - S_0 = \frac{a(S_\infty - S_{A_0}) + b(S_\infty - S_{B_0})}{a + b} \quad (4)$$

$$\frac{S_\infty - S}{S_\infty - S_0} = \frac{a(S_\infty - S_A) + b(S_\infty - S_B)}{a(S_\infty - S_{A_0}) + b(S_\infty - S_{B_0})} \quad (5)$$

From the definition of F

$$1 - F = \frac{S_\infty - S_A}{S_\infty - S_{A_0}} = \frac{S_\infty - S_B}{S_\infty - S_{B_0}} \quad (6)$$

$$(S_\infty - S_A) = (1 - F)(S_\infty - S_{A_0}) \quad (7)$$

$$(S_\infty - S_B) = (1 - F)(S_\infty - S_{B_0}) \quad (8)$$

Substitution of equations 7 and 8 in 5 gives

$$\frac{S_\infty - S}{S_\infty - S_0} = \frac{(1 - F)[a(S_\infty - S_{A_0}) + b(S_\infty - S_{B_0})]}{a(S_\infty - S_{A_0}) + b(S_\infty - S_{B_0})} = 1 - F \quad (9)$$

Therefore

$$F = 1 - \frac{S_\infty - S}{S_\infty - S_0} = \frac{S - S_0}{S_\infty - S_0} \quad (10)$$

Alternatively from the definitions of F' and F_0'

$$1 - F' = \frac{S_\infty - S}{S_\infty - S_{A_0}} \quad (11)$$

$$1 - F_0' = \frac{S_\infty - S_0}{S_\infty - S_{A_0}} \quad (12)$$

$$\frac{1 - F'}{1 - F_0'} = \frac{S_\infty - S}{S_\infty - S_0} = 1 - F \quad (13)$$

$$F = 1 - \frac{1 - F'}{1 - F_0'} = \frac{F' - F_0'}{1 - F_0'} \quad (14)$$

Summary

1. In aqueous perchloric acid solution a slow exchange between Tl(I) and Tl(III) has been observed. The exchange rate in aqueous solutions 0.8 to 3.5 f. $HClO_4$, 0.0 to 0.4 f. $NaNO_3$, 10–25 mf. $TlClO_4$, 5–25 mf. $Tl(ClO_4)_3$, 10 to 50°, and μ adjusted to 3.68 with $NaClO_4$ is well represented by

$$R = [\mathrm{Tl(I)}][\mathrm{Tl(III)}]\left\{k + \frac{k'}{[H^+]} + k''[NO_3^+]\right\}$$

where

$$k = 3.8 \times 10^8\, e^{-17{,}600/RT}\ \mathrm{mole^{-1}\cdot liter\cdot sec.^{-1}}$$

$$k' = 7.9 \times 10^2\, e^{-10{,}300/RT}\ \mathrm{sec.^{-1}}$$

$$k'' = 2.5 \times 10^8\, e^{-16{,}000/RT}\ \mathrm{mole^{-2}\cdot liter^2\cdot sec.^{-1}}$$

2. The presence of platinum black in the exchange solution caused a marked increase in the exchange rate; the presence of finely divided silica gel caused no measurable change in the rate.

3. Four precipitation methods for the separation of Tl(I) and Tl(III) were studied. All caused measurable and reproducible apparent zero-time exchanges due to coprecipitation or separation-induced exchange or both. It was found that separation-induced exchange was the predominant effect for at least two of the methods studied.

4. The following expression is derived which relates F, the fraction exchange that occurs in solution in time t, to F', the observed fraction exchange at time t, and F_0', the observed fraction exchange at time zero (apparent zero-time exchange).

$$F = (F' - F_0')/(1 - F_0')$$

This expression is valid as long as the separation-induced exchange and the degree of separation are reproducible in a given exchange run. The expression has been checked experimentally.

ST. LOUIS 5, MISSOURI RECEIVED NOVEMBER 26, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

A Magnetic Study of Sulfur Vapor[1,2]

BY ALLEN B. SCOTT

By comparison with O_2, it has long been assumed that diatomic sulfur molecules are in the $^3\Sigma$ state and are thus paramagnetic. Neel[3] has measured the susceptibility of sulfur vapor at several temperatures, and, basing his calculation of the concentration of S_2 upon the vapor density measurements of Preuner and Schupp,[4] showed that this assumption was approximately correct, though his value for $\chi_M T$ was about 40% different from the theoretical value, and varied considerably with temperature. He was unable to conclude whether the disagreement was due to error in his magnetic data, error in the vapor equilibrium data, or was really an indication that S_2 was not truly in the triplet state.

An attempt has been made in this Laboratory to reinvestigate the susceptibility of sulfur vapor as a step in elucidating the complex equilibrium among the aggregates in sulfur vapor. If it can be established that S_2 has the theoretical moment of the triplet state, the measurement of susceptibility will then suffice to determine the concentration of S_2 in the presence of higher aggregates. In this paper are reported the results of a determination of the susceptibility of sulfur vapor at several temperatures between 550 and 850° which indicate that S_2 has the correct moment for the triplet state.

Experimental

The method was essentially that used in the measurement of the susceptibility of thermally dissociated iodine vapor.[5] A method for detecting the amount of displacement of the balance beam, consisting of a micro-

(1) The work described in this paper was supported by a grant-in-aid from the Cottrell Fund of the Research Corporation, whose assistance is gratefuly acknowledged. Published with the approval of the Oregon State College Monographs Committee as Research Paper No. 136, Department of Chemistry, School of Science.

(2) Presented before the Division of Physical and Inorganic Chemistry at the San Francisco Meeting of the American Chemical Society, March 28, 1949.

(3) Neel, *Compt. rend.*, **194**, 2035 (1932).

(4) Preuner and Schupp, *Z. physik. Chem.*, **68**, 129 (1909).

(5) Scott and Cromwell, THIS JOURNAL, **70**, 3981 (1948).

metrically adjustable scale in place of the photographic recording device, was found time-saving and gave more consistent results. By means of a micrometer, the scale could be positioned so that the oscillations of the slit image were symmetrical about the scale index, as viewed through a telescope; after applying the field or lifting the calibrating weight, the scale was again positioned and the difference between micrometer readings was proportional to the displacing force.

In practice, it was found that small changes in the location of the bulb in the field caused a significant change in the force of the field upon the bulb. In the previous work with iodine errors due to slight positional changes were overcome by taking a large number of measurements over an extended period of time. In order to save time and eliminate constructively the source of these errors, the height of the bulb was adjusted by always bringing the balance beam to the same initial position by means of a small solenoid acting upon a fine iron wire at the end of the beam opposite the bulb suspension. The current through the solenoid was adjusted manually to bring the slit image to a constant initial scale position; the current was maintained while the field was applied, and the new scale position obtained.

The furnace was made of somewhat larger (19 mm. o.d.) quartz tubing, which necessitated less lagging in order that it could be placed between the magnet poles. The variation in temperature throughout the length of the bulb was 33°. The average temperature was obtained from several measurements along the length of the bulb and was correct within about 5°. The thermocouples used were chromel–alumel, calibrated at the freezing points of C. P. $K_2Cr_2O_7$, KCl, and NaCl.

C. P. sulfur was recrystallized twice from redistilled carbon disulfide and then twice distilled in a stream of nitrogen. At each distillation approximately one-fourth of the original amount was rejected. On the second distillation, the vapor was condensed in the Vycor tube, of 10 mm. i. d., to be used in the magnetic measurements, and the tube was evacuated and sealed. The mass of sulfur contained was determined after the experiments by evaporating all sulfur out of the tip of the bulb, breaking the tip, weighing before and after driving the sulfur out at 500° in the muffle furnace. Two samples were used in the measurement, one of volume 9.90 cc. containing 57.0 mg. S, and the other 9.85 cc. containing 46.7 mg.

The field strength was 8080 oersteds.

The force due to the magnetic field upon the bulb alone was taken as the force on the bulb and contents at room temperature, since the force upon small amounts of solid sulfur condensed in the tips of the bulb in regions of approximately constant field strength is negligible. The temperature independence of susceptibility of the Vycor tubing used was verified by measurements at room temperature and 850° upon an empty bulb. The force upon the empty bulb was, within the average deviation, the same at both temperatures.

Results and Discussion

At 850° and vapor density 5.76 mg./cc., the force of the field upon the sulfur vapor, after correcting for the force due to the bulb, was 1.69 mg. in the direction of paramagnetism. The cross-sectional area of the bulb was 0.785 sq. cm. The calculated volume susceptibility was 6.47×10^{-8} c. g. s. unit. The volume susceptibility due to the diamagnetism of sulfur may be calculated from the mass susceptibility which was assumed to be -0.49×10^{-6} c. g. s. unit; this leads to a diamagnetic volume susceptibility at this density of -2.8×10^{-9} c. g. s. unit. Thus the paramagnetic volume susceptibility, κ, was 6.75×10^{-8} unit.

In the same manner were calculated the susceptibilities at other temperatures and those for the sample of density 4.74 mg./cc. The cross-sectional area of the second bulb was 0.810 sq. cm. These data are tabulated in Table I.

In order to compute the molar susceptibility of S_2, it is necessary to evaluate its partial pressure in the mixed vapor. Preuner and Schupp[2] have determined the equilibrium constants for the reactions

$$S_8 = 4S_2 \quad (1)$$
$$S_6 = 3S_2 \quad (2)$$

at several temperatures, including 550, 650 and 850°, and these constants were used directly. A plot of log κ against $1/T$ from 450 to 850° is very nearly linear in both cases, and the constants at 750°, obtained from the plot, were: (1) $K_{mm.} = 1.5 \times 10^{12}$ and (2) $K_{mm.} = 5.1 \times 10^{7}$. These direct constants differ somewhat from those calculated from the standard free energy equations of Kelley,[6] since his equations are based on the average data in a lower temperature range; however the difference is not of great significance in view of the relatively large probable error in the magnetic measurements.

It must be noted also that the above data were obtained at pressures generally below 1000 mm., while the present work necessitated pressures up to six times as high to obtain sufficient force on the sample. In the absence of thermodynamic data for the vapor species present it is impossible to evaluate what error is introduced by making this extrapolation; however, since the temperatures are high, it is unlikely that the error is of serious consequence. Similarly, it was necessary to assume ideal behavior for the computation of total pressures.

For the case of density 5.76 mg./cc., at 850°, the equilibrium data give the proportion of S_2 in the vapor as 90.2 weight per cent. This leads to a molar paramagnetic susceptibility of 8.3×10^{-4} c. g. s. unit and a Curie constant, $\chi_M T$, of 0.93. Similar results for the other cases are tabulated in Table I. The susceptibilities given are the paramagnetic part only, as in each case the observed volume susceptibility was corrected for the diamagnetism of the entire mass of sulfur present.

TABLE I

PARAMAGNETIC SUSCEPTIBILITY OF S VAPOR

t	Force of field, mg.	$\kappa \times 10^8$	$\chi_M \times 10^4$	$\chi_M \times 10^4$ (theoret.)	$\chi_M T$
		Density, 5.76 mg./cc.			
850	1.69	6.75	8.3	8.83	0.93
750	1.18	4.80	9.3	9.70	0.95
650	0.42	1.9	9.8	10.8	0.91
550	0.11	0.71	14	12.1	
		Density, 4.74 mg./cc.			
850	1.73	6.65	9.6	8.83	1.08
750	0.92	3.63	7.7	9.70	0.79
650	0.35	1.6	8.8	10.8	0.81
550	0.19	0.94	19	12.1	

(6) Kelley, *U. S. Bur. Mines, Bull. No.* **406** (1937).

In Fig. 1 is shown the observed variation of combined paramagnetic and diamagnetic volume susceptibility with temperature, compared to that calculated by the use of the Van Vleck equation, the diamagnetism of sulfur, and the equilibrium constants of Preuner and Schupp.

The relative probable error in the measurements based solely upon the distribution of values of the force of the field upon the sample, as a result of four or five determinations at each temperature, was about 3% at 850° and increased progressively to about 20% at 550° where the force was much smaller. Errors in temperature, field strength, and equilibrium data would increase the relative error at 850° to perhaps 7% but would be swamped by the observational error at the lower temperature. The error in the average $\chi_M T$ (excluding values at 550°) is thus about 10%.

The theory of Van Vleck[7] predicts that the molar susceptibility of molecules in the $^3\Sigma$ state, having small multiplet intervals, is

$$\chi_M = \frac{N\beta^2}{3KT}[4S(S+1)] = \frac{0.993}{T}$$

At 850° this leads to a value of 8.83×10^{-4} unit, in good agreement with the observed average of the two samples, $9.0 \times 10^{-4} \pm 0.6 \times 10^{-4}$. Neel[3] reported 5.4×10^{-4} unit.

The average value of $\chi_M T$, excluding the values at 550°, is 0.91 ± 0.09, compared to the theoretical value of 0.993.

These data serve to show that the ground state of diatomic sulfur is undoubtedly the triplet state, and further that the equilibrium data of Preuner and Schupp predict quite satisfactorily the proportion of S_2 in sulfur vapor between 550 and 850°.

A similar study of the ground state of Se_2 is to be undertaken by this laboratory in the near future.

(7) J. H. Van Vleck, "Electric and Magnetic Susceptibilities, Oxford University Press, Oxford, England, 1932, p. 266.

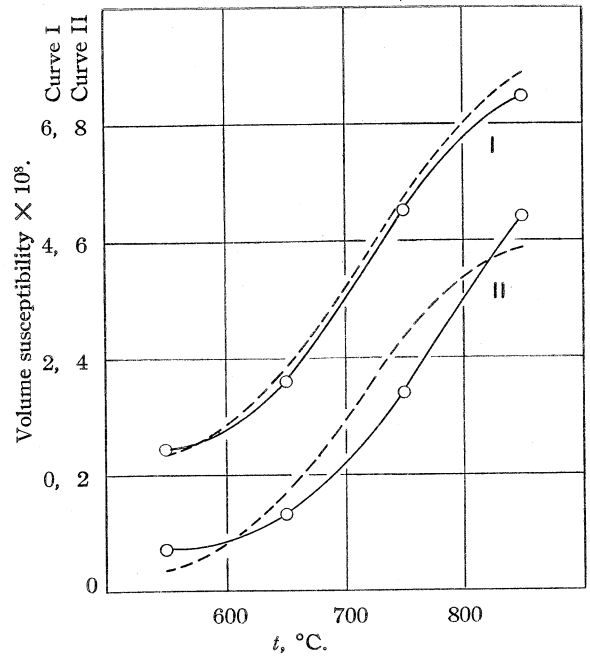

Fig. 1.—Volume susceptibility of S vapor: I, density 5.76 mg./cc.; II, density 4.74 mg./cc.; broken curves, calculated.

Summary

The molar susceptibility of S_2 at temperatures between 550 and 850° has been measured and found to agree with the theoretical value within the limits of experimental error. The existing equilibrium data predict satisfactorily the proportion of S_2 in sulfur vapor between 550 and 850°.

CORVALLIS, OREGON RECEIVED APRIL 21, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

The Solubility of Nitrogen in Carbon Disulfide, Benzene, Normal- and Cyclo-hexane, and in Three Fluorocarbons

BY J. CHR. GJALDBAEK[1] AND J. H. HILDEBRAND

Introduction.—The extraordinary solubility relations of fluorocarbons have been the subject of three recent papers from this Laboratory; Scott[2] assigned figures for the "solubility parameters" needed in order to apply the modern theory of regular solutions, and showed their general consistence with the initially fragmentary data. Benesi and Hildebrand[3] determined the solubility of iodine in perfluoro-*n*-heptane, finding a value which, although only 0.027 of its solubility in normal heptane, is nevertheless consistent with theory. Hildebrand and Cochrane[4] determined liquid–liquid solubility curves for perfluoromethylcyclohexane with five organic liquids and likewise found reasonably good agreement with theory. The most illuminating investigation to undertake next appeared to us to be the solvent powers of these substances for gases. Their exceedingly low solvent power for a substance such as iodine implies high solvent power for gases, but there remained the question

(1) Holder of a scholarship from the Danish Council for applied Science. Home address, Department of Inorganic Chemistry, the Pharmaceutical College of Denmark, Copenhagen.

(2) R. L. Scott, THIS JOURNAL, **70**, 4090 (1948).

(3) H. A. Benesi and J. H. Hildebrand, *ibid.*, **70**, 3978 (1948).

(4) J. H. Hildebrand and D. R. F. Cochrane, *ibid.*, **71**, 22 (1949).

whether the gases, at the one end of the scale, would fit the theory as well as does iodine, at the other.

Since the theory has been derived from a model process in which two pure liquids are mixed, the reference of the activity of a gas to a hypothetical liquid above its critical temperature has made the values for ideal solubility[5] heretofore used rather uncertain. An additional uncertainty is introduced by the large discrepancy between the molal volumes of nitrogen and the solvents, particularly the fluorocarbons.

Apparatus and Procedure.—The apparatus and procedure were approximately those of Lannung.[6] The volume of the gas buret was 7 cc., that of the flask, 55 cc. The temperature of the air thermostat was constant within 0.05° in the range 25–50° and within 0.1° at the lowest temperatures, which were in the neighborhood of 2°.

Materials.—The nitrogen was from Stuart Oxygen Co. (99.996% N_2). The three fluorocarbons, from E. I. du Pont Co., were fractionated by distilling in a Vigreux column and the middle portions used showed the following boiling points: perfluoro-*n*-heptane (C_7F_{16}) 82.3–82.4° (753.7 mm.), perfluoromethylcyclohexane (C_8F_{14}) 76.5–76.6° (760.0 mm) and perfluorodimethylcyclohexane (C_8F_{16}) 102.4–102.6° (760.0 mm.). Carbon disulfide ("analytical reagent") by Mallinckrodt showed a negative test for polysulfides and a fraction was used boiling at 45.80–45.85° (750.1). *n*-Hexane ("research grade") by Phillips Petroleum Company was used without further treatment. Cyclohexane by Paragon Testing Laboratories was fractionated by distillation and a portion with boiling point 80.63–80.66° (755.7 mm.) was taken. The benzene was that used by Benesi and Hildebrand.[3]

It is necessary to know the vapor pressure of the solvent in each experiment in order to calculate the solubility of the solute gas at a partial pressure of one atmosphere. For the three fluorocarbons we used the values given by Fowler and co-workers.[7] Their values for perfluoro-*n*-heptane are in good agreement with those of Barber.[8] For the other solvents, we used the values given in "International Critical Tables."

The densities of perfluoro-*n*-heptane were those of Grosse and Cady[9]; for perfluoromethylcyclohexane we determined $d^{25.0}$ 1.7859, and for perfluorodimethylcyclohexane $d^{25.0}$ 1.8400, $d^{35.1}$ 1.8126 and $d^{46.8}$ 1.7834. The other densities needed were taken from the "International Critical Tables."

(5) J. H. Hildebrand and R. L. Scott, "Solubility of Non-electrolytes," third edition, Reinhold Publ. Corp., New York, N. Y., 1949.

(6) A. Lannung, *Det Kgl. Danske Vidensk. Selskab. Mat.-fys. Medd.*, **XX**, no. 3 (1942).

(7) R. D. Fowler, J. M. Hamilton, J. S. Kasper, C. E. Weber, W. B. Burford and H. C. Anderson, *Ind. Eng. Chem.*, **39**, 375 (1947).

(8) J. Barber, Thesis, University of Washington, 1948.

(9) A. V. Grosse and G. H. Cady, *Ind. Eng. Chem.*, **39**, 367 (1947).

Results.—The results are expressed in Table I in terms of the Bunsen absorption coefficient, $\alpha = 760\ V^g/pV^l$; V^g referring to the volume of the gas measured at the temperature of the experiment in the volume, V^l that of the solvent. Pressure is in mm. mercury. An example of the calculation is given in detail in an earlier paper.[10] The table gives, also, values of x_2, the mole fraction of the dissolved gas, at 0, 25, and 50°, derived from the observed values.

TABLE I

SOLUBILITIES OF NITROGEN EXPRESSED IN BUNSEN ADSORPTION COEFFICIENT, α, AND MOLE FRACTION, x_2

Solvent	t, °C.	α	Interpolated or extrapolated value: t, °C.	α	$x_2 \cdot 10^4$
	1.98	0.406 (1)[a]	0	0.411	40.1
	2.13	.409 (1)			
	2.45	.404 (2)			
	4.10	.406 (1)			
C_7F_{16}	24.90	.384 (2)	25	.385	39.1
	24.97	.387 (1)			
	46.91	.362 (2)			
	48.60	.362 (1)	50	.360	38.0
C_7F_{14}	24.90	.371 (1)			
	25.00	.384 (2)	25	.375	31.8
	25.00	.324 (1)			
C_8F_{16}	25.00	.329 (2)	25	.328	33.0
	37.97	.330 (2)			
	40.52	.319 (1)			
	47.10	.319 (2)	50	.317	31.9
	24.95	.239 (2)			
n-C_6H_{14}	24.95	.241 (2)	25	.239	14.0
	25.30	.237 (1)			
	24.98	.156 (1)			
c-C_6H_{12}	24.98	.155 (2)	25	.156	7.55
C_6H_6	25.0	.124 (1)	25	.124	4.48
CS_2	24.89	.0822 (2)			
	24.96	.0823 (1)	25	.0823	2.23

[a] (1) indicates that the experiment was performed from the same charge of solvent and gas; (2) indicates experiments with a new charge.

Guerry[11] reported $\alpha = 0.213$ for nitrogen in *n*-hexane at 25° and 0.149 in cyclohexane, both lower than our values. Just[12] reported $\alpha = 0.0526$ for its solubility in carbon disulfide, much lower than our figure. These redeterminations were made because of gross discrepancies[5] for other gases between Guerry and McDaniel, on the one hand, and Just and Horiuti,[13] on the other. One may infer from a comprehensive survey of the data on gas solubilities that all the results published by McDaniel and by Just are somewhat low, due possibly to insufficient degassing of solvents. Our figure for benzene, $\alpha = 0.124$, agrees well with the one found by Horiuti, 0.121.

(10) J. Chr. Gjaldbaek, *Det Kgl. Danske Vidensk. Selskab. Matt.-fys. Medd.*, **XX**, no. 3 (1942).

(11) D. Guerry, Thesis, Vanderbilt University, 1944.

(12) G. Just, *Z. physik. Chem.*, **37**, 342 (1901).

(13) J. Horiuti, *Sci. Papers, Inst. phys.-chem. Research, Tokio*, **17**, no. 341, 125 (1931).

Correlation with Theory.—The senior author[14] pointed out, in 1916, that Raoult's law, $p = p^0x = 1$ atmosphere, could be used to define an "ideal" gas solubility, even above the critical temperature of the gas, by obtaining a fictitious value for p^0 by plotting log p *vs.* $1/T$ for the vapor pressure of the gas. This gives a practically straight line right up to the critical point,[5] and its extrapolation to still higher temperatures yields values of p/p^0 which are close to the measured solubilities of gases in solvents of low internal pressure such as hexane. He showed, further, that the solubility falls off regularly with increasing internal pressure of the solvent. We had long ago obtained in this way, for nitrogen $p^0 = 1000$ atmospheres and $x^i = 0.0010$ when $p = 1$ atmosphere, while Guerry reported 0.00125 in *n*-hexane.

In order to take into account the different internal pressures of the solvents, we may use the equation[15]

$$-\ln x_2 = -\ln x_2^i + (\bar{v}_2/RT)(\delta_1 - \delta_2)^2 \qquad (1)$$

where the subscript 2 now refers to the solute gas and subscript 1 to the solvent, and the δ's are "solubility parameters," defined, for liquid components, as the square roots of their energy of vaporization per cc. The senior author[16] found that an equation of this type, with a semi-empirical adjustment of parameters, could account well for the solubilities of argon, and Gonikberg[17,5] applied it successfully to the solubilities of hydrogen.

When pure normal liquids are mixed, the expansion is ordinarily very small, and we can set $\bar{v}_2 = v_2$ with but little error. In the case of nitrogen solutions at 25° we have no pure liquid volume but we can use the values of $\bar{v}_2$ determined by Horiuti,[13,5] who found 53 cc. per mole in both benzene and carbon tetrachloride, and values not significantly different from 53 in other solvents. Although ideally one would wish to calculate solubility from the properties of the pure components, the values obtained by Horiuti for all the gases in this class can be used in combination with the other necessary data for the practical task of calculating the solubilities of these gases in new solvents. The proper value of δ_2 to use for nitrogen solutions can best be determined, for practical purposes, from the data themselves, but if we adjust one uncertain parameter in order to fit the data we might as well adjust another also. It is possible to use $x_2^i = 10^{-3}$ and $\bar{v}_2 = 53$ cc. and to select empirically a value for δ_2 which permits the calculation of solubilities agreeing rather well with the measured ones in all solvents except the fluorocarbons, where the calculated values are definitely too small. This suggests introducing a correction of the Flory–Huggins[18] type based upon the ratio of molal volumes, which alters Eqn. 1 to

$$-\log x_2 = -\log x_2^i + \log(\bar{v}_2/v_1) + 0.434(1 - \bar{v}_2/v_1) + \bar{v}_2(\delta_1 - \delta_2)^2/4.575T \qquad (2)$$

We have set $x_2^i = 1.6 \times 10^{-3}$, $\bar{v}_2 = 53$ cc., and $\delta_2 = 5.2$ to obtain the calculated values of solubility given in the fourth column of figures in Table II.

TABLE II

SOLUBILITY OF NITROGEN, 25°, 1 ATM., COMPARISON OF OBSERVED AND CALCULATED VALUES

			$-\log x_2$				
Solvent	v_1, cc.	δ_1	Meas.	Calcd. Eqn. 2	Δ_2	Calcd. Eqn. 1[a]	Δ_1
n-C_7F_{16}	227	5.9	2.41	2.52	+0.11	2.72	+0.31
C_7F_{14}	196	6.0	2.48	2.57	+ .09	2.73	+ .25
C_8F_{16}	217	6.1	2.50	2.54	+ .04	2.73	+ .23
n-C_6H_{14}	132	7.3	2.85	2.83	− .02	2.87	+ .02
$(C_2H_5)_2O$	105	7.45	2.90[13]	2.91	+ .01	2.90	.00
c-C_6H_{12}	109	8.2	3.12	3.06	− .06	3.05	− .07
CCl_4	97	8.6	3.19[13]	3.18	− .01	3.15	− .04
m-$C_6H_4(CH_3)_2$	123	8.9	3.21[12]	3.18	− .03	3.31	+ .10
$CHCl_3$	81	9.0	3.35[12]	3.32	− .03	3.26	− .09
C_6H_6	89	9.15	3.35	3.35	.00	3.31	− .04
C_6H_5Cl	102	9.5	3.36[13]	3.43	+ .07	3.42	+ .06
CS_2	60	10.0	3.65	3.69	+ .04	3.60	− .05

[a] With $-\log x_2^i = 2.70$.

The differences, Δ_2, between calculated and experimental values in the next column, give an idea of the errors involved. Going from C_7F_{16} to CS_2, the value of $\log \bar{v}_2 - \log v_1 + 0.434(1 - \bar{v}_2/v_1)$ increases from −0.30 to 0.00 while the value of $\bar{v}_2(\delta_1 - \delta_1)^2/4.575T$ increases from 0.02 to 0.90. We see that Eqn. 2 accounts for solubilities greater than the ideal value in liquids with large v_1, and for solubilities less than the ideal value in liquids with large δ_1, while Eqn. 1 is only able to account for solubilities less than the ideal value since the term $\bar{v}_2(\delta_1 - \delta_2)^2/4.575\,T$, is always positive. The degree of agreement yielded by this equation with "best" values of the parameters is shown in the last two columns of Table II. A few polar but not associated liquids are included in Table II.

From a practical standpoint, the solubility of any of the super-critical gases can now be approximately predicted in any new non-polar solvent from the δ-value of the latter by simple interpolation with known solvents, since we are in possession of data for all of these gases in a series of solvents. It will be seen that the order of the measured solubilities in Table II closely follows the δ-values of the solvents. It is obvious, nevertheless, from the data in this paper, that there is much room for refinement in the present theory of gas solubility.

We may note that, having measured the solubility of nitrogen in two of the solvents at more

(14) J. H. Hildebrand, THIS JOURNAL, **38**, 1452 (1916); **42**, 1067 (1919); also, N. W. Taylor and J. H. Hildebrand, *ibid.*, **45**, 682 (1923).

(15) For the history of this equation see ref. 5, Chapter VII.

(16) J. H. Hildebrand, "Solubility of Non-electrolytes," 3rd edition, Reinhold Publ. Corp., New York, N. Y., 1936, p. 135.

(17) M. G. Gonikberg, *J. Phys. Chem., USSR*, **14**, 582 (1940).

(18) For an account of this development, see ref. 5, also, J. H. Hildebrand, *J. Chem. Phys.*, **15**, 225 (1947).

than one temperature, we are in a position to calculate the heat of solution of nitrogen in these solvents by the aid of the relation

$$\left(\frac{\partial \ln x_2}{\partial T}\right)_{p_2} = -\left(\frac{\partial \ln x_2}{\partial \ln p_2}\right)_T \left(\frac{\partial \ln p_2}{\partial T}\right)_{x_2} = \frac{-\bar{H}_2}{RT^2}$$

since the nitrogen obeys Henry's law in these very dilute solutions and therefore $(\partial \ln x_2/\partial \ln p_2)_T = 1$. The values in Table I yield $\bar{H}_2 = -140$ cal. in perfluoro-*n*-heptane and -260 cal. in perfluorodimethylcyclohexane. These values are small and obviously subject to considerable percentage error.

A few remarks may be added concerning the point mentioned above, that of stretching a theory based upon mixing liquids to cover the solubility of a gas above its critical temperature. First it would be quite possible to go back to an early step in the derivation of Eqn. 1 where the potential energy of a liquid mixture relative to its two gaseous components is expressed in terms of the liquid structure, and to subtract therefrom only the potential energy of the pure liquid solvent, which would give an expression for the partial molal energy of the solution of the gas. Its free energy of solution at the equilibrium pressure and composition is of course zero. If we had a satisfactory expression for the entropy of solution of the gaseous component, the problem would be solved, but unfortunately we have not been able to express the entropy of this process as satisfactorily as we have the entropy of mixing two liquids to form a regular solution.

Acknowledgment.—We express our gratitude to Dr. J. M. Tinker, Director of the Jackson Laboratory, E. I. du Pont de Nemours Co., for the substituted perfluoro-cyclohexanes used in this research, and to the Office of Naval Research for financial support.

Summary

1. Values for the solubility of nitrogen have been determined, expressed as Bunsen coefficient. In *n*-perfluoroheptane, 0°, 0.411; 25°, 0.385; 50°, 0.360; perfluoromethylcyclohexane, 25°, 0.375; perfluorodimethylcyclohexane, 25°, 0.328; 50°, 0.317; *n*-hexane, 25°, 0.239; cyclohexane, 25°, 0.156; benzene, 25°, 0.124; carbon disulfide, 25°, 0.0823.

The above data are tabulated with existing data for six other solvents and it is shown that the order of solubility, expressed as mole fraction, closely parallels the order of the "solubility parameters," defined as the square roots of their energies of vaporization per cc.

3. The solubility equation for regular solutions, with a semiempirical adjustment of its parameters, yields calculated values in fair agreement with the experimental ones, except in the case of the fluorocarbons, where the experimental values are larger. This discrepancy is attributed to the unusually large molal volumes of these solvents because it is considerably reduced by introducing a correction of the Flory–Huggins type.

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Ultraviolet Absorption Study of the Ionization of Substituted Phenols in Ethanol

BY NORMAN D. COGGESHALL AND ALVIN S. GLESSNER, JR.

It is well known that the ultraviolet absorption spectra for the anions or cations of many polar substituted aromatic materials are markedly different from the spectra obtained for the compounds themselves. The spectra of the ions generally exhibit a large bathochromic shift of the absorption ascribed to the phenyl ring chromophore. In addition the intensity of absorption is increased. Since the spectral shift is large, often of the order of 20 mμ or larger, it provides a method whereby dissociation constants may be determined. Ordinarily these cannot be calculated from the spectrophotometric data alone but depend also on separately determined values of *p*H or on previously determined equilibrium constants which are pertinent to the processes involved.

In this manner Stendstrom and co-workers[1,2] demonstrated that the shift of the phenol spectrum induced by the addition of sodium hydroxide is due to the creation of the phenolate ions. From their data they obtained a value of the dissociation constant for phenol. Using the same procedure, Flexser, Hammett and Dingwall[3] calculated the ionization constants for benzoic acid, 2,4-dinitrophenol and acetophenone. More recently Ewing and Steck[4] have utilized this phenomenon in studies of the acidic and basic properties of quinolinols and isoquinolinols. Similar studies were made of various 4-aminoquinolines by Irvin and Irvin.[5]

The present studies are of the substituted phenols. The substituted phenols may be divided into three classes according to their steric hindrance to inter-molecular hydrogen bonding.[6] Phenols with the ortho positions either unsubsti-

(1) W. Stendstrom and M. Reinhard, *J. Phys. Chem.*, **29**, 1477 (1925).

(2) W. Stendstrom and N. Goldsmith, *ibid.*, **30**, 1683 (1926).

(3) L. A. Flexser, L. P. Hammett and A. Dingwall, THIS JOURNAL, **57**, 2103 (1935).

(4) G. W. Ewing and E. A. Steck, *ibid.*, **68**, 2181 (1946).

(5) J. L. Irvin and E. M. Irvin, *ibid.*, **69**, 1091 (1947).

(6) N. D. Coggeshall, *ibid.*, **69**, 1620 (1947).

tuted or occupied by a small group such as a methyl are known as unhindered phenols. Those with one ortho position occupied by a large group such as a *t*-butyl and the other either unsubstituted or occupied by a small group are known as partially hindered phenols. Those with both ortho positions occupied by large groups are known as the hindered phenols. It is well known that the same type of hindrance that influences intermolecular hydrogen bonding is effective in hindering intermolecular association effects which influence the ultraviolet absorption spectra of the phenols.[7] The hindered phenols, for example, exhibit quite small spectral changes between examination in paraffin and in polar solvents such as ethanol whereas large changes are observed for the unhindered and partially hindered phenols. The differences have been interpreted as due to the different degrees of proximity possible between the hydroxyl groups of the phenols and the polar groups of the solvent.

In view of the above results it is to be expected that the behavior of the various phenols in a solvent containing a strong base such as sodium hydroxide will vary in accordance with the steric hindrance of the above type. Since the formation of a phenolate ion involves the removal of the hydrogen nucleus from the hydroxyl group any shielding such as offered by large groups on the ortho positions would be expected to be effective in reducing the ionization. It is important to evaluate such effects not only as a method of determining the relative acidity of the various phenols, but also in order to provide information pertinent to a detailed consideration of the ionization processes in the liquid phase. The present report is of a study of the ultraviolet absorption spectra of a series of substituted phenols in ethanol and in ethanol containing sodium hydroxide. The data are interpreted in terms of the influence of steric hindrance on the ionization.

Experimental

All of the absorption spectra were obtained with the use of a Beckman Quartz Spectrophotometer equipped for work in the ultraviolet. In some of the preliminary investigations a study was made of the dependence of spectral changes on temperature. For this the temperature controlled absorption cell compartment previously described[7] was used. A Precision Scientific Company constant temperature bath was employed to provide the water used to regulate the temperature of this compartment.

With the exception of the simpler ones, the substituted phenols studied were prepared in this Laboratory.[8,9] There was evidence that each compound used was at least 99% pure. Such other chemicals as were used were the best available commercially and were, when necessary, further purified by recrystallization. Absolute ethanol was used as the solvent in all cases. Effects due to benzene in the ethanol were eliminated by using the same solvent in the comparison cell as used in the sample cell.

In these studies the ethanol solutions containing hydroxyl ions were prepared by the use of aqueous solutions containing one mole/liter or more of sodium hydroxide or of other bases. Solutions containing other inorganic materials were prepared in the same general manner. In every case the reference cell was filled with the same combination solvent as used for the particular phenol being investigated. In this manner any errors or discrepancies which might have been introduced through impurities in the sodium hydroxide or other inorganic material were avoided.

Data and Discussion

Preliminary Experiments.—In examining the literature on the subject of changes of ultraviolet absorption spectra of polar substituted aromatics induced by addition of specific types of ions in the solvent, it was apparent that sufficient proof that the shifted spectra are due to ionized solute was lacking. It was desirable to obtain further data to verify that this explanation is correct and the effect is not due to intermolecular effects such as hydrogen bonding or the formation of transient complexes between neutral molecules and ions. For that reason a number of experiments were performed on phenols in ethanol containing various inorganic materials. The fact that the present work was done with ethanol as the solvent instead of water, as was the case for most of the previous work, made it further desirable that such experiments be done. This was to verify that the processes were the same for the two solvents.

p-Cresol was examined in solutions containing the bases sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, and ammonium hydroxide. The same spectral shift was observed in every case although with differences in degree of ionization. For a concentration of 3×10^{-4} mole/liter of *p*-cresol in solution a concentration of about 12 moles/liter of the weak base ammonium hydroxide was required for complete ionization whereas for lithium, sodium and potassium hydroxides, concentrations of less than one tenth mole/liter were sufficient. These data confirm previous work, but do not rule out the possibilities of complexes being responsible for the shift. Hence to determine if the phenomenon depended specifically upon the addition of hydroxyl ions data were obtained for *p*-cresol in solutions containing sodium chloride and hydrogen chloride. The resulting spectra were virtually indistinguishable from the spectrum obtained with pure ethanol as the solvent. Next a reversal procedure was tested on several phenols. In this the spectra were shifted by the addition of sodium hydroxide and then brought back to that observed

(7) N. D. Coggeshall and E. M. Lang, *ibid.*, **70**, 3283 (1948).
(8) D. R. Stevens, *Ind. Eng. Chem.*, **35**, 655 (1943).
(9) G. H. Stillson, D. W. Sawyer and C. K. Hunt, THIS JOURNAL, **67**, 303 (1945).

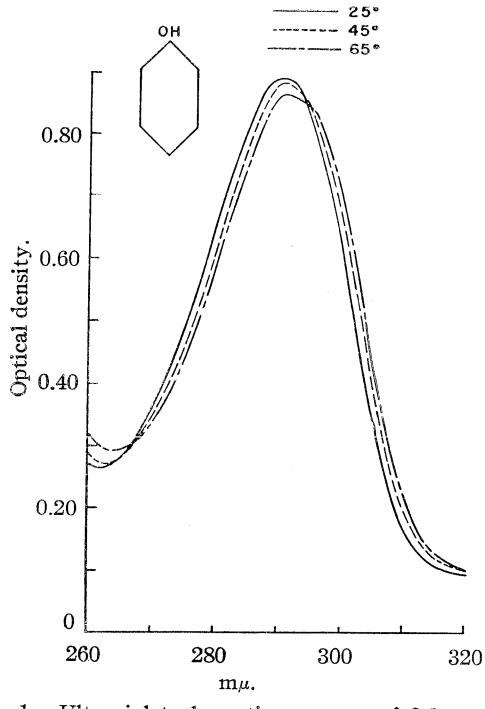


Fig. 1.—Ultraviolet absorption spectra of 2.8×10^{-4} mole/liter of phenol at various temperatures in ethanol containing 1.0×10^{-1} mole/liter of sodium hydroxide.

for pure ethanol solvent by the addition of hydrogen chloride to the same solutions. A complete reversal was achieved for each of the phenols tested, namely, *p*-cresol, 2-methyl-4,6-di-*t*-butylphenol and 2,4,6-tri-*t*-butylphenol.

nol and dioxane in a carbon tetrachloride solution is very strongly reduced by an increase of temperature from 20 to 55°. It would be expected that the energy per intermolecular hydrogen bond or complex between a phenol molecule and an ion would be of the same order of magnitude as for the complexes studied by Errera and Sack. Therefore, if the spectral shift considered here were due to such effects we would get at least a partial reversion to that observed for the ethanol solution when the temperature was elevated. In Fig. 1 may be seen the results for such a test on 2.8×10^{-4} mole/liter of phenol in an ethanol solution containing one-tenth mole/liter of sodium hydroxide. Here the optical density is plotted *versus* wave length. The optical density D is defined by $D = \log I_0/I$, where I_0 and I are the incident and transmitted energies, respectively. It may be seen that the rise in temperature to 65° produces only a very minor change and it is in the opposite direction to that which would be expected if the spectral changes were due to intermolecular effects. The same results were also obtained for 2-methyl-4,6-di-*t*-butylphenol and for 2,6-di-*t*-butyl-4-ethyl phenol. The preliminary experiments therefore all definitely confirm the ionization explanation for the spectral shift observed for the phenols.

Unhindered Phenols.—In Fig. 2 may be seen the data for three of the unhindered phenols examined. Here are given the spectra for the materials in pure ethanol and in ethanol containing one-tenth mole/liter of sodium hydroxide. The concentration of absorbing material is about the same in each case being 2.5×10^{-4} mole/liter for the *p*-*t*-butylphenol, 2.0×10^{-4} mole/liter for

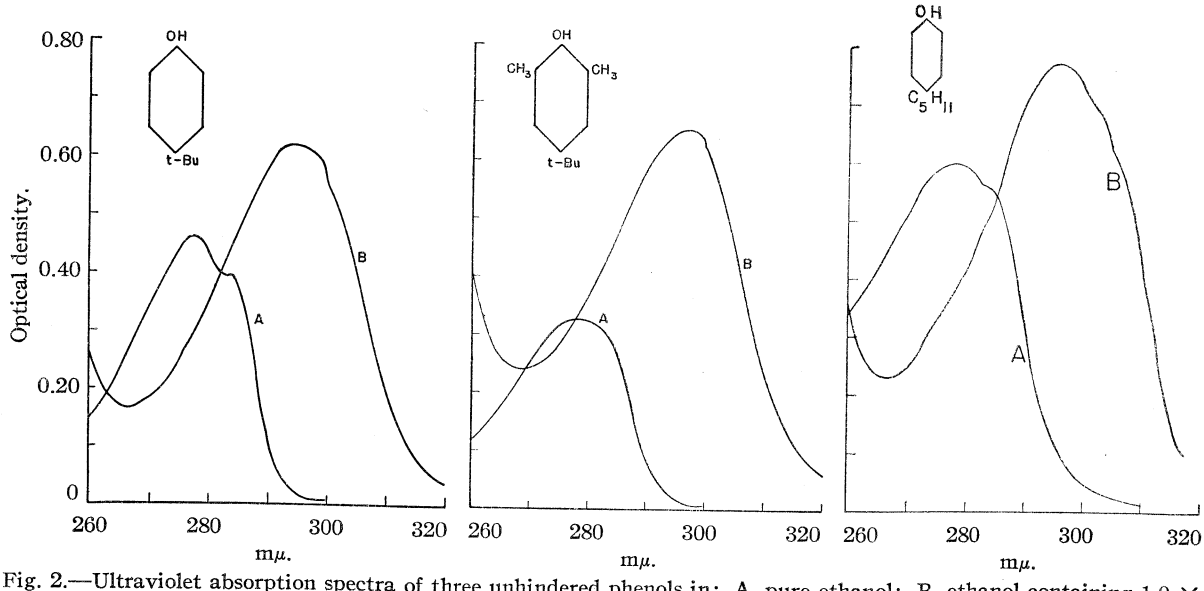


Fig. 2.—Ultraviolet absorption spectra of three unhindered phenols in: A, pure ethanol; B, ethanol containing 1.0×10^{-1} mole/liter of sodium hydroxide.

Errera and Sack[10] have shown that the population of intermolecular complexes between etha-

the 2,6-dimethyl-4-*t*-butylphenol, and 2.0×10^{-4} mole/liter for the *p*-*t*-amylphenol. It is to be noted that in each case there is a complete spectral

(10) J. Errera and H. Sack, *Trans. Faraday Soc.*, **34**, 728 (1938).

shift. By this is meant that the spectra observed for the solutions containing sodium hydroxide show no evidence for any un-ionized phenol molecules, *i. e.*, no maxima at the wave lengths at which the maxima occur for the compounds in pure ethanol solutions.

For solutions containing lower concentrations of sodium hydroxide two absorption maxima are observed, one representing the un-ionized phenol molecules, and one representing the phenolate ions. For the unhindered phenols a sodium hydroxide concentration of less than 1.0×10^{-1} mole/liter is sufficient to produce the complete spectral shift. However, as will be discussed below, the concentrations of sodium hydroxide at which the shifts become apparently complete were not determined as there are difficulties in utilizing these data in a quantitative manner. The sodium hydroxide concentration of 1.0×10^{-1} mole/liter was chosen as a convenient reference for comparison between the different classes of phenols. In Table I may be seen the wave lengths of maximum absorption for the various unhindered phenols in pure ethanol and in ethanol plus 1.0×10^{-1} mole/liter of sodium hydroxide. The spectral shift $\Delta(1/\lambda)$, calculated from these wave lengths, is also given. As the absorption bands are broad the maxima are only given to the nearest mμ. The values of $\Delta(1/\lambda)$ are therefore only reliable to two significant figures.

TABLE I

WAVE LENGTHS OF MAXIMUM ABSORPTION FOR UNHINDERED PHENOLS IN ETHANOL AND ETHANOL PLUS SODIUM HYDROXIDE AND $\Delta(1/\lambda)$ VALUES

Compound	λ max. (mμ) (ethanol)	λ max. (mμ) (ethanol plus NaOH)	$\Delta(1/\lambda)$ cm.$^{-1}$
p-Cresol	280	299	2200
p-*t*-Butylphenol	278	294	2000
p-*t*-Amylphenol	278	295	2100
m-Cresol	274	291	2100
o-Cresol	274	291	2100
2,6-Di-methyl-4-*t*-butylphenol	278	297	2300
	Average value of $\Delta(1/\lambda)$ =		2100

Partially Hindered Phenols.—In Fig. 3 may be seen the behavior of three partially hindered phenols. The concentrations were: 1.5×10^{-4} mole/liter of 2-methyl-4,6-di-*t*-butylphenol, 1.7×10^{-4} mole/liter of 2,4-di-*t*-butylphenol, and 2.0×10^{-4} mole/liter of 2-*t*-butyl-4-methylphenol. It is immediately evident that a concentration of 1.0×10^{-1} mole/liter of sodium hydroxide which produced a complete spectral shift for the unhindered phenols, produces only a partial shift in the present cases. This is evident from the fact that the B curves all show maxima representative of the un-ionized material. In each case it is seen that these maxima are shifted to the red as compared to the maxima for the A curves. This is believed to be the result of an actual change in the absorption frequencies of the un-ionized material and of the geometrical superposition of the independent effects of the ionized and un-ionized materials. The latter effect was confirmed in a number of cases by the numerical construction of such intermediate curves. This was done by making suitable combinations of the data for the case of ethanol alone and the data for the 5.0×10^{-1} mole/liter of sodium hydroxide solutions wherein complete shifts were exhibited. The concentration of 5.0×10^{-1} mole/liter was somewhat more than necessary to produce the complete spectral shift, but was chosen as a convenient reference for comparisons between the various classes of phenols. In Table II are the values of the absorption maxima and of the $\Delta(1/\lambda)$'s.

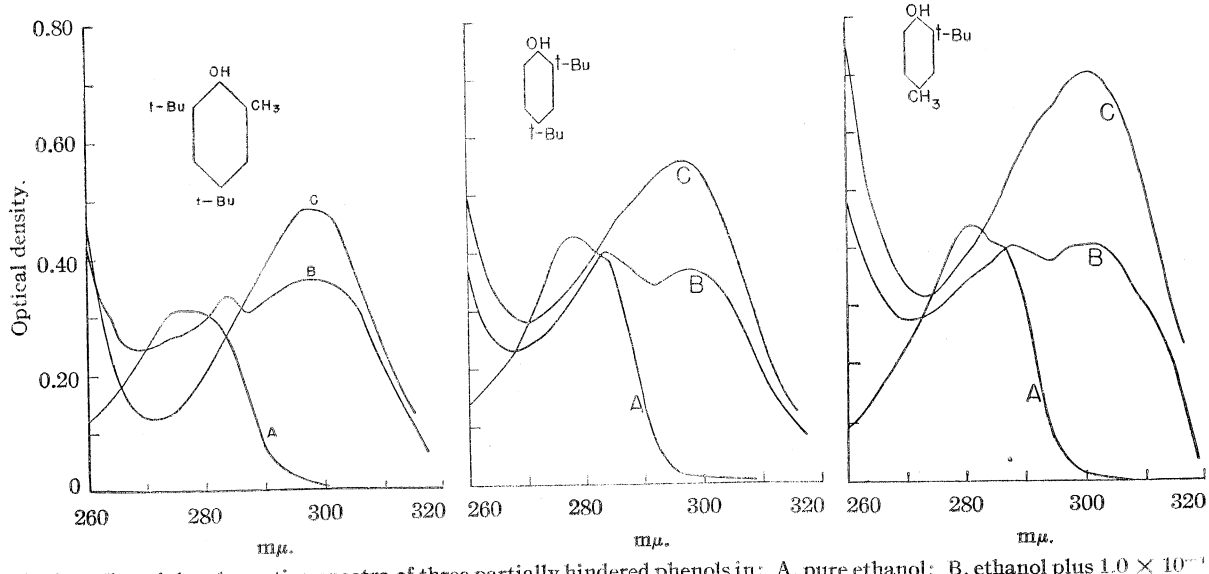


Fig. 3.—Ultraviolet absorption spectra of three partially hindered phenols in: A, pure ethanol: B, ethanol plus 1.0×10^{-1} mole/liter of sodium hydroxide, and C, ethanol plus 5.0×10^{-1} mole/liter of sodium hydroxide.

TABLE II

WAVE LENGTHS OF MAXIMUM ABSORPTION FOR PARTIALLY HINDERED PHENOLS IN ETHANOL AND ETHANOL PLUS SODIUM HYDROXIDE AND $\Delta(1/\lambda)$ VALUES

Compound	λ max. (mμ) (ethanol)	λ max. (mμ) (ethanol + NaOH)	$\Delta(1/\lambda)$ cm.$^{-1}$
2-Methyl-4,6-di-*t*-butylphenol	277	298	2500
2-*t*-Butyl-4-methylphenol	281	301	2300
2,4-Di-*t*-butylphenol	278	297	2300
3-Methyl-6-*t*-butylphenol	276	294	2200

Average value of $\Delta(1/\lambda)$ = 2300

Hindered Phenols.—In Fig. 4 may be seen the data for three hindered phenols. In each case the concentration of the phenol is approximately 1.7×10^{-4} mole/liter. It may be seen that a sodium hydroxide concentration of 1.0×10^{-1} mole/liter produces only minor spectral changes and that a concentration of 5.0×10^{-1} mole/liter which produces a complete shift for the partially hindered phenols is responsible here for only a partial shift. In the D curves are given the spectra for the phenols in the presence of 5.0 mole/liter of sodium hydroxide. Even this concentration does not produce a complete ionization.

TABLE III

WAVE LENGTHS OF MAXIMUM ABSORPTION FOR HINDERED PHENOLS IN ETHANOL AND ETHANOL PLUS SODIUM HYDROXIDE AND $\Delta(1/\lambda)$ VALUES

Compound	λ max. (mμ) (ethanol)	λ max. (mμ) (ethanol + NaOH)	$\Delta(1/\lambda)$ cm.$^{-1}$
2,6-Di-*t*-butyl-4-methylphenol	277	303	3100
2,6-Di-*t*-butyl-4-cyclohexylphenol	275	300	3100
2,4,6-Tri-*t*-butylphenol	275	302	3300
2,6-Di-*t*-butyl-4-ethylphenol	276	303	3200
2,6-Di-*t*-butyl-4-phenylphenol	266	302	4500

Average value of $\Delta(1/\lambda)$ = 3400

Discussion.—It is obvious from the data given in the figures that great differences exist between the three classes of phenols as regards their ease of ionization in ethanol solution. These differences are ascribed to the steric hindering effects of the large ortho substituents. Although one-tenth mole/liter of sodium hydroxide was sufficient to achieve complete ionization for the unhindered phenols it resulted in only partial ionization of the partially hindered phenols. A sodium hydroxide concentration of 5.0×10^{-1} mole/liter was sufficient to produce complete

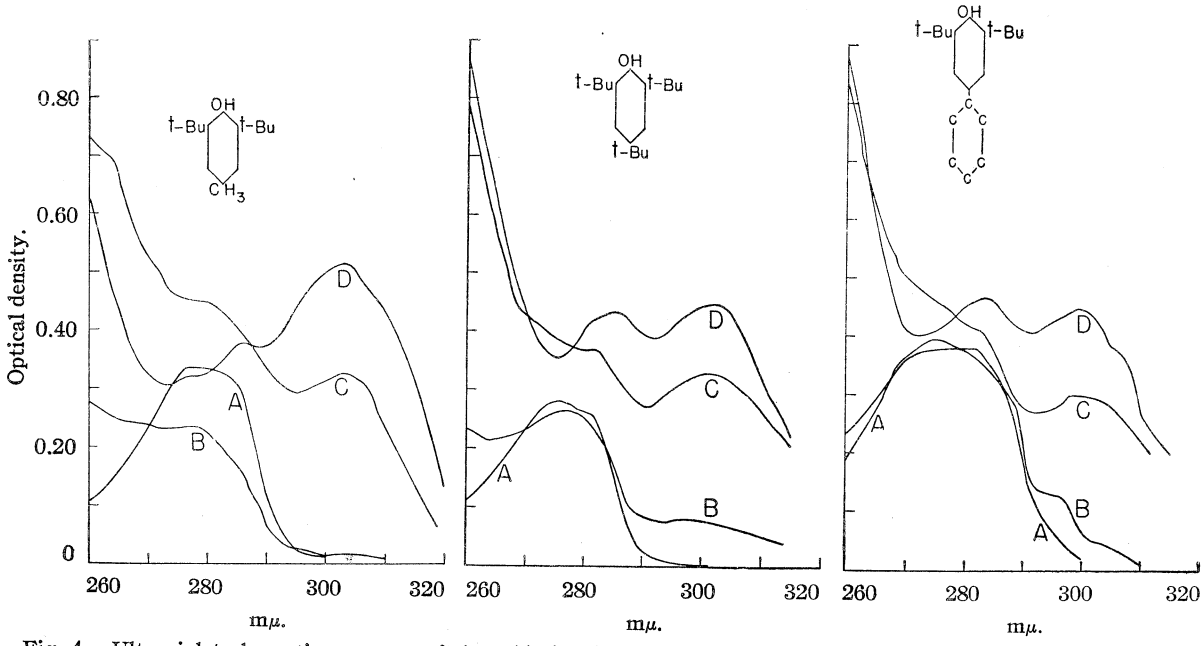


Fig. 4.—Ultraviolet absorption spectra of three hindered phenols in: A, pure ethanol; B, ethanol plus 1.0×10^{-1} mole/liter of sodium hydroxide; C, ethanol plus 5.0×10^{-1} mole/liter of sodium hydroxide, and D, ethanol plus 5.0 mole/liter of sodium hydroxide.

With the dilution scheme used it was impossible to go over about 5.0 mole/liter of sodium hydroxide due to the precipitation of sodium hydroxide. Hence the complete ionization of the unhindered phenols cannot be achieved in this manner. In Table III may be seen the wave lengths of maximum absorption and the $\Delta(1/\lambda)$ values.

ionization for the latter compounds but definitely only produced a partial ionization of the hindered phenols. In addition the hindered phenols were not completely ionized by as much as 5.0 mole/liter of sodium hydroxide. This positively establishes the role of the large ortho groups in hindering the ionization.

There is a very interesting implication in the above data regarding the processes of ionization. The data show that the large groups on the ortho position sterically hinder the ionization. They are large in spatial extension and therefore shield the phenolic hydroxyl group from close approach by other molecules or ions. Since they also hinder the ionization, we may therefore assume that the ionization process is a result of a close approach or collision between a phenolic hydroxyl group and other molecules or ions. With this assumption the primary factors affecting ionization are the details of geometry and electric fields of the molecules and ions involved rather than gross dielectric properties.

It is evident from the data in the tables that there is a further difference between the spectral behavior of the phenols. The difference in frequency of maximum absorption $\Delta(1/\lambda)$ between the molecules and the phenolate ion is in each case expressed in wave numbers. This provides a measure of the differences of transition energies between the ground and first excited electronic states. As was stated above the wave lengths of maximum absorption are only reliable to about 1 mμ. Hence the $\Delta(1/\lambda)$ values are reliable to only two significant figures. Despite this limitation it is clear that a definite difference exists between the unhindered and partially hindered phenols. For the former the average value of $\Delta(1/\lambda)$ was 2100 cm.$^{-1}$, whereas it was 2300 cm.$^{-1}$ for the latter. This implies that the size of the ortho substituent affects the transition energy for the phenolate ion. This implication is further confirmed by a comparison between the partially hindered and the hindered phenols. The average value of $\Delta(1/\lambda)$ for the latter was 3200 cm.$^{-1}$, excluding a consideration of 2,6-di-*t*-butyl-4-phenylphenol. This compound has an anomalously high $\Delta(1/\lambda)$ value presumably due to some effect of the conjugation of the phenyl rings.

The data then show that the large groups on the ortho positions affect the energy of transition between the ground and the first excited electronic states of the phenolate ions. This may be explained as the result of the energy of polarization of the *t*-butyl groups by the electric fields resulting from the polar resonance forms of the first excited state. This carries a further implication that in the polar resonance forms which contribute the most to the first excited state there is an accumulation of electric charge on the number one position of the phenyl ring. This is necessary since it is the ortho substituents that affect the energy. Such an accumulation of charge would create large fields which would polarize the ortho substituents.

The above results make another tool available for the determination of molecular structure of phenols of unknown composition. Since the behavior of the three classes is different for each, a phenol of unknown composition may be examined under the various conditions and thereby assigned to one of the classes. Another application has been made to analytical problems. Ordinarily it is impossible to quantitatively analyze a mixture of mononuclear aromatic hydrocarbons and phenols by ultraviolet absorption. This is because the absorption is approximately the same for each class, being due to the phenyl ring chromophore. The addition of sodium hydroxide however results in the ionization of the phenols with the resultant spectral shift. This allows data to be obtained independently for the aromatics and for the phenols. Similar considerations apply to other polar substituted aromatics. If the material in question is basic the addition of an acid will result in ionization and the same type of spectral shift.

Acknowledgment is gratefully made to Dr. Donald R. Stevens and Dr. G. Stillson for furnishing some of the substituted phenols examined. Appreciation is also due Dr. Paul D. Foote, Executive Vice-President of Gulf Research & Development Company, for permission to publish this material.

Summary

A study has been made of the ultraviolet absorption spectra of substituted phenols in ethanol solutions containing sodium hydroxide. Preliminary work was done to verify that the spectral shift which occurs when sodium hydroxide is added is due to the formation of phenolate ions. This comprised tests with different bases, acids and salts; the reversal of the effect by the addition of acid to a basic solution; and a study of the temperature dependence of the spectral shift. The unhindered phenols gave evidence of complete ionization in solutions containing 1.0×10^{-1} mole/liter of sodium hydroxide. The partially hindered phenols were only partially ionized at this concentration of sodium hydroxide, but demonstrated complete ionization for a concentration of 5.0×10^{-1} mole/liter of sodium hydroxide. The hindered phenols were neither completely ionized with the latter concentration of sodium hydroxide nor for the much larger concentration of 5.0 mole/liter. These results demonstrate the great differences in acidity between the different classes of phenols and show that ionization is hindered by the presence of large ortho substituents. This leads to the conclusion that the process of ionization is the result of a collision or of a small distance of approach between the phenolic hydroxyl and other molecules or ions. The difference of energy of transition between the ground and first excited state for the neutral molecule and for the phenolate ion depends upon the type of phenol. An explanation is given which is based on the energy of polarization of the large ortho groups. Applications of the phenomenon to analytical and molecular structure problems are given.

PITTSBURGH 30, PA. RECEIVED APRIL 8, 1949

[DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF PENNSYLVANIA]

The Reaction of Acetylene–Air Mixtures with Supported Silver Nitrate

BY K. A. KRIEGER

In the course of a study of methods for the removal of traces of acetylene from air, we have investigated the reaction of silver nitrate on various inert supports with air–acetylene mixtures.[1] These studies suggest the existence of a critical lower limit for the concentration of active component. We find that the concentration of silver nitrate required to produce measurable activity is a function of the surface area of the support material and is relatively independent of the structure of the support.

Experimental

Materials.—Silver nitrate was J. T. Baker C. P. grade, used without further purification.

Activated Alumina and Tabular Alumina were obtained from the Alumina Ore Company and used as received.

Prest-O-Lite acetylene was used usually without further treatment, but sometimes purified by passage through sodium bisulfite and sodium hydroxide solutions. No difference in behavior was observed. Measured quantities were introduced into steel pressure cylinders and made up to a total pressure of about 3000 lb./sq. in. with compressed air.

The oil used in the oil saturator was Socony-Vacuum DTE Heavy.

Catalysts were prepared by impregnation of the support with cold aqueous solutions of silver nitrate, followed by slow evaporation of the excess water at its boiling point and final drying at 100°. In all the preparations the weight of support and volume of impregnating solution were kept approximately constant, the concentration of solution being varied to give the desired final silver content. Activation was by heating in air for two hours at 200°, except as noted.

Methods and Apparatus.—As the primary purpose of this program was to find catalysts suitable for the removal of acetylene from air of composition similar to that at the output of oil lubricated compressors designed for air liquefaction equipment, the catalytic apparatus was set up to simulate these conditions. Air–acetylene mixtures were introduced into the apparatus through a reducing valve and rotameter, then passed through water saturator, oil saturator and reaction chamber, each electrically heated. The reaction chamber was a short length of stainless steel pipe provided with a thermocouple well. The water saturator was maintained at 65° and the oil saturator and catalyst chamber at 149°. Temperature could be controlled to about ±2°. In all runs the space velocity was 100,000 (S.T.P.) per hour, and the pressure 100 lb./sq. in. gage. Twenty cc. of catalyst was used in each run.

Known volumes of gas were collected for analysis through by-passes located immediately before and after the catalyst chamber, and acetylene was determined by a modification of the Ilosvay procedure.[2]

The operation of the apparatus has been described elsewhere.[1]

The catalytic activities reported are the results of at least two determinations and the reproducibility is of the order of ±3%.

Surface areas were measured with nitrogen using the BET method[3] and apparatus described by Krieger.[4]

X-Ray data were obtained with a Norelco X-ray Spectrometer using Cu Kα radiation.

Results and Discussion

The data obtained with Activated Alumina F-10 as support are shown in Table I. In this table the surface area has been calculated on two bases, S_c being the area per gram of catalyst and S_s the area per gram of support. S_{cx} is the area of the "exhausted" catalyst per gram of catalyst. The catalytic activity is expressed as per cent. acetylene removed from the air–acetylene mixture, A_3 being the activity after three hours operation and A_0 the activity at the beginning of the run. Under X are recorded the relative concentrations of silver nitrate and under Y those of metallic silver, as

TABLE I

CATALYSTS CONTAINING SILVER NITRATE IN VARYING CONCENTRATION ON ACTIVATED ALUMINA F-10

Cat.	Silver content %	Area, sq. m./g. S_c	S_s	S_{cx}	A_3, %	A_0, %	X_f (Arbitrary units)	X_x	Y_x
	1. Catalysts Tested with 4–6 p. p. m. Acetylene								
F-10	0	128	128		0	0	0	0	0
226	1.10	125	127	62	0	0	0	0	0
227	2.08	132	136	..	0	0	0	0	0
232	3.08	130	137	94	0	30	0	0	0
...	4.06	122	130	..	..	...	0	..	..
228	4.89	114	124	..	0	100	0	0	0
233	5.22	110	120	91	9	92	0	0	0
...	6.19	108	120	..	..	...	0	..	..
230	7.55	106	120	..	69	100	5	0	6.5
217	7.84	100	114	91	81	100	6	0	6
...	9.02	96	112	..	..	...	11	..	..
234	9.54	100	118	82	71	100	14.5	0	7
192	9.67	97	114	86	88	100	11.5	0	6.5
236	11.20	92	112	..	88	100	13.5	0	11
221	13.60	75	95	83	92	100	16	0	8
...	14.55	73	95	..	..	...	18	..	..
239	17.75	57	79	..	92	100	23.5	0	8
222	19.08	46	66	..	93	100	21	7.5	6.5
229	20.28	49	72	71	95	100	19.5	12	6.5
...	21.94	37	57	..	..	...	23	..	..
235	22.44	35	54	..	82[a]	100	18.5	..	..
216	24.52	32	52	67	94	100	25.5	14.5	6
223	28.46	18	33	37	97	100	21.5	17	5
	2. Catalysts Tested with 8–10 p. p. m. Acetylene								
206	1.02	132	134	98	0	0	0	0	0
205	2.01	133	137	97	0	0	0	0	0
204	4.96	120	130	88	0	88	0	0	0
211	6.98	101	113	84	8	100	0	0	6.5
225	7.89	97	111	85	54	100	10.5	0	0
192	9.67	97	114	..	67	100	11.5	0	6.5
221	13.60	75	95	..	68	100	16	0	8.5
222	19.08	46	66	74	75	100	21	7.5	5
212	19.72	44	64	71	84	100	22	9	6.5
224	24.16	29	47	..	75	100	19.5	13	5
223	28.46	18	33	..	82	100	21.5	14	3

[a] Probably heated above 200° during activation.

(1) Annual Reports of the Thermodynamics Research Laboratory, University of Pennsylvania. Navy Contracts NObs-2477, July 1, 1945, to April 30, 1946; *ibid.*, May 1, 1946, to June 30, 1947; *ibid.*, July 1, 1947, to June 30, 1948.

(2) Geissman, Kaufman and Dollman, *Ind. Eng. Chem., Anal. Ed.*, **19**, 919 (1947).

(3) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

(4) Krieger, *Ind. Eng. Chem., Anal. Ed.*, **16**, 398 (1944).

determined by the intensity of X-ray diffraction, the subscripts f and x referring, respectively, to fresh catalysts and those partially exhausted by four hours of use.

The rapid decline in catalytic activity with use as shown by the differences between A_0 and A_3 raises the question as to whether the reaction is actually catalytic. Although under these conditions the total acetylene removed has never exceeded the ratio of one mole of acetylene to one of silver nitrate, other experiments[5] with higher acetylene and lower oxygen pressures have given a ratio greater than one. Since catalytic action is normally preceded by the formation of a complex between reactant and substrate, our conclusions would not, moreover, be affected even if the reaction were not truly catalytic.

Silver Concentration and Activity.—The very sudden rise in A_3 beginning at about 5% and approaching a maximum at about 12% is a striking feature of these data (Fig. 1), and as it can be calculated from the dimensions of the silver nitrate

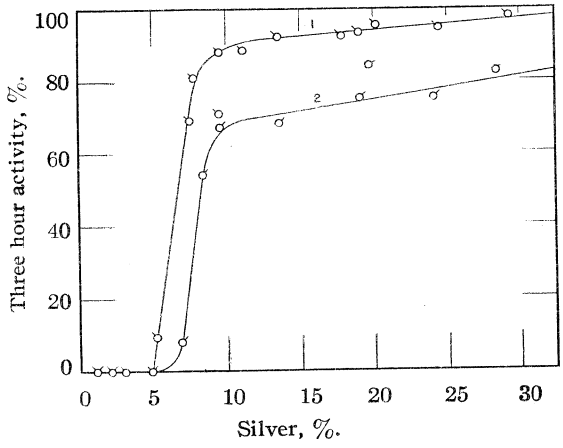


Fig. 1.—Catalytic activity *vs.* silver concentration on activated alumina F-10: ♉ 1, with 4–6 p. p. m. of acetylene; ♂, 2–10 p. p. m. of acetylene.

unit cell that about 12% silver would be required to produce a monolayer of the salt, it is tempting to ascribe the maximum to the completion of such a layer. Such a layer would not, however, be expected to yield a sharp diffraction pattern and Figure 2 shows that a strong pattern is produced considerably before 12% silver concentration is attained. As all of the diffraction patterns exhibited sharp lines we are compelled to conclude that even at the lowest concentrations which yield diffraction lines the silver nitrate crystals contain at least several hundred silver atoms, and that the failure to detect them at lower concentrations is to be attributed to limitations imposed by the sensitivity of the method itself. A comparison of A_0 with A_3 will show, furthermore, that the correspondence of X-ray detectable silver nitrate with catalytic activity does not hold where the activity

(5) To be published.

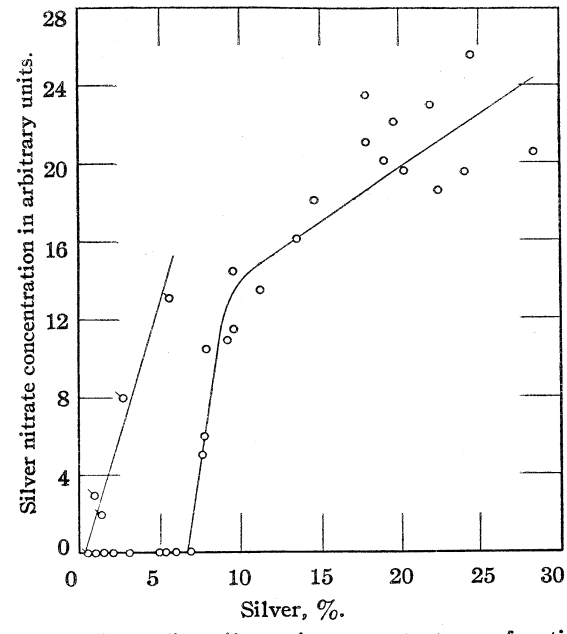


Fig. 2.—Crystalline silver nitrate content as a function of total silver concentration: O on F-10; ♉ on T-72.

is measured at the beginning of the run. The behavior of a second series of catalysts in which Tabula Alumina T-72 was used as support provides additional evidence against the monolayer hypothesis. Since the area of this support is about 0.2 sq. m./g. compared with nearly 130 sq. m./g. for F-10, maximum catalytic activity, if conditioned exclusively by the completion of a monolayer, should appear at about 1/600 of the silver concentration required to produce it on the high area support. The data of Table II demonstrate, however, that on T-72 maximum activity is not reached until the silver concentration is at least one-fifth of that required on F-10. This latter observation strongly suggests that in the case of the high area porous support a very considerable fraction of the silver nitrate is contained in pores so small that it

TABLE II

CATALYSTS CONTAINING VARYING CONCENTRATIONS OF SILVER NITRATE ON TABULAR ALUMINA T-72; 5 P. P. M. ACETYLENE

Cat.	Silver content, %	A_3, %	A_0, %	X^f (arbitrary units)
T-72	0	0	0	0
256	0.56	0	39	0
253	0.74	0	39	3
257	1.37	21	69	2
252	2.09	18	75	..
254	2.71	33	70	8
255	3.34	33	70	..
251	4.57	44	74	..
258	5.48	44	72	13
250	7.14	52	76	..
259	8.22	44	77	..
260	13.24	53	78	..

is catalytically inactive because diffusion limits access of the reactants to, or removal of the products from, the active surface. Taken in conjunction with these facts the similar maximum activities of catalysts prepared upon supports of such widely different areas points to catalytic activity confined to the "external" surface of the granules and practically precludes the possibility of specific effects due to differences in the support materials.

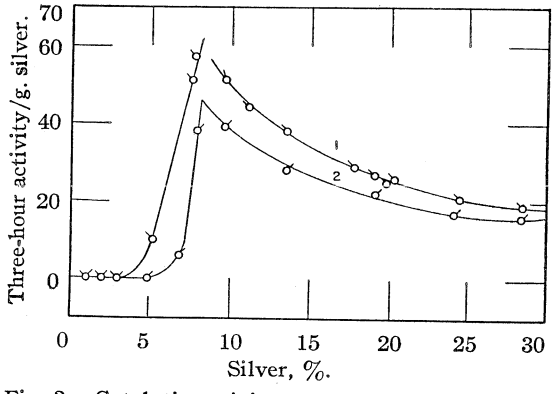


Fig. 3.—Catalytic activity per gram of silver *vs.* silver concentration: 1, with 4–6 p. p. m. of acetylene on activated alumina F-10; 2, with 8–10 p. p. m. of acetylene on activated alumina F-10.

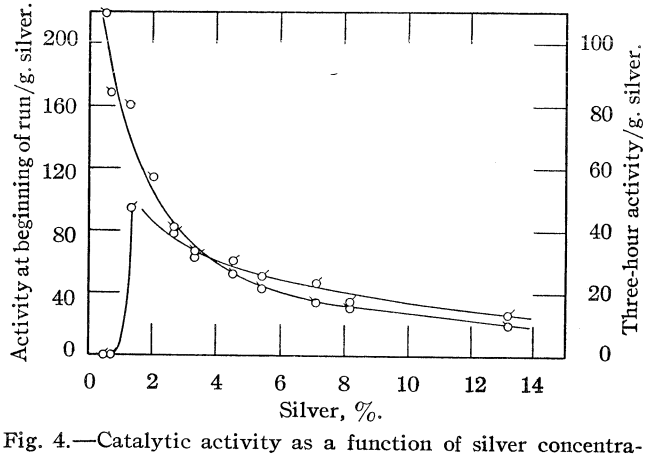


Fig. 4.—Catalytic activity as a function of silver concentration on T-72; 5 p. p. m. of acetylene: ♉, A_0; ♂, A_3.

The fact that the ratio of silver concentrations required to give measurable X-ray diffraction intensities on the two supports (Fig. 2) is of the same order as that needed to produce maximum values of A_3 seems to support the belief that the carriers are almost entirely non-specific in their action, functioning merely to provide more or less extended areas upon which the silver nitrate may be spread.

Although the close correspondence between the silver concentration required to give detectable diffraction effects and that at which A_3 is greater than zero must be regarded as fortuitous, the fact that the break in the curve for F-10 supported catalysts (Fig. 2) corresponds in silver concentration to the leveling off in Fig. 1 may be interpreted to mean that the thickness of the silver nitrate layer has become sufficiently great so that the lower layers contribute little either to catalytic activity or to diffraction intensity.

All of these data require that an explanation other than the completion of a monolayer be found for the sudden increase in activity with rising concentration. The nature of the problem can perhaps be clarified by plotting the specific activity (per gram of silver) as a function of silver concentration. This has been done in Figs. 3 and 4, inspection of which will show that there are two distinct regions to be accounted for. The higher concentration range, where the specific activity decreases with increasing concentration, is the more easily understood. Recent work[6] has shown that the specific activity of copper oxide and of chromia on alumina steadily decreased with increasing concentration of the active component and that at least in the case of chromia there was a distinct correlation between activity and dispersion as indicated by measurements of magnetic susceptibility. Selwood very reasonably interprets these results to mean that a high degree of dispersion is favorable to good catalytic activity. Though our data at higher concentrations support these experimental findings, the probability of occlusion of part of the silver nitrate in pores of the support or by overlying additional layers of the salt appears to offer an alternative explanation for the decrease in specific activity at the higher concentrations. The latter explanation may be offered with greater confidence in the case of catalysts supported on T-72, since even at the lowest concentrations studied there is enough silver nitrate present to furnish a covering ten "molecules" thick, and it is difficult to understand how the effective dispersion could change much in the higher concentration range.

The abrupt rise in activity (A_3) at lower concentrations is remarkable in that it does not begin at the concentration origin but is delayed to about 5 and 1% silver on F-10 and T-72, respectively. This observation would not be surprising if the supports themselves possessed any catalytic activity, since examples of this sort of promoter action are well known. Separate experiments have shown, however, that neither support has measurable activity by itself, and we have been unable to discover similar phenomena in the literature. It is worth noting that Selwood, whose measurements dealt in part with the same variables considered here, though in very different chemical systems, did not find a maximum.

There are several possible explanations for the delayed appearance of catalytic activity. The assumption might be made that a certain minimum "crystal" size of active component is necessary for activity. Such an assumption is not in itself un-

(6) Selwood and Dallas, THIS JOURNAL, **70**, 2145 (1948); Eischens and Selwood, *ibid.*, **70**, 2271 (1948); **69**, 2698 (1947).

reasonable, for it is generally recognized that heterogeneous reactions are normally preceded by an activated adsorption resulting from the operation of rather strong forces between catalyst and reactant. As these forces are clearly of the same general kind as those responsible for crystal growth, and are therefore probably coöperative in nature, it might be expected that they will not reach important magnitudes until the crystals attain sizes larger than those which correspond to the collection of but a few molecules. It should be emphasized that this picture does not conflict with Selwood's arguments in favor of a direct relationship between dispersion and activity, but simply serves to set a lower limit to the permissible dispersion. If this assumption is to be entertained, however, it is pertinent to inquire why Selwood did not find a similar maximum, and the explanation is perhaps to be found in the very different properties of the active materials in his experiments. Chromia and copper oxide are obviously substances in which the cohesive forces are very much greater than those in silver nitrate, as is evidenced, for example, by their much higher melting points and greater thermal stabilities, and it is quite possible that these cohesive forces are great enough to entirely prevent dispersion to the extent required to produce a diminution in activity or at least to limit such dispersion to still lower concentration ranges than those reported. It is a corollary of this explanation that maxima such as we have found ought to occur most readily when the active material is of low melting point.

Alternative explanations for the delayed rise in activity are possible, however. Since both oil vapor and acetylene, to a lesser extent, are known to cause a decrease in activity with time, it might be argued that the effects observed are due merely to the inactivation of the surface by these means. But experiments in which the time of exposure to oil vapor was purposely varied produced no appreciable effect and since the acetylene concentration does not much affect the position of maximum specific activity (Fig. 1), it does not appear that the observations can be accounted for exclusively by these processes.

A second explanation requires the assumption that small quantities of silver nitrate are lost by reaction with the support material to yield a compound not catalytically active. Although it is practically impossible to entirely rule out this possibility, since very small amounts of impurity might under certain circumstances have large effects, it is difficult to believe that the loss of as much as 5% silver could be accounted for by this means, and still more difficult to explain the relationships observed on high and low area supports in this way.

On the whole the catalytic evidence strongly suggests that crystal size has an important role in determining activity.

Surface Area and Activity.—The variation of surface area, per gram of support (S_s of Table I) with silver content is shown in Fig. 5, where the solid line is the least squares line calculated from all the points except "A." A decrease in area with rising concentration of active component has been observed before[6] and is what would be expected where a substance of low specific area covers pores in one of much higher area. Because of the scatter of experimental points, it is difficult to be sure that the slight rise in area up to about 3% silver is real, but there can be no question that other straight lines drawn through point "A" would not fit the data nearly so well, and it seems quite safe to say that the area does not begin to decrease significantly below about 5% silver. This observation again suggests that at low concentrations the crystals of silver nitrate are too small to effectively close the pores of the support.

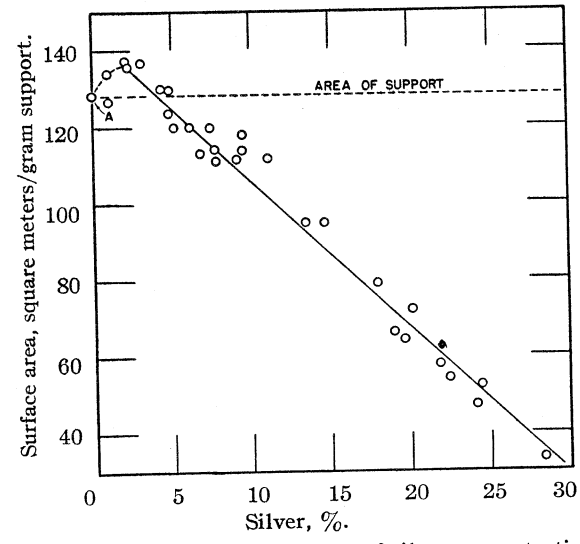


Fig. 5.—Surface area as a function of silver concentration on activated alumina F-10.

The effects of concentration on catalytic activity and surface area are all consistent with a picture of the catalyst as a collection of silver nitrate crystals, held mechanically on the carriers, whose size depends upon the surface concentration of the salt and whose activity in turn depends strongly upon size below a certain minimum size. At silver concentrations below about 12% on F-10 and about 2% on T-72 these crystals are discrete, but at higher concentrations they substantially cover the external surface of the supports.

Activation Temperature and Activity.—The effect of alterations on the time and temperature of activation are shown in Fig. 6. Both relative shapes and relative placement of the curves for one and two hour activation times indicate that the decline in activity occurring beyond the maximum is due to decomposition of the silver nitrate. In this connection the rise in area is significant; since it is found to correspond closely with the decrease in activity it may be interpreted to represent the gain in area resulting from the

decomposition of relatively compact silver nitrate crystals. Separate experiments have shown only a very slight decrease in the area of the support itself over the 200–400° temperature change. The sharp rise in activity to the maximum is probably associated with dehydration of the silver nitrate.

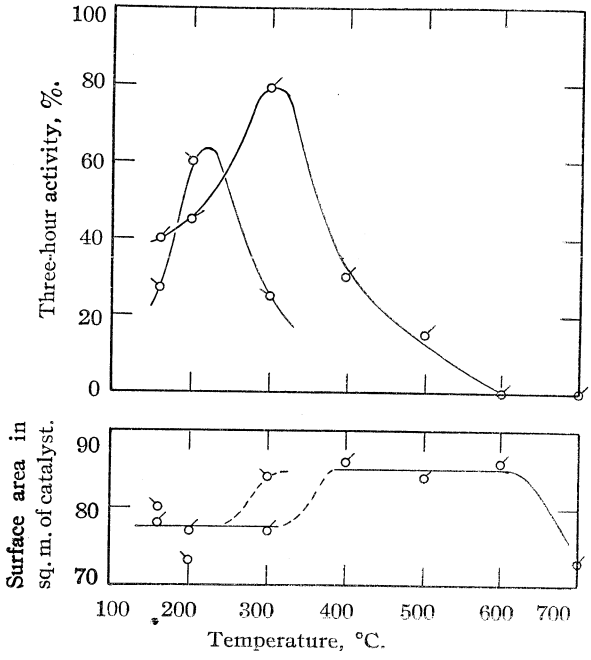


Fig. 6.—Activity and surface area as a function of time and temperature of activation, F-10, 5 p. p. m. C_2H_2: ♂, 1 hr. activation; ♁, 2 hr. activation.

Exhausted Catalysts.—During operation, changes in surface area and partial conversion of silver nitrate to metallic silver occur. Figure 7 (X_x and Y: of Table I) illustrates the latter change. Comparison of these data with those of Fig. 2 demonstrates that the minimum silver concentration required to yield detectable silver nitrate in fresh catalysts is very nearly the same as that required for metallic silver in an exhausted one and that for concentrations up to about 15% no crystalline silver nitrate is left unconverted by four hours of operation. That the diffraction intensity of silver does not continue to rise with increasing silver content means that conversion of silver nitrate to silver proceeds only to a fixed depth, no doubt because the silver itself protects the lower layers from attack. The slight but measurable decrease in silver intensity, coincident with the first appearance of unreduced silver nitrate at about 15% total silver, is probably due to the solvent effect of silver nitrate. The curve for silver nitrate intensity *vs.* total silver is practically congruent with that found for fresh catalysts (Fig. 2) but is translated to about 10% higher total silver concentrations; the magnitude of this translation sets only an upper limit to the amount of silver nitrate decomposed during operation,

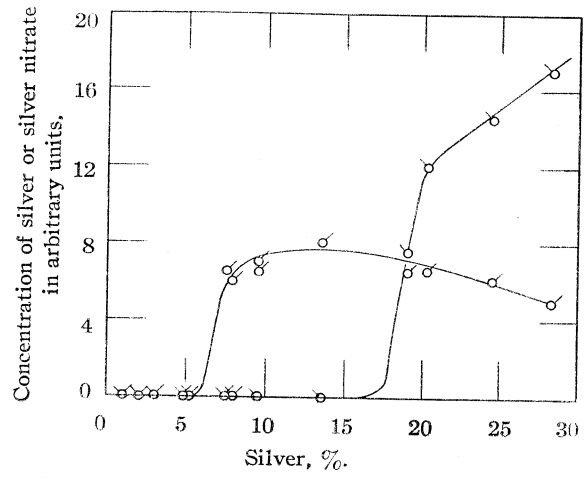


Fig. 7.—Crystalline silver and silver nitrate concentration on exhausted catalysts as a function of total silver concentration on F-10, 5 p. p. m. of C_2H_2: ♂, silver; ♁, silver nitrate.

because a correction of unknown size would have to be applied to the diffraction intensities observed in exhausted samples on account of the screening effect of the overlying layer of metallic silver. Data for a similar set of catalysts run with 10 p.p.m. of acetylene (Table I) give curves indistinguishable, within the experimental error, from Fig. 7.

Changes in surface area with use are shown in Table I and Fig. 8. The decrease in area at low silver concentrations is to be attributed to covering of exposed support surface by deposited oil vapor. As the silver concentration rises, so that more and more of the support surface is protected from oil vapor by silver nitrate, the decrease in area becomes less, and at about 12% silver the

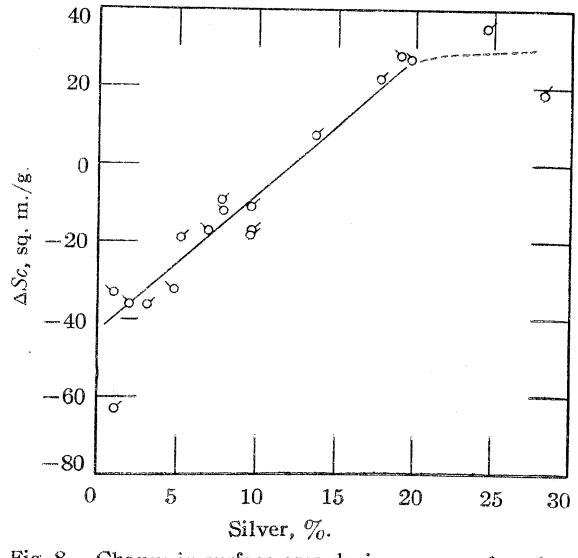


Fig. 8.—Change in surface area during use as a function of total silver content on F-10: ♂, 5 p. p. m. of acetylene; ♁, 10 p. p. m. of acetylene.

area does not change during use. It is noteworthy that this is about the silver concentration at which the catalytic activity levels off. The increase in area at still higher concentrations is probably due to increases in the area of the upper layers of the silver nitrate itself, accompanying its reduction to metallic silver, which has already been shown to occur. If this latter supposition is correct the increase in area might be expected to become nearly constant at the higher concentrations since data presented earlier indicate that only a limited amount of decomposition can occur. The points lying above 15% total silver which represents the largest amount of silver nitrate which can be decomposed under these conditions, do in fact suggest such a leveling off with ΔS_c equal to about 30 sq. m./g.

Acknowledgment.—The author wishes to express his thanks to the Thermodynamics Research Laboratory of the University of Pennsylvania and its sponsors the Navy Department, Bureau of Ships, for the support of this project, to Dr. T. A. Geissman for the design of the apparatus and for many contributions to the planning of the program, and to Messrs. D. Y. Dolman, R. F. Cree, Philip Mahoney and E. A. Fiero for much of the experimental work.

Summary

1. The activity of silver nitrate supported on alumina for reaction with acetylene–air mixtures has been studied as a function of silver nitrate concentration, area of support, temperature of activation, and acetylene concentration. Surface areas and X-ray diffraction patterns have been determined.

2. The activity is found to depend upon the ratio of surface area of support to concentration of silver nitrate, and arguments are advanced to show that maximum activity is attained when the support is covered with a multi-layer of silver nitrate.

3. Evidence is presented which leads to the hypothesis that a certain minimum crystal size is required for reactivity.

4. The effect of changes in activation temperature is related to chemical changes in the silver nitrate.

5. Factors causing decreased activity during the reaction are analyzed, and reduction of silver nitrate in the active layer is shown to occur to a limited extent. The change in surface area during use is found to be related to the decline in activity.

PHILADELPHIA, PA. RECEIVED FEBRUARY 1, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

New Synthetic Methods for the Preparation of Lysine[1]

BY DAVID CYR SAYLES[2] WITH ED. F. DEGERING

Many syntheses of lysine have been published,[3] but only the von Braun[4] method and its improvement by Eck and Marvel[5] and Galat[6] seem to have commercial application. More recently, two closely related syntheses of DL-lysine, using dihydropyran as starting material[7,8] have been published by Rogers[7] and Gaudry.[8]

During this research, several methods were investigated. The first involves the splitting of ϵ-caprolactam[9] by hydrochloric acid and neutralization to give 6-aminohexanoic acid.[10] The rest of the process is similar to that developed by Eck and Marvel.[11] The ammonolysis of 2-bromo-6-benzoylaminohexanoic acid, however, is effected by the use of aqueous ammonia and ammonium carbonate in the presence of cuprous chloride, with a decided increase in yield.

Several methods which entail the use of 1-bromo-4-chlorobutane and 1-chloro-4-nitrobutane were investigated. These intermediates are prepared by direct chlorination of 1-bromobutane and 1-nitrobutane, respectively, in yields of 30–40%. Their utilization in the preparation of lysine are indicated by: n-BuBr $\rightarrow$ $Cl(CH_2)_4Br$ (35%) $\rightarrow$ $Cl(CH_2)_4CH(CO_2Et)_2$ (65%) $\rightarrow$ $Cl(CH_2)_4CBr(CO_2Et)_2$ (70%) $\rightarrow$ $Cl(CH_2)_4CHBrCO_2H$ (50%) $\rightarrow$ lysine dihydrochloride (55%).

n-$BuNO_2$ $\rightarrow$ $Cl(CH_2)_4NO_2$ (35%) $\rightarrow$ $O_2N(CH_2)_4CH(CO_2Et)_2$ (20%) $\rightarrow$ $O_2N(CH_2)_4C(:NOH)CO_2Et$ (25%) $\rightarrow$ $H_2N(CH_2)_4CHNH_2CO_2Et$ (9%) $\rightarrow$ lysine dihydrochloride (5%).

1,4-Dichlorobutane was first converted to 1-chloro-4-phenoxybutane, as indicated by: $Cl(CH_2)_4Cl$ $\rightarrow$ $PhO(CH_2)_4Cl$ (60%) $\rightarrow$ $PhO(CH_2)_4CHAcCO_2Et$ (40%) $\rightarrow$ $PhO(CH_2)_5CO_2H$ (50%) $\rightarrow$ $PhO(CH_2)_4CHBrCO_2H$ (85%) $\rightarrow$ $Br(CH_2)_4CHBrCO_2H$ (87%) $\rightarrow$ lysine dihydrochloride (81%).

(1) This paper was reported at the Washington meeting of the American Chemical Society in September, 1948.

(2) Present address: Lowe Brothers Company, Dayton, Ohio.

(3) C. L. A. Schmidt, Editor, "The Chemistry of the Amino Acids and Proteins," 2nd ed., Charles C. Thomas, Baltimore, Md., 1944.

(4) J. von Braun, *Ber.*, **42**, 839 (1909).

(5) J. C. Eck and C. S. Marvel, "Org. Syntheses," **19**, 18, 20, 61 (1939).

(6) Galat, THIS JOURNAL, **69**, 86 (1947).

(7) Rogers, Emmick, Tyran, Levine and Scott, report given before the Organic Division of the American Chemical Society at St. Louis in September, 1948.

(8) Gaudry, *Can. J. Research*, **26B**, 387 (1948).

(9) Available from E. I. du Pont de Nemours & Company, Wilmington, Delaware.

(10) Eck, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., 1943, p. 28.

(11) Eck and Marvel, *J. Biol. Chem.*, **106**, 387 (1934).

An alternative method is: $PhO(CH_2)_5CO_2H \rightarrow Br(CH_2)_4CO_2H$ (60%) $\rightarrow Br(CH_2)_4CHBrCO_2H$ (85%) $\rightarrow$ lysine dihydrochloride (81%).

Reduction of monoethyl adipate, either catalytically using copper chromite and hydrogen or sodium and alcohol, yields a mixture of 6-hydroxyhexanoic acid and its lactone which can be converted to 6-bromohexanoic acid and finally lysine.

Experimental

Ammonolysis of 6-Benzoylamino-2-bromohexanoic Acid.—Ammonium hydroxide (250 ml., d. 0.98, 3.75 moles), ammonium carbonate (75 g., 0.9 mole), cuprous chloride (1 g., 0.005 mole) and 6-benzoylamino-2-bromohexanoic acid[11] (70 g., 0.22 mole) are placed in a shaking autoclave and heated at 100 to 150° for twelve to fourteen hours. The solution is then boiled for thirty minutes to decompose the ammonium carbonate, cooled, crystallized, filtered by suction, and washed with alcohol (50 ml.) and then with ether (50 ml.). The aqueous filtrate is evaporated to dryness under reduced pressure, the residue washed with two portions of water (50 ml.), then with ethanol (25 ml.), and finally with ether (25 ml.) to give 55 g. of product (m. p. 260–265°, 98–99%).

Lysine Dihydrochloride.—This compound can be prepared according to the method of Eck and Marvel.[11]

1-Bromo-4-chlorobutane.—A mixture of 1-bromobutane (1000 g., 7.4 moles), sulfuryl chloride[12] (1000 g., 7.4 moles), and benzoyl peroxide (20 g., 0.16 mole) is refluxed for ten to twelve hours until the evolution of gases ceases. The reaction product is then separated by distillation under diminished pressure. The final cut (b. p. 100 to 120° at 100 mm.) is fractionated through a 36-inch glass-packed column (b. p. 110–112° at 100 mm., yield 360 g., 35% of theory).

1-Bromo-4-chlorobutane.—1-Bromobutane (1000 g., 7.4 moles) was placed in a dispersion tube,[13] which was equipped with a condenser attached to a dry ice trap and a hydrogen chloride absorber. Chlorine (519 g., 7.3 moles) is bubbled slowly through the solution, which is illuminated by six 150-watt Mazda light bulbs. The unreacted chlorine is recycled. After complete addition of the chlorine, carbon dioxide is passed through the reaction product to displace the hydrogen chloride. The resulting product is fractionated through a 36-inch column (yield 350 g., 35% of theory, b. p. 110–112° at 100 mm.).

Diethyl 4-Chlorobutylmalonate.—Sodium (96 g., 3.0 moles) is dissolved in absolute alcohol (1000 g.) in a three-necked three-liter flask which is fitted with a mercury-seal stirrer, reflux condenser, dropping funnel, and drying tubes. Then, in order, are added diethyl malonate (480 g., 3.0 moles) and 1-bromo-4-chlorobutane (518 g., 3.0 moles). The reaction mixture is refluxed for four to five hours, the alcohol removed by distillation, and water added to the residue to dissolve the sodium bromide. The oil is separated and the aqueous solution is extracted with ether. The combined organic material is washed with water and dried over anhydrous sodium sulfate. The ether is evaporated, and the residue is distilled under diminished pressure through a 36-inch glass-packed column (500 g., 65% conversion, b. p. 145–148° at 10 mm.).

Diethyl 4-Chlorobutylbromomalonate.—A mixture of diethyl 4-chlorobutylmalonate (550 g., 2.2 moles) and chloroform (1000 ml.) is placed in a three-liter three-necked flask which is fitted with a stirrer, dropping funnel, reflux condenser, and drying tubes. Iodine (5 g.) is added, and then bromine (365 g., 2.3 moles) dissolved in chloroform (200 ml.) is added dropwise. The reaction mixture is then refluxed on a steam-bath for two to three hours until the evolution of hydrogen bromide ceases. The chloroform is recovered and the residue distilled under diminished pressure (b. p. 147–155° at 30 mm., yield 340 g., 70% of theory).

(12) Kharasch and Brown, THIS JOURNAL, **61**, 2142 (1939).

(13) Degering, *Ind. Eng. Chem.*, **24**, 181 (1932).

2-Bromo-6-chlorohexanoic Acid.—Diethyl 4-chlorobutylbromomalonate (387 g., 1.2 moles) is refluxed with concentrated hydrochloric acid (1500 ml., 9.8 moles) containing zinc chloride (100 g., 0.5 mole) for eighteen to twenty-four hours. The reaction mixture is cooled, extracted with benzene, and the benzene extract filtered. The filtrate is then extracted with aqueous sodium carbonate, and the alkaline solution is cooled and acidified with concentrated hydrochloric acid. The organic layer is taken up in ether, and the aqueous solution is then extracted with ether. The combined organic material is washed with water, dried over anhydrous sodium sulfate, and the ethereal solution is filtered, the ether recovered, and the residue distilled under reduced pressure (b. p. 93–95° at 5 mm., yield 135 g., 50% of theory).

Lysine Dihydrochloride.—Ammonium hydroxide (250 ml., 3.75 moles), ammonium carbonate (75 g., 0.87 mole), cuprous chloride (1 g.) and 2-bromo-6-chlorohexanoic acid (57 g., 0.25 mole) are placed in a shaking autoclave and heated at 175–200° for twelve hours. The contents of the autoclave are removed and filtered, the filtrate evaporated to dryness under diminished pressure, and concentrated hydrochloric acid (1000 ml., 6.6 moles) is added to the residue, which is then warmed for ten to fifteen minutes on a steam-bath. The solution is then evaporated, hot absolute alcohol (200 ml.) is added, the solution is filtered, then cooled to 10–15°. A small quantity of absolute ether is added to the filtrate to precipitate any ammonium bromide which is dissolved in the alcohol, and then filtered. Anhydrous ether (200 ml.) is slowly added with continuous stirring to the filtrate. The solid which separates is collected by filtration and dried (m. p. 183–185°, yield 30 g., 55% of theory).

1-Chloro-4-nitrobutane.—1-Nitrobutane (870 g., 7.7 moles) is placed in a dispersion tube[13] equipped with a reflux condenser, which is connected to a Dry Ice trap for the recovery of unreacted chlorine. Phosphorus pentoxide (30 g., 0.1 mole) is added, and chlorine (628 g., 8.9 moles) is slowly bubbled through the solution which is illuminated with nine 150-watt Mazda bulbs. Reaction occurs slowly, with a brief induction period, and the chlorination temperature ranges from 70–80°. The hydrogen chloride is then displaced by a stream of carbon dioxide. The product is poured into water, washed several times with water, and dried over anhydrous sodium sulfate. The material is distilled under reduced pressure (b. p. 100–105° at 10 mm. 370 g., 35% of theory).

Ethyl 2-Acetyl-6-nitrohexanoate.—Sodium (48.3 g., 2.1 moles) is dissolved in absolute alcohol (400 ml.) in a two-liter three-necked flask which is fitted with a mercury-seal stirrer, reflux condenser, dropping funnel, and drying tubes. Ethyl acetoacetate (273 g., 2.1 moles) is added, followed by the slow addition of 1-chloro-4-nitrobutane (214 g., 1.6 moles). The reaction mixture is refluxed on a steam-bath for four to six hours. The alcohol is then distilled, the residue diluted with water, the organic material separated, and the aqueous solution extracted with ether. The combined organic material is washed with water and dried over anhydrous sodium sulfate. The ether is evaporated, and the residue is distilled under diminished pressure (b. p. 153–158° at 9 mm., yield 67 g., 20% conversion).

Ethyl 6-Nitro-2-oximidohexanoate.—Ethyl 2-acetyl-6-nitrohexanoate (160 g., 0.7 mole), chilled to 0°, is mixed with *n*-butyl nitrite (120 g., 1.2 moles), chilled to 0°, and the mixture is then added gradually to a solution of sodium (20 g., 0.95 mole) in cold absolute alcohol (400 ml.) in a one-liter, three-necked flask, which is fitted with a mercury-seal stirrer, dropping funnel, reflux condenser, and drying tubes. The reactants are maintained at −10° for twenty-four to thirty hours by the use of an ice-salt-bath, then permitted to warm up to room temperature, and stirred an additional two to three hours. The alcohol is recovered under diminished pressure, the residue diluted with water, and the organic layer separated. The aqueous solution is extracted with ether, and then the aqueous solution is cooled and acidified with dilute sulfuric acid. The organic layer is again separated, and the aqueous

solution is extracted with ether. The combined organic material is washed with water, and then dried over anhydrous sodium sulfate (yield 38 g., 25% conversion).

Lysine Dihydrochloride.—Tin (60 g., 0.5 mole), water (60 ml.) and ethyl 6-nitro-2-oximidohexanoate (10 g., 0.046 mole) are placed in a 500-ml. three-necked flask, which is equipped with a stirrer, dropping funnel, and reflux condenser. Hydrochloric acid (100 ml., 0.65 mole) diluted with water (150 ml.) is slowly added, and the reaction mixture is then refluxed for four to six hours. The excess tin is removed by filtration, the aqueous solution is extracted once with ether, the filtrate is evaporated to dryness, and the residue is dried in a vacuum desiccator over concentrated sulfuric acid. The residue is then transferred to a Soxhlet thimble and extracted with absolute alcohol. The solvent is evaporated, and the residue is refluxed with 50% aqueous alcohol (100 ml.) containing sodium hydroxide (10 g., 0.25 mole) for four to five hours. The alcohol is recovered, the residue is acidified with hydrochloric acid and the solvent is then evaporated under diminished pressure. The residue is dissolved in a small quantity of alcohol, picric acid in alcohol is added, and the monopicrate is isolated. The product darkens above 215° and decomposes at about 233° (yield 0.9 g., 7% of theory).

4-Phenoxybutyl Chloride.—A mixture of water (1000 g.), 1,4-dichlorobutane (320 g., 2.5 moles), and phenol (185 g., 2.0 moles) is placed in a three-liter, three-necked flask which is equipped with a mercury-seal stirrer, reflux condenser, and a dropping funnel. The mixture is heated to boiling, a solution of sodium hydroxide (75 g., 1.9 moles) in water (250 ml.) is slowly added during one to two hours, and the reaction mixture is refluxed for seven to nine hours. The lower layer is separated, washed twice with 10% aqueous sodium hydroxide to remove any unreacted phenol, then washed with water, and finally dried over anhydrous sodium sulfate. The product is then distilled under diminished pressure (b. p. 135–138° at 12 mm., yield 200 g., 60% conversion).

Ethyl 4-Phenoxybutylacetoacetate.—Absolute ethanol (500 ml.) is placed in a two-liter three-necked flask, which is fitted with a mercury-seal stirrer, reflux condenser, dropping funnel, and drying tubes. Sodium (58 g., 2.5 moles) is added. After complete reaction, freshly distilled ethyl acetoacetate (325 g., 2.5 moles) is added dropwise while the reaction mixture is maintained under gentle reflux, and the mixture is then refluxed ten to twelve hours. The solvent is distilled, the residue is diluted with water, the organic material is separated, and the aqueous solution is extracted with ether. The combined organic material is washed with water, dried over anhydrous sodium sulfate, the ether recovered, and the residue distilled under diminished pressure. The distillate consists of unreacted materials, whereas the residue is crude ethyl 4-phenoxybutylacetoacetate, which is an oily, low melting solid (yield 240 g., 40% conversion).

6-Phenoxyhexanoic Acid.—Ethyl 4-phenoxybutylacetoacetate (110 g., 0.4 mole) is heated on a steam-bath for seven to nine hours with a mixture of potassium hydroxide (110 g., 2.0 moles), water (80 ml.) and ethanol (100 ml.)., while vigorously stirring throughout. The mixture is allowed to cool, diluted with water, extracted with ether to remove the alkali-insoluble material, and the alkaline solution boiled with Norite (1 g.) for one-half hour. The solution is filtered, the filtrate cooled in an ice-bath, then acidified with dilute hydrochloric acid, and the solid which separates is filtered, washed with water, and dried in a vacuum desiccator (m. p. 69°, yield 40 g., 50% of theory).

2-Bromo-6-phenoxyhexanoic Acid.—6-Phenoxyhexanoic acid (100 g., 0.5 mole) is placed in a one-liter three-necked flask, which is equipped with an efficient stirrer, reflux condenser, dropping funnel, and drying tubes. Red phosphorus (15 g.) is then added, followed by the cautious addition of a slight excess of bromine (93.5 g., 0.55 mole). The reaction mixture is then heated on a steam-bath for five to six hours, allowed to stand overnight, the product poured into water, and the mixture heated on a steam-bath to ensure the complete hydrolysis of the acid bromide. The acid is dissolved in aqueous sodium carbonate, acidified with dilute aqueous hydrochloric acid, and the acid which separates is filtered, dried in a vacuum desiccator, and crystallized from hexane (m. p. 114–7°, yield 117 g., 85% of theory).

2,6-Dibromohexanoic Acid.—A mixture of 2-bromo-6-phenoxyhexanoic acid (20 g., 0.07 mole) and aqueous hydrobromic acid (200 ml., 48%, 1.7 moles) is refluxed for eight to ten hours. The phenol is steam distilled, the residue is allowed to cool, the acid separated by extraction with ether, and the ethereal solution extracted with dilute aqueous sodium carbonate. The aqueous extract is extracted with ether, and the alkaline solution is acidified with dilute hydrochloric acid. The oil which separates is extracted with ether, the ethereal extract washed with water, dried over anhydrous sodium sulfate, the ether evaporated, and the residue is distilled under diminished pressure (b. p. 144–146° at 2 mm., yield 17.4 g., 87% of theory).

Lysine Dihydrochloride.—A mixture of ammonium hydroxide (110 ml., 1.7 moles), ammonium carbonate (48 g., 0.5 mole), 2,6-dibromohexanoic acid (27.4 g., 0.1 mole) and cuprous chloride (1 g.) is placed in a hydrogenation bomb and heated at 125–150° for eighteen to twenty-four hours. The solution is then removed from the bomb, boiled for ten to twenty minutes to decompose the ammonium carbonate, and then evaporated to dryness under diminished pressure. The residue is treated with hydrochloric acid, evaporated to a thick sirup, dissolved in hot alcohol, and filtered. The filtrate is cooled to 15 to 20°, and absolute ether is slowly added. The solid which separates is collected by filtration, and dried (m. p. 185–189°, yield 18 g., 81% of theory).

6-Bromohexanoic Acid.—This compound can be prepared by the method of Marvel[14] in yields of 60 to 65%, or according to the method of Brown and Partridge[15] in 80% yields, or by the reaction of aqueous hydrogen bromide on 6-hydroxyhexanoic acid and its lactone which is prepared by the reduction of monoethyl adipate.

6-Hydroxyhexanoic Acid.—Monoethyl adipate (180 g., 1.0 mole) is neutralized with potassium hydroxide (30% aqueous), the solution is evaporated to dryness under diminished pressure and then dried in a vacuum desiccator over concentrated sulfuric acid and finally over phosphoric anhydride. Potassium ethyl adipate (106 g., 1.0 mole) is placed in a three-liter, three-necked flask, which is fitted with a reflux condenser, mercury-seal stirrer, and drying tubes. Absolute ethanol (1500 ml.) is added, the solution refluxed to effect as complete solution as possible, and sodium (80 g., 3.5 moles) is then added in small quantities. After the complete disappearance of the sodium metal, the alcohol is removed by distillation, leaving a crude residue of 6-hydroxyhexanoic acid and its lactone in almost quantitative yields.

6-Hydroxyhexanoic Acid.—Monoethyl adipate (200 g., 0.85 mole) and copper chromite catalyst (20 g.) are placed in a hydrogenation bomb. Hydrogen at a pressure of 2000 pounds per square inch is introduced, and the temperature is rapidly raised to 225–250°. Hydrogen is then introduced at intervals so that the hydrogen pressure is maintained above 2000 pounds pressure. The bomb and contents are then allowed to cool to room temperature, the contents removed, the catalyst removed by filtration, and the solvent recovered, yielding a crude residue of 6-hydroxyhexanoic acid and its lactone in almost quantitative yields.

The crude 6-hydroxyhexanoic acid and its lactone are converted directly into 6-bromohexanoic acid.[15]

Summary

Several methods for the synthesis of lysine dihydrochloride have been developed during the course of this research.

The most promising method in this study for the

(14) Marvel, THIS JOURNAL, **46**, 2841 (1924).

(15) Brown and Partridge, *ibid.*, **66**, 839 (1944).

commercial production of this essential amino acid appears to involve the use of ϵ-caprolactam.

The second most practical method involves the reduction of monoethyl adipate, and conversion to 6-bromohexanoic acid.

The conversion of tetramethylene chlorobromide, tetramethylene chloride, 1-nitro-4-chlorobutane to lysine may be somewhat inferior methods but are significant in case raw material values change and the by-products formed in the reactions can be utilized.

LAFAYETTE, INDIANA RECEIVED JANUARY 17, 1949

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Acrylic Esters of Amino Alcohols

BY C. E. REHBERG AND W. A. FAUCETTE[2]

According to the patent literature, several amino alcohols have been converted into the acrylic[3] or methacrylic[4] esters. Gilman and co-workers[5] prepared diethylaminoethyl acrylate hydrochloride, but, since their interest was in its physiological activity, they did not prepare the free ester or make any attempt to polymerize the salt.

Our principal object in preparing the aminoalkyl acrylates was to copolymerize them with alkyl acrylates and thus obtain acrylic elastomers containing basic functional groups. However, they did not readily polymerize alone, nor did they copolymerize with ethyl acrylate. Hence, their properties were not extensively studied.

It has been stated that aminoalkyl methacrylates act as polymerization inhibitors and are difficult to polymerize with benzoyl peroxide[4b] but are readily polymerized by ultraviolet light.[4b] Diethylaminoethyl methacrylate has been reported[4b,d,e] to polymerize spontaneously at 0° in the absence of light or catalysts. In general, these observations were confirmed in the present work with acrylic esters.

Experimental

Amino Alcohols.—The diethyl- and dibutylaminopropanols were obtained from Eastman Kodak Company; dimethylaminoethanol and 2-N-morpholinoethanol were kindly supplied by the Carbide and Carbon Chemicals Corporation, and we are indebted to Sharples Chemicals, Inc., for diethyl- and dibutylaminoethanol and ethyldiethanolamine. All were used after a simple distillation.

TABLE I

PREPARATION AND PROPERTIES OF AMINOALKYL ACRYLATES

Acrylate	Boiling point °C.	Mm.	Yield, %	$n^{20}D$	d^{20}_4	Mol. refraction Calcd.	Found	Nitrogen Calcd.	Found
Dimethylaminoethyl	61	11	36	1.4375	0.9434	39.65	39.80	9.8	9.2
Diethylaminoethyl	70	5	94	1.4425	.9251	48.89	49.02	8.2	8.3
2-(1,1′-Dibutylamino)-ethyl	82	0.3	93	1.4460	.8977	67.36	67.53	6.2	6.4
3-Diethylaminopropyl	44	.1	65	1.4441	.9180	53.50	53.61	7.6	7.5
2-(1,1′-Dibutylamino)-propyl	77	.2	40	1.4440	.8880	71.98	72.20	5.8	5.4
3-(1,1′-Dibutylamino)-propyl	83	.2	85	1.4480	.8952	71.98	72.18	5.8	5.6
2-N-Morpholinoethyl	67	.2	96	1.4728	1.0711	48.33	48.49	7.6	7.6
N-Ethyl-N-(2-hydroxyethyl)-aminoethyl	77	.2	76	1.4662	1.0211	50.41	50.79	7.4	8.3

The aminoalkyl acrylates (Table I) were prepared readily, and usually in high yield, by the alcoholysis of methyl or ethyl acrylate. This method had been used previously in the preparation of alkyl,[6] alkenyl[7] and alkoxyalkyl[8] acrylates.

Monomeric Acrylates.—The esters were prepared by the alcoholysis of methyl or ethyl acrylate. Aluminum isopropoxide was used as a catalyst and phenyl-β-naphthylamine as a polymerization inhibitor. In one experiment, no inhibitor was used, and a lowered yield of monomer, together with a large distillation residue, was obtained. The procedure and equipment have been described in previous papers.[6-8]

In the one experiment in which ethyldiethanolamine was used, only one mole of methanol was produced in the reaction. The molecular refraction of the constant-boiling product agreed with the expected value for the monoacrylate. The nitrogen analysis was somewhat high for the monoacrylate, indicating that some free amine was present. However, two fractional distillations through a 3-ft. Vigreux column failed to effect any separation.

The esters were colorless liquids having mild, ammoniacal odors and appreciable water solubility.

Polymerization Experiments.—Addition of benzoyl peroxide (1%) to the monomers or to their solutions (10%) in ethyl acetate resulted in instant discoloration. Sub-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Present address: Corn Products Refining Company, Argo, Illinois.

(3) Graves, U. S. Patent 2,138,031, November 29, 1938.

(4) (a) Heckert, *ibid.*, 2,168,338, August 8, 1939; (b) Graves, *ibid.*, 2,138,763, November 29, 1938; (c) Harmon, *ibid.*, 2,138,762, November 29, 1938; (d) Izard, *ibid.*, 2,129,694, September 13, 1938; (e) Barrett and Strain, *ibid.*, 2,129,662, September 13, 1938.

(5) Gilman, Heckert and McCracken, THIS JOURNAL, **50**, 437 (1928).

(6) (a) Rehberg and Fisher, THIS JOURNAL, **66**, 1203 (1944); (b) Rehberg, Faucette and Fisher, *ibid.*, 1723; (c) Rehberg, *Org. Syntheses*, **26**, 18 (1946).

(7) Rehberg and Fisher, *J. Org. Chem.*, **12**, 226 (1947).

(8) Rehberg and Faucette, "Acrylic Esters of Ether-Alcohols," submitted for publication in *J. Org. Chem.*

sequent heating at 90–100° had no effect. Addition of benzoyl peroxide or ammonium persulfate to aqueous emulsions of the esters had a similar result. Several attempts to copolymerize diethylaminoethyl and ethyl acrylates (weight ratio 1:10) in ethyl acetate solution and in aqueous emulsion, with benzoyl peroxide and ammonium persulfate, respectively, as catalysts, resulted in discoloration of the monomer but no appreciable polymerization. Diethyl- and dibutylaminoethyl acrylates were sealed in glass tubes and heated at 90° for one week without visible change. The tubes were than irradiated with ultraviolet light. Viscous, liquid polymers were thus formed.

No polymerization occurred when a 10% aqueous solution of the acetate of diethylaminoethyl acrylate containing 1% of benzoyl peroxide was refluxed for twenty-four hours. A 10% aqueous solution of the acrylate (salt) of diethylaminoethyl acrylate containing 0.06% (based on ester) of ammonium persulfate was placed in sunlight. After a few hours it polymerized vigorously, the entire solution being converted to a soft, pasty solid. This was soluble in water, from which it could be precipitated by sodium chloride. A sample of the polymer which had been precipitated from dilute hydrochloric acid and then from water was analyzed: N, found 2.95% (calcd. 5.75%).

A 1% aqueous solution of morpholinoethyl polyacrylate (prepared from polymer formed spontaneously while in the refrigerator) was added to a 1% aqueous solution of polyacrylic acid. A voluminous precipitate formed instantly. When dried it was hard and brittle.

Summary

The acrylic esters of eight alcohols containing tertiary amino groups were prepared by the alcoholysis of methyl or ethyl acrylate.

All attempts to polymerize the esters with benzoyl peroxide, ammonium persulfate or heat, whether in bulk, in solution or in aqueous emulsion, were failures. Ultraviolet light was effective in promoting polymerization.

PHILADELPHIA 18, PENNA. RECEIVED APRIL 30, 1949

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

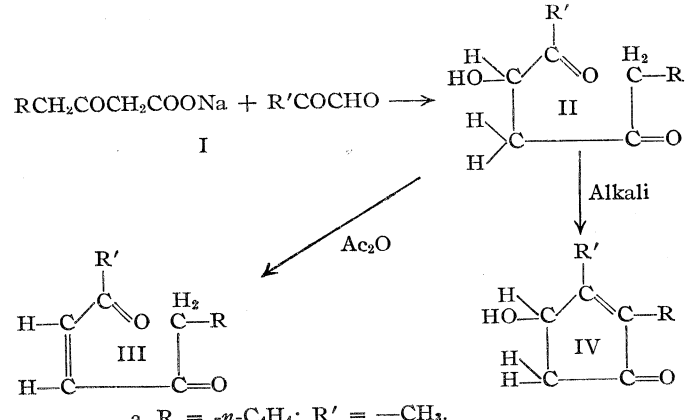
Constituents of Pyrethrum Flowers. XXIII. Cinerolone and the Synthesis of Related Cyclopentenolones[1]

BY MILTON S. SCHECHTER, NATHAN GREEN AND F. B. LAFORGE

Of the two substituted cyclopentenolones, pyrethrolone and cinerolone, the chrysanthemum acid esters of which constitute the principal insecticidal constituents of pyrethrum flowers, cinerolone, 2-(2-butenyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one, possesses the simplest structure. When it is re-esterified with *d-trans*-chrysanthemum monocarboxylic acid, the resulting cinerin I has been shown to be of about the same order of toxicity[2] as pyrethrin I, and it has the added advantage of decidedly greater stability. For these reasons cinerolone has been given first consideration from the standpoint of synthesis.

In previous articles[3,4] the synthesis of 2-*n*-butyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (*dl*-dihydrocinerolone) and the corresponding 2-*n*-amyl compound (*dl*-tetrahydropyrethrolone) has been described. The method employed consisted in the introduction of bromine in the 4-position of dihydrocinerone and tetrahydropyrethrone, respectively, by the agency of N-bromosuccinimide and the replacement of the halogen by hydroxyl. This method failed[5] when the side chain was unsaturated, as it is in cinerone and pyrethrone.

It has been shown[6] that 3-methyl-2-cyclopentenones with a side chain in position 2 are readily obtained by the cyclization of 1,4-diketones con-



a, R = -*n*-C_4H_4; R′ = $-CH_3$.
b, R = $-CH_2CH{=}CHCH_3$; R′ = $-CH_3$.
c, R = $-CH_2CH{=}CH_2$; R′ = $-CH_3$.
d, R = $-CH_2C(CH_3){=}CH_2$; R′ = $-CH_3$.
e, R = $-CH_2CH_2CH{=}CH_2$; R′ = $-CH_3$.
f, R = $-CH_2CH{=}C(CH_3)_2$; R′ = $-CH_3$.
g, R = —H; R′ = $-CH_3$.
h, R = $-CH_2CH{=}CH_2$; R′ = $-C_6H_5$.

taining a $-CH_2-$ group in the 5-position. If 2-hydroxy-1,4-diketones also having a $-CH_2-$ group in the 5-position could be prepared, they might be expected to cyclize with the elimination of a molecule of water to 2,3-disubstituted-4-hydroxy-2-cyclopenten-1-ones. It will be shown that this

(1) A communication to the Editor on this subject appeared in THIS JOURNAL, **71**, 1517 (1949), and an article in *Agr. Chemicals*, **4**, [6], 57 (1949). This article not copyrighted.

(2) Gersdorff, *J. Econ. Entom.*, **40**, 878 (1947).

(3) Soloway and LaForge, THIS JOURNAL, **69**, 979 (1947).

(4) Dauben and Wenkert, *ibid.*, **69**, 2074 (1947).

(5) LaForge, Green and Gersdorff, *ibid.*, **70**, 3707 (1948).

(6) Hunsdiecker, *Ber.*, **75B**, 455 (1942); see also Blaise, *Compt. rend.*, **158**, 708 (1914).

route can, in fact, be used to prepare a variety of substituted cyclopentenolones.

Only two 2-hydroxy-1,4-diketones appear to have been described in the literature—3-hydroxy-2,5-hexanedione ($CH_3COCHOHCH_2COCH_3$) and 2-hydroxy-1-phenyl-1,4-pentanedione ($C_6H_5COCHOHCH_2COCH_3$)—the chemistry and biochemistry of which have been extensively studied by Henze and colleagues.[7] They were obtained by the aldol condensation of methylglyoxal (pyruvaldehyde) and phenylglyoxal, respectively, with sodium acetoacetate in faintly alkaline aqueous solution at room temperature. In addition, Shaffer, Friedemann, and co-workers,[8] who were also interested in antiketogenesis, investigated the reaction of a number of aldehydes, glyoxal, etc., on alkali acetoacetate both with and without the addition of peroxide, but they failed to isolate or characterize the reaction products.

Henze represented his reaction as proceeding *via* an intermediate condensation product containing a carboxyl group (as the sodium salt), which had to be decarboxylated by warming with acid in order to produce the hydroxydiketone. We have found that the decarboxylation proceeds spontaneously under the conditions of the reaction, the final product being the hydroxydiketone, which can be extracted directly from the alkaline reaction mixture. We have also shown that the reaction can be carried out under acidic conditions, in which case carbon dioxide is liberated instead of being converted to alkali bicarbonate.

Hunsdiecker and Blaise[6] specified that a $-CH_2-$ group in the 5-position of 1,4-diketones is an essential condition for their cyclization to cyclopentenones, and that hence a compound such as acetonylacetone cannot be cyclized. This rule probably holds true in the case of 2-hydroxy-1,4-diketones, since we were unable to cyclize Henze's ketol, 3-hydroxy-2,5-hexanedione (IIg).

Preparation of 2-Hydroxy-1,4-diketones (Formula II).—Convenient methods for the preparation of saturated and unsaturated β-keto esters with a $-CH_2-$ group in the γ-position are described elsewhere[9,10] and in this article. With these esters as starting materials, a number of 2-hydroxy-1,4-diketones of the general formula II have now been prepared by the condensation of pyruvaldehyde with the alkali salts of the β-keto acids of formula I. Also, 2-hydroxy-1-phenyl-7-octene-1,4-dione (IIh), has been prepared by the condensation of phenylglyoxal with the potassium salt of Ic.

Although the reactions can be carried out under acid conditions, we have generally prepared the hydroxydiketones by the reaction of a substituted glyoxal, R'COCHO, with a faintly alkaline aqueous solution of an alkali salt of a β-keto acid, RCH_2COCH_2COOH, in substantially equimolecular proportions, the final solution being adjusted so that it is near *p*H 8. It is inadvisable to have the solution too alkaline or too acidic. If it is too alkaline, some of the substituted glyoxal may dismutate to a hydroxy acid, whereas, if it is too acidic, some of the β-keto acid may decompose; in either case, the yield of desired product will be lowered. In order to carry out the reaction under acid conditions, buffers may be used or acid may be added as the reaction proceeds. Provided that the reaction is not made too acidic nor too alkaline at first, the *p*H will tend to adjust itself to a suitable value because of the production of alkali bicarbonate. The reactions are practically complete in about six hours at room temperature but they may be allowed to proceed for a day or two. In general, the hydroxydiketones were isolated in about 50–75% yields by extraction with ether and distillation *in vacuo*.

With the exception of 2-hydroxy-1-phenyl-7-octene-1,4-dione, IIh, which is a colorless, crystalline solid, all of the hydroxydiketones are practically colorless liquids. They all reduce Fehling solution rapidly in the cold.

Attempts to prepare acetates by treatment with acetic anhydride and sodium acetate led instead to the formation of anhydro compounds of formula III. The anhydro compounds form disemicarbazones almost instantaneously upon treatment with semicarbazide hydrochloride in pyridine–ethanol solution. In contrast to this behavior, the hydroxydiketones form semicarbazone derivatives very slowly. However, the semicarbazone derivatives of the hydroxydiketones are identical with those from the corresponding anhydro compounds as shown by analysis and mixed melting point behavior. Furthermore, these semicarbazones show dimorphism when recrystallized from different solvents, ethanol usually giving a higher melting form than acetic acid. We were not able to obtain the simple disemicarbazones of our hydroxydiketones; in every case dehydration occurred. The possibility of pyrazoline formation as noted by Henze[7g] is not excluded.

It is interesting to note that the formation of the hydroxydiketones from pyruvaldehyde and salts of β-keto acids takes place under what is considered to be physiological conditions and there is a possibility that the synthesis of pyrethrolone and cinerolone may proceed via a similar mechanism in the pyrethrum plant. In fact, there is a strong resemblance between this reaction and the elegant "physiological" synthesis of tropinone by Schöpf and Lehmann.[11]

(7) (a) Henze, *Z. physiol. Chem.*, **189**, 121 (1930); (b) **195**, 248 (1931); (c) **198**, 82 (1931); (d) **200**, 232 (1931); (e) **232**, 117 (1935); (f) **232**, 123 (1935); (g) Henze and Müller, *ibid.*, **193**, 88 (1930); (h) **200**, 101 (1931); (i) **214**, 281 (1933); (j) Stöhr and Henze, *ibid.*, **206**, 1 (1932); (k) **212**, 111 (1932); (l) Stöhr, *ibid.*, **235**, 265 (1935); (m) **240**, 23 (1936); (n) Henze and Stöhr, *Wien. klin. Wochschr.*, **50**, 721 (1937).

(8) Shaffer and Friedemann, *J. Biol. Chem.*, **61**, 585 (1924); Friedemann, *Proc. Soc. Expll. Biol. Med.*, **23**, 370 (1926); and other articles mentioned in these references.

(9) Soloway and LaForge, THIS JOURNAL, **69**, 2677 (1947).

(10) Green and LaForge, *ibid.*, **70**, 2287 (1948).

(11) Schöpf and Lehmann, *Ann.*, **518**, 1 (1935); see also Schöpf and Arnold, *ibid.*, **558**, 109 (1947), and Schöpf and Thierfelder, *ibid.*, **518**, 127 (1935).

Cyclization of 2-Hydroxy-1,4-diketones (II) to 4-Hydroxycyclopentenones (IV).—The cyclization is accomplished by agitation of the hydroxydiketones with aqueous alkali at room temperature yielding the substituted cyclopentenolones. Employing about 10–20 volumes of 1 to 10% sodium hydroxide solution for several hours, yields of about 50–65% were obtained. The distilled products are practically colorless oils except IVh, which is crystalline. When pure, they do not reduce Fehling solution in the cold but only on warming.

Among the cyclopentenolones prepared, the one of formula IVb, obtained by the cyclization of the hydroxydiketone IIb, merits special consideration because it corresponds to the structure assigned to cinerolone.[12] The synthetic 2-(2-butenyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (IVb) was characterized by the preparation of the semicarbazone, acetate semicarbazone and the 3,5-dinitrobenzoate. The corresponding derivatives prepared from natural *dl*-cinerolone, with the exception of the semicarbazone, have melting points near those derived from the synthetic cyclopentenolone. In each case, however, mixed melting points of the corresponding derivatives from the two sources showed very definite depressions leaving no doubt as to their non-identity (see Table I).

Catalytic hydrogenation of the synthetic compound IVb furnished as the major product 2-butyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (*dl*-dihydrocinerolone) identical with the compound (IVa) obtained by direct synthesis. The identity of the hydrogenated compound with compound IVa and also with *dl*-dihydrocinerolone prepared by the hydrogenation of *dl*-cinerolone from the natural source, has been established by mixed melting point determinations of the corresponding semicarbazones, the 3,5-dinitrobenzoates, and the 2,4-dinitrophenylhydrazones. The identity of the semicarbazones was further confirmed by a comparison of their X-ray diffraction patterns.

The possibility that the crotyl halide and hence all of the subsequent intermediates employed in the synthesis of 2-(2-butenyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (IVb), contained any considerable amount of the methyl vinyl carbinyl isomer due to an allylic rearrangement[13] has been excluded by the hydrogenation result. The only remaining explanation for the difference between this synthetic cyclopentenolone (IVb) and natural *dl*-cinerolone seems to be that of *cis–trans* isomerism. Harper[14] has also attributed the lack of identity of synthetic 2-(2-butenyl)-3-methyl-2-cyclopenten-1-one with cinerone obtained from natural cinerolone to geometric isomerism. In addition to isomerism due to the allylic rearrangement, crotyl halides may exist as mixtures of *cis* and *trans* isomers but there is scant information on this point.[15] However, it is probable that crotyl halides exist predominantly in the *trans* form, and that hence our synthetic product (IVb) has a *trans* configuration at the double bond in the side chain, whereas natural cinerolone is probably the *cis* isomer.

All of the substituted cyclopentenolones described in this article have been esterified[16] with natural *d-trans*-chrysanthemum monocarboxylic acid yielding esters analogous to cinerin I. In addition, two of them, IVb and IVc, have been esterified with synthetic *dl-cis*- and *dl-trans*-chrysanthemum monocarboxylic acids.[17]

Most of these esters exhibited a high order of insecticidal activity, with associated knock-down and paralytic effects characteristic of pyrethrum extracts. Some of them (those of IVc and IVd) exceeded the reference test standard (pyrethrin I + cinerin I 50%, pyrethrin II + cinerin II 50%) in their toxic action against house flies when tested by the turntable method.[18] Natural *d-trans*-chrysanthemum monocarboxylic acid yielded esters more toxic than the synthetic *dl-cis–trans* mixture.

The processes for the preparation of these substituted cyclopentenolones utilize starting materials which are readily available commercially. Although the yields are fair, they undoubtedly could be increased by systematic study. Campbell and Harper[19] have recently improved the synthesis of chrysanthemum monocarboxylic acid and it is possible that other acids may be found that might replace it in the synthesis of insecticidally active esters. A technical synthesis of insecticides of the pyrethrum type now seems to have been brought within the realm of possibility.

Experimental

All melting points are corrected.

α-Alkenyl Acetoacetic Esters

Ethyl α-Allylacetoacetate.[20]—A solution of sodium ethoxide prepared by dissolving 46 g. (2 moles) of sodium in 700 ml. of absolute ethanol was cooled to 15° and 286 g. (2.2 moles) of ethyl acetoacetate was added to the stirred solution. After one-half hour 153 g. (2 moles) of allyl chloride was added at once, and the stirring was continued for a short time. The reaction was then allowed to proceed overnight, and completed by refluxing for one hour. After the sodium chloride had been removed by filtration, and most of the ethanol by distillation, the reaction product was distilled and a fraction collected between 85 and 105° (15 mm.), yield of crude product 250–300 g. The purity as calculated from ethoxyl determinations was found to range from 75–90%. This fraction, which contained some unreacted ethyl acetoacetate, was generally employed for the preparation of 5-hexen-2-one (allyl acetone). Pure ethyl α-allyl acetoacetate obtained by

(12) LaForge and Soloway, THIS JOURNAL, **69**, 2932 (1947).

(13) Winstein and Young, *ibid.*, **58**, 104 (1936).

(14) Harper, *J. Chem. Soc.*, 892 (1946).

(15) Van Dormael, *Bull. soc. chim. Belg.*, **52**, 100 (1943); Young and Andrews, THIS JOURNAL, **66**, 421 (1944); Hatch, Gordon and Russ, *ibid.*, **70**, 1093 (1948). In a recent private communication, Prof. Hatch has informed use of the successful preparation of *cis*-crotyl chloride; Hatch and Nesbitt, THIS JOURNAL, in press.

(16) LaForge and Barthel, *J. Org. Chem.*, **12**, 199 (1947).

(17) We are indebted to Dr. S. H. Harper for samples of the synthetic *dl-cis* and *dl-trans* acids.

(18) Gersdorff, *J. Econ. Entom.*, **42**, 532 (1949).

(19) Campbell and Harper, *J. Chem. Soc.*, 283 (1945).

(20) Philippi, *Monatsh.*, **51**, 278 (1929).

careful fractionation through a packed column distilled at 96–97° (14 mm.), $n^{26}D$ 1.4365.

Anal. Calcd. for $C_9H_{14}O_3$: OC_2H_5, 26.5. Found: OC_2H_5, 26.8.

Ethyl α-Crotylacetoacetate.[5]—The method employed was essentially the same as in the previous preparation, the proportions in a typical experiment being 260 g. (2 moles) of ethyl acetoacetate, 23 g. of sodium (1 mole) dissolved in 600 ml. of absolute methanol and 135 g. (1 mole) of crotyl bromide that had been fractionated through a glass helix-packed column, b. p. 106–109° (765 mm.), $n^{25}D$ 1.4786, d^{25}_4 1.3357. The constants reported[13] for crotyl bromide are b. p. 107° (760 mm.), $n^{25}D$ 1.4795, d^{25}_4 1.3335.

The excess of the solvent and the ethyl acetoacetate were removed by vacuum distillation and the 203 g. of residue was employed for the preparation of 5-hepten-2-one, any ester exchange which might have occurred being of no importance.

Ethyl α-methallylacetoacetate was prepared by the same procedure from 286 g. (2.2 moles) of ethyl acetoacetate, 46 g. (2 moles) of sodium dissolved in 600 ml. of absolute ethanol, and 181 g. (2 moles) of methallyl chloride. After removal of the solvent and the excess of ethyl acetoacetate, the residue was distilled and the fraction b. p. 98–112° (15 mm.) collected, $n^{26}D$ 1.4408; yield 280 g. (77%).

Anal. Calcd. for $C_{10}H_{16}O_3$: OC_2H_5, 24.4. Found: OC_2H_5, 24.0.

Methyl Alkenyl Ketones

5-Hexen-2-one (Allyl Acetone).[21]—Three hundred grams of crude ethyl α-allylacetoacetate (92% pure) was added to an aqueous solution of 112 g. of potassium hydroxide (100% basis) in 1 l. of water at 0° and the suspension was stirred until all but a small residue had dissolved. The solution was then kept in the refrigerator for three days. After the small amount of undissolved oil had been removed with petroleum ether, 60 ml. of sulfuric acid in 100 ml. of water was added to the aqueous solution in a flask equipped with a water condenser and the flask was heated on the steam-bath until no more carbon dioxide evolved. The separated oil was removed and the aqueous solution, after saturation with sodium chloride, was extracted with petroleum ether. The extract was combined with the separated oil, and the solution was washed with dilute alkali and with saturated salt solution. After drying the solution over potassium carbonate and removing the solvent, the residue was distilled; yield 93 g. (60% based on 92% ester, 48% based on the allyl chloride), b. p. 127–132° (760 mm.).

By the same procedure 170 g. (1 mole) of the pure ester yielded 83 g. (85%) of allyl acetone, b. p. 127–132° (760 mm.), $n^{27}D$ 1.4170.

5-Hepten-2-one (Crotyl Acetone).[5,21b]—Two hundred and three grams of crude ethyl α-crotylacetoacetate dissolved in 1 l. of a cold aqueous solution of 73 g. of potassium hydroxide (100% basis) after three days in the refrigerator furnished crude crotyl acetone on decarboxylation and isolation in the manner described for allyl acetone. Fractionation through a concentric tube column gave a forerun of 2.4 g., b. p. 148–151°, and 90.2 g. (81% overall yield based on crotyl bromide) of the desired product, b. p. 151–154° at 770 mm., $n^{25}D$ 1.4280.

5-Methyl-5-hexen-2-one (Methallyl Acetone).[21b]—This compound was prepared by saponification of 280 g. (1.52 moles) of ethyl α-methallylacetoacetate with 96 g. (1.71 moles) of potassium hydroxide (100% basis) in 650 ml. of water for four days in the refrigerator. The ketone was obtained in the usual manner. Fractionation gave 15 g. of forerun and 117 g. (69% yield) of the desired product, b. p. 142–154° at 760 mm., 90% of which distilled at 145–150°, $n^{27}D$ 1.4278. The **semicarbazone** was prepared, **m. p. 136–137°.**

(21) (a) Hibbert and Timm, THIS JOURNAL, 45, 2438 (1923); (b) Kimel and Cope, *ibid.*, 65, 1992 (1943).

Anal.[22] Calcd. for $C_8H_{14}ON_3$: N, 24.83. Found: N, 24.98.

Ethyl Esters of 3-Oxo-alkenoic Acids

The preparation of ethyl β-oxocaprylate and of ethyl 3-oxo-6-octenoate by carbethoxylation of 2-heptanone and 5-hepten-2-one, respectively, by the agency of sodium hydride has been described in previous articles.[5,9] By the same procedure the following esters have been prepared.

Ethyl 3-Oxo-6-heptenoate.—The proportions of the reactants were 90 g. (0.92 mole) of 5-hexen-2-one (allyl acetone), 44 g. (1.84 moles) of sodium hydride, and 218 g. (1.84 moles) of ethyl carbonate: yield 120 g. (77%), b. p. 107–111° (14 mm.), $n^{28}D$ 1.4393.

Anal. Calcd. for $C_9H_{14}O_3$: OC_2H_5, 26.5. Found: OC_2H_5, 25.8.

This ester has also been prepared by the forced condensation method. Ethyl carbonate, 350 g. (3 moles), and commercial sodium methylate, 30 g. (0.55 mole), were placed in a 2-l. flask equipped with a dropping funnel, a thermometer, a stirrer having a lubricated rubber seal, and a short column surmounted with a total reflux take-off head. Employing a vacuum of about 100 mm., 49 g. (0.5 mole) of allyl acetone was added dropwise over a period of three hours while about 100 ml. of distillate was collected using a take-off ratio of about 1 to 4. The temperature of the bath was about 90° and of the vapor about 62°. Two 50-ml. portions of ethyl carbonate were added at intervals of one hour during the distillation. A part of the remaining ethyl carbonate was distilled off; the solution was cooled and acidified with a slight excess of glacial acetic acid. Water was then added and the produced isolated in the usual manner to yield 60.7 g. (70.6%).

Ethyl 6-Methyl-3-oxo-6-heptenoate.—One hundred and twelve grams (1.04 moles) of 5-methyl-5-hexen-2-one (methallyl acetone), 50 g. (2.08 moles) of sodium hydride, and 248 g. (2.1 moles) of ethyl carbonate were employed in one experiment: yield 134 g. (70%), b. p. 119–125° (16 mm.), $n^{27}D$ 1.4468.

Anal. Calcd. for $C_{10}H_{16}O_3$: OC_2H_5, 24.4. Found: OC_2H_5, 24.1.

Ethyl 7-Methyl-3-oxo-6-octenoate.—This compound was obtained from 126 g. (1 mole) of 6-methyl-5-hepten-2-one,[23] 48 g. (2 moles) of sodium hydride, and 236 g. (2 moles) of ethyl carbonate: yield 141 g. (71%), b. p. 135–136° (15 mm.), $n^{25}D$ 1.4519.

Anal. Calcd. for $C_{11}H_{18}O_3$: OC_2H_5, 22.7. Found: OC_2H_5, 23.2.

The refractive indices of some of these β-keto esters were observed to change on standing due to a shift of the keto-enol ratio.

β-Keto Acids

β-Oxocaprylic Acid (Ia).—This acid was prepared by the method of Locquin,[24] m. p. 75–76° (dec.).

3-Oxo-6-octenoic Acid (Ib).—Twenty-eight grams of the ethyl ester was saponified for three days at about 5° with 100 ml. of 10% aqueous potassium hydroxide. Upon acidification to congo red with hydrochloric acid the free acid was obtained in crystalline form, m. p. (air dried) 71–72° (dec.). This acid and the previous one, Ia, are stable for months in the refrigerator but slowly decompose at room temperature with the liberation of carbon dioxide.

Anal. Calcd. for $C_8H_{12}O_3$: mol. wt., 156. Found: mol. wt. (titration), 160.

3-Oxo-6-heptenoic Acid (Ic).—This compound was prepared in the same manner but isolated as an oil. It is crystalline when cooled with dry ice, but melts with slow decomposition on warming to room temperature.

2-Hydroxy-1,4-diketones of Formula II

The general procedures used in the preparation of the

(22) Microanalyses by Oakwold Laboratories, Alexandria, Va.

(23) Hey and Morris, *J. Chem. Soc.*, 48 (1948); Verley, *Bull. soc. chim.*, 17, 176 (1899).

(24) Locquin, *Bull. soc. chim.*, [3], 31, 597 (1904).

hydroxydiketones will be outlined, and supplementary details will be described for each experiment when necessary.

In **Procedure A** the β-keto acid was isolated, stored in a desiccator in the refrigerator until ready to be used, and then mixed with ice-cold water and exactly neutralized with cold 10% sodium hydroxide solution. The pyruvaldehyde prepared by a modification of the method of Riley[25a,b] usually dissolved in a little water, was added, and the alkalinity adjusted to approximately *p*H 8. It is immaterial whether or not the pyruvaldehyde has polymerized on storage in the refrigerator, for either it dissociates on standing in dilute aqueous solution[25b] or else the equilibrium shifts to the monomer as it reacts. If the reaction medium is too alkaline, some of the substituted glyoxal may be converted to a hydroxy acid before it can react with the salt of the β-keto acid. In those cases where the hydroxydiketones are difficultly soluble, the reaction mixture turns cloudy in about two hours, and during several more hours the oily reaction product separates almost completely. The hydroxydiketones of lower molecular weight may separate partially or not at all, depending on their solubility and the volume of the reaction mixture. In these cases the solution was saturated with sodium chloride before extraction. After about sixteen hours to several days the reaction mixture was extracted with peroxide-free ether. The ether solution was washed with saturated salt solution, and after drying over sodium sulfate the solvent was removed and the residue distilled in high vacuum. There was little or no forerun, but a fraction, not further investigated, having a considerably higher boiling point than the desired compound was present in all the preparations.

Procedure B was the same as A except that the β-keto ester was saponified with a slight excess of a 5 to 20% potassium hydroxide solution for several days in the refrigerator. The excess alkali was neutralized with dilute sulfuric acid, the pyruvaldehyde solution added, and the alkalinity finally adjusted to approximately *p*H 8.

Procedure C was the same as procedure B except that, instead of neutralizing the alkaline solution of the β-keto acid with dilute sulfuric acid, the solution was saturated with carbon dioxide employing a porous disperser. The excess alkali was thereby converted to bicarbonate, giving a suitable *p*H, and the pyruvaldehyde solution could be added without further adjustment of the alkalinity.

3-Hydroxy-2,5-decanedione (IIa). (Procedure A).—Thirty grams (0.19 mole) of β-oxocaprylic acid, Ia, mixed with 50 ml. of cold water in a glass-stoppered flask was kept cold in an ice-bath and titrated with 10% sodium hydroxide solution until just alkaline to phenolphthalein. The stoppered flask was shaken vigorously near the end of the titration. Eighteen grams of pyruvaldehyde (87.6% assay[26]) (0.22 mole) was added and rinsed in with a little water. The alkalinity of the reaction mixture was adjusted to approximately *p*H 8 by the careful addition of a little 10% sodium hydroxide solution. The total volume of the reaction mixture was 200 ml. After about two hours at room temperature the solution turned milky and the oily reaction product rose to the surface. By placing the solution in a graduated cylinder the progress of the reaction could be measured by noting the increase in volume of the oil layer. After two days the reaction mixture was still faintly alkaline. It was extracted several times with ether, the extracts were combined and washed several times with saturated sodium chloride solution and, after drying over anhydrous sodium sulfate, the ether was distilled off leaving a residue of 32 g. of yellow oil which was distilled *in vacuo*. After a small forerun the main fraction was collected at 89–95° (0.05 mm.), most of it distilling at 93–95°, $n^{25}D$ 1.4514, yield 23 g. (65%). There was also a higher boiling fraction, b. p. 150–155° at 0.15 mm., which was not investigated. After redistillation, the 3-hydroxy-2,5-decanedione, $n^{25}D$ 1.4508, d^{25}_4 0.9967, was analyzed.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74; *MR*D, 49.93. Found: C, 64.10; H, 9.56; *MR*D, 50.29.

An aliquot of the reaction mixture, after it had been extracted with ether, was titrated for sodium bicarbonate, using 1 *N* sulfuric acid solution and methyl orange indicator, the solution being boiled near the end of the titration. The theoretical amount of sodium bicarbonate was found.

A similar experiment was performed with 10.2 g. (0.065 mole) of β-oxocaprylic acid and 18.1 g. (0.065 mole) of pyruvaldehyde-sodium bisulfite compound[27] (instead of pyruvaldehyde) with final adjustment of the alkalinity to approximately *p*H 8. After standing for two days very little oil separated. The reaction mixture was acidified to congo red with dilute sulfuric acid (1:4) and heated for fifteen minutes on the steam-bath under a reflux condenser in order to decompose any bisulfite addition compounds. The product was isolated as usual by extraction with ether and distillation *in vacuo*, giving only a 19% yield of 3-hydroxy-2,5-decanedione.

Another experiment was performed with commercially available pyruvaldehyde.[28] Procedure B was used. Ninety-nine grams (0.53 mole) of ethyl β-oxocaprylate was mixed with 195 ml. of an ice-cold solution containing 39 g. of potassium hydroxide (86% assay) (0.60 mole). After standing for three days in the refrigerator, the excess alkali was approximately neutralized by the slow addition of dilute sulfuric acid (1:4). One hundred and forty grams of commercial pyruvaldehyde (30%) (0.58 mole) was added, and the solution was adjusted to approximately *p*H 7.5 to 8 by the addition of 10% potassium hydroxide solution. The total volume of the reaction mixture was 537 ml. In ninety minutes the reaction product began to separate as an oil. After four hours 104 ml. had separated, after which there was no further increase. The product was isolated in the usual manner by extraction with ether and distillation to yield, after a small forerun, 50.9 g. (52%), b. p. 105–110° at 0.4 mm., $n^{25}D$ 1.4532. Redistillation gave 41.7 g., b. p. 90–98° at 0.05 mm., $n^{25}D$ 1.4528.

To illustrate that these reactions can be run under acidic conditions, a solution of sodium β-oxocaprylate (0.05 mole) was mixed with a slight excess of pyruvaldehyde in the presence of a buffer consisting of a solution of citric acid (0.1 mole) partially neutralized with sodium hydroxide. The initial *p*H of the reaction mixture was 4.9. The reaction was allowed to proceed for twenty-four hours during which time carbon dioxide was evolved and the reaction product separated as an oil, the final *p*H being 5.1. Extraction and distillation as usual yielded 5.5 g. (59%) of 3-hydroxy-2,5-decanedione.

Sometimes, after several weeks, the formation of crystals in some preparations of 3-hydroxy-2,5-decanedione was noticed. The crystals were filtered off and recrystallized from petroleum ether (b. p. 60–70°) to give colorless plates, m. p. 91–91.5°.

Anal.[22] Calcd. for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 68.26, 68.24; H, 9.66, 9.61.

Derivatives of 3-Hydroxy-2,5-decanedione (IIa)

The **anhydrodisemicarbazone** was prepared by treatment of IIa with a 50% excess of semicarbazide hydrochloride in pyridine–ethanol. The reaction required several days for completion, as did all the analogous derivatives described later. The anhydrodisemicarbazone was filtered off, washed, and dried, and after recrystallization from acetic acid was colorless, m. p. 224–225° (dec.).[29]

(25) (a) Riley, Morley and Friend, *J. Chem. Soc.*, 1875 (1932); (b) Moulds and Riley, *ibid.*, 621 (1938).

(26) Friedemann, *J. Biol. Chem.*, **73**, 331 (1927); Simon and Neuberg, *Biochem. Z.*, **232**, 479 (1931).

(27) Neuberg, *ibid.*, **255**, 1 (1932).

(28) This product was supplied as an approximate 30% aqueous solution. It contained formaldehyde, acidic substances, and other unknown impurities.

(29) The melting point behavior of many of the semicarbazone derivatives reported in this article was variable. Differences of as much as 5° were sometimes observed, depending on the rate of heating and the temperature at which the capillaries were inserted in the

Anal. Calcd. for $C_{12}H_{22}O_2N_6$: C, 51.04; H, 7.86. Found: C, 50.62; H, 7.65.

It was found to be identical with the disemicarbazone of 3-decene-2,5-dione described below. The analysis indicated that water had been eliminated. Hence the compound may be a pyrazoline derivative, as suggested by Henze[7g] for the analogous derivative of his ketol.

3,5-Dinitrobenzoate.—This derivative was obtained by using 3,5-dinitrobenzoyl chloride in benzene in the presence of pyridine. After isolation in the usual manner, the ester crystallized when kept in the refrigerator for several days and was recrystallized several times from methanol, m. p. 67–68°. The compound was unstable on storage.

Anal. Calcd. for $C_{17}H_{20}O_8N_2$: C, 53.68; H, 5.30. Found: C, 53.53; H, 5.00.

The 2,4-dinitrophenylhydrazone derivative was prepared by refluxing the hydroxydiketone for thirty minutes with an excess of 2,4-dinitrophenylhydrazine in ethanol acidified with concentrated hydrochloric acid. The compound was filtered off, washed with ethanol, dried and recrystallized from chloroform (other solvents were not as satisfactory) giving red crystals, m. p. 226–227°.

3-Decene-2,5-dione (IIIa).—To IIa was added twice its weight of acetic anhydride plus a little anhydrous sodium acetate. The following day the solution was warmed at 100° for ten minutes and the excess acetic anhydride removed under reduced pressure. The residue was dissolved in ether and washed with water, dilute sodium bicarbonate solution, and saturated sodium chloride solution. After the ether solution was dried over anhydrous sodium sulfate, the solvent was evaporated. The residue (practically theoretical yield) crystallized on standing and was recrystallized from low-boiling petroleum ether to give pale yellow crystals, m. p. 52–53°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.27, 70.86, 71.40; H, 9.44, 9.40, 9.33.

The compound (IIIa) reacted almost immediately with semicarbazide hydrochloride in pyridine–ethanol to give a yellow **disemicarbazone**, which was filtered off, washed with water and ethanol, and dried, m. p. 228–229° (dec.). This derivative was obtained in two forms. Recrystallization by solution in a large volume of boiling 95% ethanol and concentration gave one form, yellow, m. p. 228–229° (dec.).

Anal. Calcd. for $C_{12}H_{22}O_2N_6$: C, 51.04; H, 7.86. Found: C, 51.39; H, 7,94.

Recrystallization from acetic acid gave another form, colorless, m. p. 224–225° (dec.). The mixed melting point[29] of either form with the anhydrodisemicarbazone obtained from 3-hydroxy-2,5-decanedione (m. p. 224–225° dec.) was 224–225° (dec.) in each instance, indicating that the semicarbazone derivatives from the two sources are identical and that the lower melting form is the more stable one.

3-Hydroxy-8-decene-2,5-dione (IIb).—Procedure A was used. From 50.4 g. (0.27 mole) of 3-oxo-6-octenoic acid, Ib, and 29.5 g. of pyruvaldehyde (90% assay) (0.37 mole), the time of reaction being three days and the total volume 290 ml., 44.7 g. (75%) of distilled product, b. p. 97–100° at 0.1 mm., $n^{25}D$ 1.4679, was obtained.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 64.75; H, 8.79.

The **anhydrodisemicarbazone** was prepared and recrystallized from acetic acid, giving a yellow product, m. p. 227–228° (dec.).

Anal. Calcd. for $C_{12}H_{20}O_2N_6$: C, 51.41; H, 7.19. Found: C, 51.47; H, 7.02.

3,8-Decadiene-2,5-dione (IIIb).—This compound was prepared from IIb in the same manner as IIIa. Recrystallization from low-boiling petroleum ether gave pale yellow crystals, m. p. 52–53°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.74; H, 8.35.

3-Hydroxy-8-nonene-2,5-dione (IIc).—Procedure A was used, starting with 50 g. (0.35 mole) of 3-oxo-6-heptenoic acid and 32.2 g. of pyruvaldehyde (90% assay) (0.40 mole). The time of reaction was three days and the total volume 270 ml.; 35 g. (58%) of distilled product, b. p. 85–90° (mostly 86–89°) at 0.07 mm., $n^{25}D$ 1.4657, was obtained.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 62.82; H, 8.05.

There was also a higher boiling fraction, 5.2 g., b. p. 142–152° at 0.5 mm., $n^{25}D$ 1.4977, which was not investigated.

The **anhydrodisemicarbazone** of IIc was prepared and recrystallized from acetic acid, giving a yellow compound, m. p. 228–229° (dec.), identical with the disemicarbazone of 3,8-nonadiene-2,5-dione described below.

Anal. Calcd. for $C_{11}H_{18}O_2N_6$: C, 49.61; H, 6.81. Found: C, 49.65; H, 6.85.

3,8-Nonadiene-2,5-dione (IIIc).—This compound was prepared from IIc in the same manner as the other analogs. The oily product crystallized in the refrigerator but melted on warming to room temperature.

Its **disemicarbazone** was obtained in two forms. By solution in a large volume of boiling 95% ethanol and concentration, a bright yellow compound was obtained, m. p. 231–232° (dec.). Recrystallization from acetic acid gave the bright yellow lower-melting form, m. p. 228–229° (dec.). A mixed melting point of the latter with the anhydrodisemicarbazone of IIc was 228–229° (dec., no depression).

An experiment to determine the feasibility of using pyruvaldehyde diethyl acetal as a source of the pyruvaldehyde proceeded satisfactorily. Seventeen and a half grams (0.12 mole) of pyruvaldehyde diethyl acetal was refluxed for one hour with 1.6 g. of concentrated sulfuric acid in 60 ml. of water. The solution was cooled in an ice-bath and neutralized by the slow addition of about 3 g. of sodium bicarbonate. Procedure C was used. Starting with 17 g. (0.10 mole) of ethyl 3-oxo-6-heptenoate, saponified in the usual manner with 7.1 g. of potassium hydroxide (87.5% assay) (0.11 mole) in 80 ml. of water, and the hydrolyzed pyruvaldehyde diethyl acetal solution, after two days, 10.6 g. (62%) of distilled product (IIc), $n^{25}D$ 1.4660, was obtained. Pyruvaldehyde diisopropyl acetal[30] was also used successfully in a similar manner.

3-Hydroxy-8-methyl-8-nonene-2,5-dione (IId).—Procedure C was used. From 44 g. (0.24 mole) of ethyl 6-methyl-3-oxo-6-heptenoate and 24 g. of pyruvaldehyde (76% assay) (0.25 mole), the time of reaction being twenty-four hours and the total volume 254 ml., 25.7 g. (58%) of distilled product, b. p. 98–102° at 0.3 mm., $n^{25}D$ 1.4687, was obtained.

Anal.[22] Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.28; H, 8.38.

The **anhydrodisemicarbazone** was prepared in the usual manner and when recrystallized from acetic acid was bright yellow, m. p. 225–226° (dec.).

Anal.[22] Calcd. for $C_{12}H_{20}O_2N_6$: C, 51.41; H, 7.19. Found: C, 50.76; H, 6.80.

3-Hydroxy-9-decene-2,5-dione (IIe).—Procedure C was used. Starting with 50 g. (0.27 mole) of methyl 3-oxo-7-octenoate,[14] and 32.2 g. of pyruvaldehyde (72.4% assay) (0.32 mole), the time of reaction being sixteen hours and

bath. Some of the differences in the values given in the literature may be due to this factor in addition to the usual thermometer inaccuracies. Where comparisons and mixed-melting-point determinations were made, the capillaries containing the individual samples and the mixture were placed adjacent to the thermometer and all three run at the same time in a modified type of Hershberg apparatus. It was found that results were more reproducible when the capillaries were inserted in the bath about 10–15° below the expected melting point and the temperature raised about 10° per minute.

(30) Guest, MacDowell and McNamee, U. S. Patent 2,421,559 (1947).

the total volume 255 ml., 38.4 g. (77%) of distilled product, b. p. 94–97° at 0.2 mm., $n^{25}D$ 1.4675, was obtained.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.01; H, 8.52.

The **anhydrodisemicarbazone** was prepared in the usual manner. It was obtained in two forms, m. p. 214–215° (dec.) from acetic acid, and m. p. 220–221° (dec.) from 95% ethanol, both of which were pale yellow. The latter form was analyzed.

Anal. Calcd. for $C_{12}H_{20}O_2N_6$: C, 51.41; H, 7.19. Found: C, 51.70; H, 6.98.

The **3,5-dinitrobenzoate** was prepared and recrystallized from ether plus low-boiling petroleum ether to give the pale yellow crystalline ester, m. p. 60–61°. The derivative is unstable on storage.

3,9-Decadiene-2,5-dione (IIIe).—This compound was prepared by treating IIe in the same manner as the other analogs. The oily product crystallized in the refrigerator but melted on warming to room temperature. The **disemicarbazone** occurred as a low-melting form, m. p. 214–215° (dec.), when recrystallized from acetic acid and as a high-melting form, m. p. 220–221°, when recrystallized from 95% ethanol, both of which were pale yellow. A mixed melting point of the latter with the high-melting form of the anhydrodisemicarbazone of 3-hydroxy-9-decene-2,5-dione, IIe, was 220–221° (dec., no depression).

3-Hydroxy-9-methyl-8-decene-2,5-dione (IIf).—Procedure C was used. Starting with 47.5 g. (0.24 mole) of ethyl 7-methyl-3-oxo-6-octenoate and 25 g. of pyruvaldehyde (76% assay) (0.26 mole), the time of reaction being one day and the total volume 300 ml., 32.2 g. (68%) of distilled product, b. p. 106–109° at 0.5 mm., $n^{25}D$ 1.4715, was obtained.

Anal.[22] Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.80; H, 8.75.

The **anhydrodisemicarbazone** was prepared and recrystallized from acetic acid, m. p. 238–239° (dec.).

3-Hydroxy-2,5-hexanedione (Henze's Ketol, IIg).—Procedure C was used, starting 65 g. (0.50 mole) of ethyl acetoacetate and 41.4 g. of pyruvaldehyde (88.6% assay) (0.51 mole). After three days the solution was saturated with sodium chloride (no separation of oil) and extracted with ether in a continuous extractor. It was not necessary to acidify and heat the solution as Henze[7a,g,h,i] specified; therefore, decarboxylation must have taken place spontaneously during the reaction as in the other analogous reactions described in this article. The ether was distilled off and the residue dried by refluxing with benzene by use of a Dean–Stark trap. The benzene was removed with a water pump and the residue distilled in high vacuum. The yield of distilled product was 24.1 g. (37%), b. p. 62–67° (mostly 65–67°) at 0.5 mm., $n^{25}D$ 1.4497.

2-Hydroxy-1-phenyl-7-octene-1,4-dione (IIh).—Procedure B was used. Since phenylglyoxal hydrate is not readily soluble in water, the reaction mixture was shaken for five hours and then allowed to stand overnight. Starting with 28 g. (0.16 mole) of ethyl 3-oxo-6-heptenoate and 22.5 g. (0.17 mole) of phenylglyoxal hydrate,[31] m. p. 83–84°, the total volume of reaction mixture being 210 ml., 23.3 g. (68%) of distilled product, b. p. 154–157° at 0.8 mm., was obtained.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 71.71; H, 6.74.

A small amount was cooled in dry ice to obtain seeds, and then the main product was recrystallized from ether plus low-boiling petroleum ether, filtered, and washed with low-boiling petroleum ether, to give colorless crystals, m. p. 38.5–39°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.56; H, 6.85.

Cyclopentenolones (Formula IV)

General Procedure for Cyclizing 2-Hydroxy-1,4-diketones to Cyclopentenolones.—The hydroxydiketone was placed in a glass-stoppered Erlenmeyer flask or bottle, and 10 to 20 volumes of 1 to 10% sodium hydroxide solution were added. Although other alkaline cyclizing agents, such as potassium hydroxide, barium hydroxide and piperidine, can be used, sodium hydroxide was found to give uniformly good yields and was generally employed. The air was displaced with nitrogen and the slightly lubricated stopper inserted. (If further precautions against oxidation are desired, boiled water may be used in making up the alkali solution, and a small amount of hydroquinone may be added to the reaction mixture.) It was then shaken for one to four hours on a shaking machine, occasionally somewhat longer. The reaction mixture turned yellow as soon as the alkali was added and usually became darker as the reaction proceeded. After extraction with peroxide-free ether (in the case of the lower molecular weight cyclopentenolones, after saturation with salt), the extract was washed several times with saturated salt solution and after drying over sodium sulfate the solvent was removed and the residue distilled in high vacuum. Sometimes there was a small forerun. In each case, as in the distillation of the hydroxydiketones, there was a fraction, not further investigated, boiling considerably higher than the desired compound.

2-Butyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (IVa, Synthetic *dl*-Dihydrocinerolone).—Fourteen grams of IIa was shaken overnight with 140 ml. of 2% sodium hydroxide solution. By the general procedure, 8.0 g. (63%) of the distilled product, b. p. 110–113° at 0.07 mm., $n^{25}D$ 1.4920, was obtained. The compound was purified by regeneration from the semicarbazone, b. p. 111–113° at 0.2 mm., $n^{25}D$ 1.4945 (literature values[3] are $n^{22}D$ 1.4958 and $n^{25}D$ 1.4955).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.10; H, 9.64.

The **semicarbazone** was prepared in pyridine–ethanol and recrystallized from methanol–ethyl acetate, m. p. 199–200° (dec.).

Anal. Calcd. for $C_{11}H_{19}O_2N_3$: C, 58.64; H, 8.50. Found: C, 58.79; H, 8.29.

A sample of *dl*-dihydrocinerolone semicarbazone prepared from natural *dl*-cinerolone had a melting point of 195–196° on our thermometer[29] instead of 185° as previously reported.[3] It probably was slightly impure, but the amount available was too small to purify further. A mixed melting point[29] of this semicarbazone with that of the synthetic dihydrocinerolone, IVa (m. p. 199–200°, dec.), was 195–196° (dec., no depression).

The **3,5-dinitrobenzoate** of IVa was prepared in benzene in the presence of pyridine and was recrystallized from methanol, m. p. 111.5–112°.

Anal. Calcd. for $C_{17}H_{18}O_7N_2$: C, 56.35; H, 5.01. Found: C, 56.27; H, 4.81.

The mixed melting point with the 3,5-dinitrobenzoate[3] *dl*-dihydrocinerolone from the natural source was 111.5–112°.

The **2,4-dinitrophenylhydrazone** of IVa was prepared and recrystallized from 95% ethanol, m. p. 140.5–141.5°.

2-(2-Butenyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (IVb).—Instead of shaking as in the general procedure, the reaction was carried out with stirring. To 500 ml. of a 1% sodium hydroxide solution in a nitrogen-swept flask fitted with a Hershberg stirrer and dropping funnel, 25 g. of IIb was added over a period of thirty minutes. Stirring was continued for another hour, after which the reaction was worked up as usual. Fourteen grams (62%) of distilled product, b. p. 110–114° at 0.15 mm., $n^{25}D$ 1.5143, was obtained.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.75; H, 8.40.

The **semicarbazone** was prepared in pyridine–ethanol and recrystallized from methanol–ethyl acetate, m. p. 222–223° (dec.).

Anal. Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.17; H, 7.68. Found: C, 59.29; H, 7.51.

The **acetate semicarbazone** was obtained by first acetyl-

(31) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 509.

ating the cyclopentenolone and then preparing the semicarbazone of the acetate. Recrystallized from ethyl acetate, it melted at 155–155.5° (without dec.).

Anal. Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.85; H, 7.22. Found: C, 58.70; H, 7.16.

The **3,5-dinitrobenzoate** was prepared and recrystallized from 95% ethanol, m. p. 125–126°.

Anal. Calcd. for $C_{17}H_{16}O_7N_2$: C, 56.66; H, 4.48. Found: C, 56.16; H, 4.53.

A comparison of synthetic 2-(2-butenyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (IVb), the natural product *dl*-cinerolone, and their derivatives is presented in Table I. The very definite depressions of the mixed melting points of the corresponding derivatives leaves no doubt as to their non-identity.

The **3,5-dinitrobenzoate** (not previously reported) of natural *dl*-cinerolone was prepared and recrystallized from methanol, m. p. 119.5–121.5°.

Anal. Calcd. for $C_{17}H_{16}O_7N_2$: C, 56.66; H, 4.48. Found: C, 57.26; H, 4.86.

TABLE I

MELTING POINTS OF SYNTHETIC AND NATURAL *dl*-2-(2-BUTENYL)-4-HYDROXY-3-METHYL-2-CYCLOPENTEN-1-ONES AND THEIR DERIVATIVES

	n_D	Semicarbazone, m. p., °C. (dec.)	Acetate semicarbazone, m. p., °C.	3,5-Dinitrobenzoate, m. p., °C.
Synthetic[a]	1.5143 (25°)	222–223	155–155.5	125–126
Natural[b]	1.5240 (28°)	199–200	151–152	.....
Natural[a]	.....	196–197	154–156	119.5–121.5
Natural + synthetic[a]	.....	192–193	143–149	100–108

[a] Melting points taken on our thermometer.[29] [b] Literature values [LaForge and Barthel, *J. Org. Chem.*, 10, 106, 114 (1945)].

Hydrogenation of Synthetic 2-(2-Butenyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (IVb).—Three and one-half grams of IVb in ethanol was hydrogenated with Adams platinum oxide catalyst until 570 ml. of hydrogen at normal temperature and pressure (20% excess over that required to saturate one double bond) was absorbed. After filtration from the catalyst, 3.25 g. of crude semicarbazone, m. p. 191–192° (dec.), was prepared directly from the concentrated solution. Recrystallization from ethanol gave 2.65 g., m. p. 197–198° (dec.).

From 2.0 g. of the recrystallized semicarbazone 1.4 g. of 2-butyl-4-hydroxy-3-methyl-2-cyclopenten-1-one was regenerated, b. p. 109–110° at 0.2 mm., $n^{25}D$ 1.4927.

When the semicarbazone, 3,5-dinitrobenzoate and 2,4-dinitrophenylhydrazone of the hydrogenated compound were mixed with the corresponding derivatives of 2-butyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (IVa), there was no depression of the melting points.[29] Mixed melting points of the semicarbazone and 3,5-dinitrobenzoate with the corresponding derivatives of *dl*-dihydrocinerolone from the natural source also did not show any depression.

The semicarbazones of IVa and of hydrogenated IVb showed the same X-ray diffraction patterns.[32] These patterns agreed with that of *dl*-dihydrocinerolone semicarbazone from the natural source except for moderate shifts in some of the lines attributable to impurities in solid solution in the latter sample. The X-ray diffraction patterns of the three semicarbazone derivatives, therefore, further confirmed their identity.

2-Allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (IVc).—Twenty-five grams of IIc was shaken for one hour with 200 ml. of 10% sodium hydroxide solution. By the general procedure 13.3 g. (59%) of distilled product, b. p. 100–103° at 0.15 mm., $n^{25}D$ 1.5141, was obtained.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.23; H, 8.07.

The **semicarbazone** was prepared and recrystallized from methanol–ethyl acetate, m. p. 213–214° (dec.).

Anal. Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.23. Found: C, 57.90; H, 7.22.

The **3,5-dinitrobenzoate** was prepared and recrystallized from 95% ethanol, m. p. 129–130°.

Anal. Calcd. for $C_{16}H_{14}O_7N_2$: C, 55.49; H, 4.07. Found: C, 55.86; H, 4.21.

4-Hydroxy-3-methyl-2-(2-methylallyl)-2-cyclopenten-1-one (IVd).—Treatment of 31.6 g. of IId with 640 ml. of 2% sodium hydroxide solution for three hours by the general procedure yielded 18.9 g. (66%) of distilled compound, b. p. 115–120° at 0.3 mm., $n^{25}D$ 1.5113. Purification by regeneration from the semicarbazone gave a product, b. p. 112–114° at 0.3 mm., $n^{25}D$ 1.5120.

Anal.[22] Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.48; H, 8.18.

The **semicarbazone** was prepared and recrystallized from methanol–ethyl acetate, m. p. 213–214° (dec.).

Anal.[22] Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.17; H, 7.68. Found: C, 59.29; H, 7.53.

2-(3-Butenyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one (IVe).—This compound was prepared in the same manner as IVb. Fifteen grams of IIe dissolved in a little 95% ethanol was dropped into 225 ml. of 2% sodium hydroxide solution during forty-five minutes with stirring, in a nitrogen-swept flask. Stirring was continued for a total of three hours, after which the reaction was worked up as usual. The yield was 6.4 g. (47%) of distilled product, b. p. 109–113° at 0.2 mm., $n^{25}D$ 1.5089.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.88; H, 8.35.

The **semicarbazone** was prepared and recrystallized from methanol–ethyl acetate, m. p. 195–196° (dec.).

Anal. Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.17; H, 7.68. Found: C, 58.78; H, 7.60.

The **acetate semicarbazone** of IVe was prepared by acetylating the cyclopentenolone and then preparing the semicarbazone of the acetate. When recrystallized from ethanol plus a little water, it melted at 136–138° (without dec.).

Anal. Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.85; H, 7.22. Found: C, 58.80; H, 7.26.

The **3,5-dinitrobenzoate** was prepared. Several recrystallizations from ethanol and from benzene–petroleum ether failed to raise the melting point above 109–112°.

Anal. Calcd. for $C_{17}H_{16}O_7N_2$: C, 56.66; H, 4.48. Found: C, 57.22; H, 4.82.

4-Hydroxy-3-methyl-2-(3-methyl-2-butenyl)-2-cyclopenten-1-one (IVf).—Treatment of 25 g. of IIf in the presence of 0.2 g. of hydroquinone with 375 ml. of 2% sodium hydroxide solution for four hours by the general procedure yielded 13.0 g. (57%) of distilled compound, b. p. 116–119° at 0.3 mm., $n^{25}D$ 1.5100.

Anal.[22] Calcd. for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95. Found: C, 73.44; H, 8.71.

The **semicarbazone** was prepared and recrystallized from methanol–ethyl acetate, m. p. 222–223° (dec.).

Anal.[22] Calcd. for $C_{12}H_{19}O_2N_3$: N, 17.70. Found: N, 17.84.

2-Allyl-4-hydroxy-3-phenyl-2-cyclopenten-1-one (IVh).—Treatment of 15 g. of IIh with 225 ml. of 2% sodium hydroxide solution for four hours according to the general procedure yielded 7.0 g. (51%) of distilled compound, b. p. 153–156° at 0.6 mm., $n^{25}D$ 1.5975. When purified by regeneration from the semicarbazone, it crystallized. Recrystallization from benzene–petroleum ether gave colorless crystals, m. p. 97.5–98.5°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.49; H, 6.56.

(32) Grateful acknowledgment is made to E. L. Gooden of this Bureau for the X-ray diffraction data.

The **semicarbazone** recrystallized from acetic acid melted at 212–213° (dec.).

Anal. Calcd. for $C_{15}H_{17}O_2N_3$: C, 66.40; H, 6.32. Found: C, 66.43; H, 6.37.

Attempted Cyclization of Henze's Ketol, 3-Hydroxy-2,5-hexanedione.—Fifteen grams of II g. was dissolved in 300 ml. of 2% sodium hydroxide solution with the addition of 0.1 g. of hydroquinone. The flask was filled with nitrogen and allowed to stand for four hours. After saturation with sodium chloride, the reaction mixture was extracted with ether in a continuous extractor for twenty-four hours. The ether was distilled off and the residue dried by refluxing with benzene by use of a Dean–Stark trap. The benzene was removed with a water pump, and the residue fractionated in a high vacuum to give three fractions as follows: (1) 0.90 g., b. p. 39–41° at 0.3 mm., $n^{25}D$ 1.4387; (2) 0.65 g., b. p. 92–103° at 0.3 mm., $n^{25}D$ 1.5104; (3) 1.75 g., b. p. 118–128° at 0.3 mm., $n^{25}D$ 1.5342. Only fraction (1) gave a semicarbazone (it precipitated immediately), but the amount was too small to characterize. It was evident from the distillation that the reaction was not clear cut and that cyclization had not taken place. By analogy with the other cyclopentenolones, which have a little higher boiling point than the respective hydroxydiketones from which they are prepared, the cyclized product from 3-hydroxy-2,5-hexanedione, if any were formed, would have an estimated boiling point in the region of 70–85° at 0.3 mm. No such fraction was obtained. If any cyclized product were formed, its detection would require a more rigorous search. The degradation of Henze's ketol by alkali apparently leads to a complex mixture of products.

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Summary

The reaction between substituted glyoxals of the type R'COCHO and salts of substituted acetoacetic acids of the type RCH_2COCH_2COOH, yields 2-hydroxy-1,4-diketones, which cyclize upon treatment with alkali to 2,3-disubstituted-4-hydroxy-2-cyclopenten-1-ones. The chrysanthemum monocarboxylic acid esters of certain of these cyclopentenolones exceed the pyrethrins in insecticidal activity to house flies.

Synthetic 2-(2-butenyl)-4-hydroxy-3-methyl-2-cyclopenten-1-one appears to be a geometric isomer of natural *dl*-cinerolone.

BELTSVILLE, MD. RECEIVED APRIL 4, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TULANE UNIVERSITY]

The Nitration of 1,1,1-Trichloro-2,2-bis-(*p*-methoxyphenyl)-ethane

BY DAVID A. SHIRLEY, THEODORE N. GOREAU AND FRED S. EISEMAN, JR.

1,1,1-Trichloro-2,2-bis-(*p*-methoxyphenyl)-ethane (methoxychlor) has recently become available commercially because of its favorable properties as an insecticide. We have investigated the nitration of methoxychlor because of the usefulness of this reaction as a route to various derivatives whose biological properties are of interest. We were primarily interested in the possible activity of methoxychlor derivatives, particularly the amino derivatives, as anti-tubercular chemotherapeutic agents in view of the observation reported by Kirkwood and Phillips[1] of the high anti-tubercular activity *in vitro* of 1,1,1-trichloro-2,2-bis-(*p*-aminophenyl)-ethane and 1,1-dichloro-2,2-bis-(*p*-aminophenyl)-ethylene.

Nitration of methoxychlor (I in Fig. 1) with concentrated nitric acid in glacial acetic acid solution produced a dinitro derivative. This dinitro compound was shown to be 1,1,1-trichloro-2,2-bis-(3-nitro-4-methoxyphenyl)-ethane (II in Fig. 1) by the methods indicated below.

Treatment of the dinitro derivative II with alcoholic base effected dehydrohalogenation to 1,1-dichloro-2,2-bis-(3-nitro-4-methoxyphenyl)-ethylene (III). Oxidation of this compound with chromic anhydride in glacial acetic acid gave 3,3'-dinitro-4,4'-dimethoxybenzophenone (VII). This ketone has been reported by several workers[2] and its melting point reported as 205°,[2a] 193°,[2d] 190°[2c] and 189–190°.[2b] Our product VII reached a maximum melting point of 187–187.5°[3] after a total of eight recrystallizations from a variety of solvents.

Conclusive proof of the structure of II was given by two independent methods. The first of these was by the condensation of chloral hydrate and *o*-nitroanisole to a product identical with II, indicating that the nitro groups in II were ortho to the methoxyl groups. In addition the nitration product (VI) of DDT (V), shown by Backeberg and Morris[4] to be 1,1,1-trichloro-2,2-bis-(3-nitro-4-chlorophenyl)-ethane, on treatment with alcoholic sodium methoxide caused dehydrohalogenation and replacement of the para chlorine atoms by methoxyl groups giving a product identical with III.

Reduction of the nitro groups in III gave the corresponding diamine, 1,1-dichloro-2,2-bis-(3-amino-4-methoxyphenyl)-ethylene, IV.

Preliminary *in vitro* tests were carried out on compounds II, III and IV by the Parke, Davis

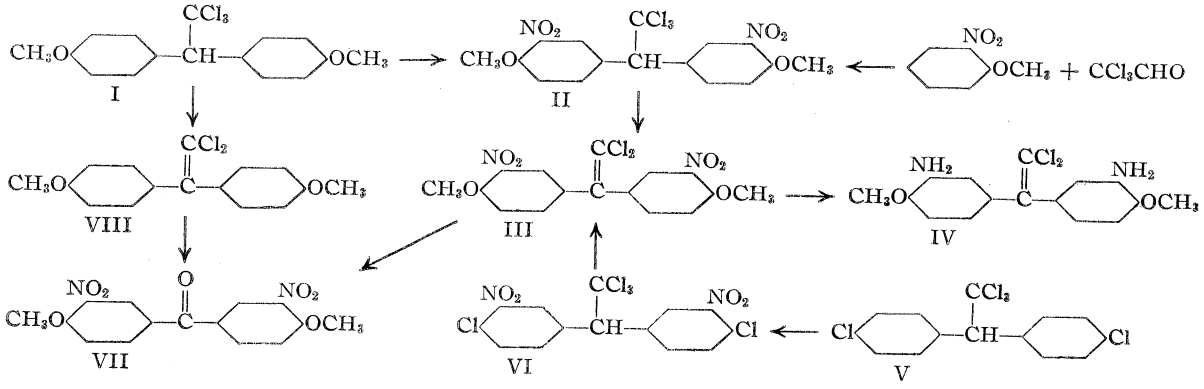
(1) Kirkwood and Phillips, THIS JOURNAL, **69**, 934 (1947).

(2) (a) Consonno, *Gazz. chim. ital.*, **34**, 376, 381 (1904); (b) van Alphen, *Rec. trav. chim.*, **49**, 153 (1930); (c) Quelet, *Compt. rend.*, **196**, 1411 (1933); (d) Matsumura, THIS JOURNAL, **57**, 128 (1935).

(3) All melting points are uncorrected and determined with a Fisher–Johns apparatus.

(4) Backeberg and Morris, *J. Chem. Soc.*, 803 (1945).

Fig. 1.—Summary of reactions.



Co. for activity against the H37Rv strain of human tuberculosis bacillus.[5] None of the compounds was active.

Experimental

1,1,1-Trichloro-2,2-bis-(3-nitro-4-methoxyphenyl)-ethane (II).—Five grams (0.0145 mole) of methoxychlor (I), prepared in essential accordance with the procedure of Schneller and Smith,[6] was dissolved in 50 ml. of glacial acetic acid and heated to reflux while a solution of 25 ml. of concentrated nitric acid was added dropwise over a period of thirty minutes. Reflux was continued for an additional hour, and the mixture allowed to stand for five hours. The reaction mixture was poured into excess water and the precipitated solid filtered off, dried, and recrystallized from alcohol. The product was 4.3 g. (68%) of small lemon yellow prisms, m. p. 166–167°. Another recrystallization from a mixture of alcohol and benzene gave 3.7 g. melting at 167–168°.

Anal. Calcd. for $C_{16}H_{13}Cl_3N_2O_6$: N, 6.43; Cl, 24.42. Found: N, 6.27 and 6.48; Cl, 24.45 and 24.40.

A mixture of 75.5 g. (0.50 mole) of *o*-nitroanisole, 37 g. (0.25 mole) of chloral hydrate, and 50 g. of concentrated sulfuric acid was stirred while 100 g. of 20% fuming sulfuric acid was added over a thirty-minute period. The temperature of the mixture increased to 65–70°. The mixture was stirred for one and one-half hours longer and then poured into excess water. The precipitated brown semi-solid mass was filtered off, washed with water, and recrystallized from glacial acetic acid and then from alcohol–benzene mixture to give 12.5 g. (12%) of yellow prisms, m. p. 168°. A mixed melting point between this material and that formed above by nitration of methoxychlor showed no depression.

1,1-Dichloro-2,2-bis-(3-nitro-4-methoxyphenyl)-ethylene (III).—A solution of 44 g. (0.10 mole) of II in a mixture of 250 ml. of alcohol and 75 ml. of benzene was heated to reflux and stirred while a solution of 8.6 g. (0.15 mole) of potassium hydroxide in 80 ml. of alcohol was added slowly. After a ten-minute reflux period, the hot mixture was filtered to remove the precipitated potassium chloride. Cooling the filtrate precipitated 31 g. (78%) of yellow prisms, m. p. 160–161°.

Anal. Calcd. for $C_{16}H_{12}Cl_2N_2O_6$: N, 7.03; Cl, 17.8. Found: N, 7.07 and 7.09; Cl, 17.4 and 17.4.

1,1-Dichloro-2,2-bis-(3-amino-4-methoxyphenyl)-ethylene (IV).—Raney nickel catalyst[7] suspended in alcohol was added to a hot solution of 8.0 g. (0.02 mole) of III in 100 ml. of alcohol. The mixture was agitated under a hydrogen pressure of 40 lb. until absorption of hydrogen was complete (about thirty minutes). The catalyst was removed by filtration, and the filtrate evaporated to a volume of 30–40 ml. Cooling precipitated 3.4 g. (50%) of the amine, m. p. 108.5°.

Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O_2$: N, 8.26. Found: N, 8.39.

Oxidation of 1,1-Dichloro-2,2-bis-(3-nitro-4-methoxyphenyl)-ethylene (III).—The ethylene derivative III (2.0 g.) was oxidized with chromium trioxide in glacial acetic acid in general accordance with a procedure used by other workers[1,8] to give 1.1 g. of crude 3,3′-dinitro-4,4′-dimethoxybenzophenone, m. p. 178–180°. Eight recrystallizations utilizing ethanol, benzene, ethyl acetate, methanol and acetophenone as solvents gave a product with a constant and maximum melting point of 187–187.5°.[2]

Anal. Calcd. for $C_{15}H_{12}N_2O_7$: N, 8.43. Found: N, 8.38 and 8.42.

Treatment of 17 g. (0.055 mole) of 1,1-dichloro-2,2-bis-(*p*-methoxyphenyl)-ethylene (VIII), prepared by dehydrohalogenation of methoxychlor,[8b] with concentrated nitric acid (75 ml.) in glacial acetic acid (200 ml.) at the reflux temperature (one hour) gave 8 g. of 3,3′-dinitro-4,4′-dimethoxybenzophenone (VII) which was shown to be identical by the method of mixed melting points with the material isolated above. This indicated that both dinitration and oxidation to the ketone had occurred.

1,1-Dichloro-2,2-bis-(3-nitro-4-methoxyphenyl)-ethylene (III) from 1,1,1-Trichloro-2,2-bis-(3-nitro-4-chlorophenyl)-ethane (VI).—DDT (V) (10 g.) was nitrated in essential accordance with the procedure of Forrest, Stephenson and Waters[8a] to form 1,1,1-trichloro-2,2-bis-(3-nitro-4-chlorophenyl)-ethane (VI) in 91% yield. The product melted at 143–144°.[8a,9]

To a solution of 2.3 g. (0.0052 mole) of the nitration product (VI) in 100 ml. of methanol was added a solution of 0.6 g. (0.026 g. atom) of sodium in 60 ml. of methanol. The mixture was refluxed for two hours and then filtered to remove the precipitated sodium chloride. The solvent was removed from the filtrate by distillation to one-half volume, and upon cooling yellow prisms precipitated. These were recrystallized from ethanol to give 0.6 g. (27%) of 1,1-dichloro-2,2-bis-(3-nitro-4-methoxyphenyl)-ethylene (III), m. p. 161–162°. A mixed melting point with a sample of III prepared as described above by dehydrohalogenation of the nitration product of methoxychlor showed no depression.

Acknowledgment.—The authors wish to express appreciation to the Research Corporation of New York for a grant which supported a portion of this work, and to Mr. G. A. Schmidt for analytical assistance.

(5) We are indebted to Dr. L. A. Sweet of the Parke, Davis Co. or arranging the pharmacological tests.

(6) Schneller and Smith, THIS JOURNAL, **70**, 4059 (1948).

(7) *Org. Syntheses*, **21**, 15 (1940).

(8) (a) Forrest, Stephenson and Waters, *J. Chem. Soc.*, 338 (1946); (b) Harris and Frankforter, THIS JOURNAL, **48**, 3149 (1926); (c) Haller, *et al.*, *ibid.*, **67**, 1596 (1945).

(9) Zeidler, *Ber.*, **7**, 1181 (1874).

Summary

Nitration of 1,1,1-trichloro-2,2-bis-(*p*-methoxyphenyl)-ethane (methoxychlor) forms 1,1,1-trichloro-2,2-bis-(3-nitro-4-methoxyphenyl)-ethane.

Two independent methods of proof showed that the structure of the nitration product is that indicated in the above name.

1,1-Dichloro-2,2-bis-(3-amino-4-methoxyphenyl)-ethylene and its precursors showed no activity *in vitro* when tested against *M. tuberculosis*.

NEW ORLEANS 15, LOUISIANA RECEIVED APRIL 18, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Racemic Glucose

BY M. L. WOLFROM AND H. B. WOOD

Racemic glucose was described as a sirup by Fischer.[1] Its purported occurrence in jute leaf[2] requires further experimental substantiation. The excellent synthesis of Sowden and Fischer[3] now makes L-glucose a readily available substance. We have succeeded in crystallizing a racemic form of this sugar. Hudson[4] has discussed the possible anomeric forms of a racemic mutarotating sugar and Fletcher and Hudson[5] have shown how these may be distinguished by acylative and crystallographic technics. Applying these criteria to our substance, we find that the X-ray powder diffraction pattern (Table I) for the racemic form of glucose isolated by us, is sensibly identical with the data reported by Sponsler and Dore[6] for anhydrous α-D-glucose. Since enantiomorphs exhibit like patterns, this is definitive proof that the racemic glucose is α-D,α-L-glucose and that it is a racemic mixture and not a true racemic compound. Supporting indirect evidence for this deduction is obtainable by acetylation technics. The racemic glucose was acetylated at low temperature with acetic anhydride and pyridine[7] and the crystalline product was characterized. L-Glucose was employed to prepare its hitherto unknown α and β pyranoid pentaacetates. These were admixed with equal quantities of their enantiomorphs and the crystalline racemic substances were characterized by melting point and X-ray powder diffraction pattern. The data of Table I show that the two racemic pentaacetates have a different crystal structure than is exhibited by either enantiomorph. Therefore α-D,α-L-glucopyranose pentaacetate (m. p. 140.5–141°) and β-D,β-L-glucopyranose pentaacetate (m. p. 125–126°) are true racemic compounds. The former was identical with the product obtained by the low temperature acetylation of the racemic glucose. This is further evidence that the racemic glucose is α-D,α-L-glucopyranose. The required assumption that the ring or anomeric structure of the sugar did not change on acetylation, while eminently probable, is not rigorous and this evidence is therefore equivocal.

TABLE I

X-RAY POWDER DIFFRACTION PATTERNS[a] OF α-D,α-L-GLUCOSE AND OF SEVERAL GLUCOSE PENTAACETATES[b]

	Pyranose pentaacetates							
α-D,α-L-Glucose I-P-S,[c] Å.	I[d]	α-L-Gluco- I-P-S, Å.	I	α-D,α-L-Gluco- I-P-S, Å.	I	β-D,β-L-Gluco- I-P-S, Å.	I	β-L-Gluco- I-P-S, Å.	I
1.22	1	1.82	1	1.77	1	1.58	1	1.47	1
1.28	1	1.85	1	1.86	2	1.65	1	1.58	1
1.34	2	2.02	1	1.92	1	1.68	1	1.62	1
1.37	1	2.08	1	2.12	2	1.77	2	1.81	3
1.49	1	2.16	3	2.22	2	1.83	2	1.85	1
1.59	2	2.25	1	2.32	1	1.92	1	1.90	2
1.63	1	2.30	1	2.47	3	2.04	1	2.01	2
1.68	1	2.40	1	2.56	3	2.11	1	2.06	1
1.79	1	2.49	1	2.76	3	2.30	1	2.11	2
1.87	1	2.59	1	2.96	1	2.62	3	2.18	3
1.91	3	2.84	1	3.10	4	2.76	1	2.34	3
1.95	3	2.88	2	3.27	4	3.07	1	2.44	2
2.06	3	2.95	1	3.54	8	3.39	5	2.55	4
2.15	1	3.05	1	3.90	9	3.57	1	2.95	2
2.24	4	3.14	2	4.35	5	3.82	1	3.07	5
2.46	8	3.32	2	4.70	6	4.04	10	3.36	4
2.56	4	3.57	7	5.36	7	4.47	6	3.51	7
2.89	3	3.91	4	6.25	1	4.71	7	3.99	1
3.13	7	4.21	9	8.05	10	5.18	4	4.17	6
3.30	1	4.42	6			5.61	9	4.44	10
3.49	5	4.80	5			6.95	2	5.23	1
3.94	3	5.12	2			8.17	5	5.59	8
4.29	10	5.47	8			11.05	8	9.94	9
4.70	9	6.22	1						
5.21	4	7.09	1						
6.06	6	9.25	10						
7.40	3								
8.53	4								

[a] Filtered CuKα radiation, effectively 1.5148 Å.; film exposure two hours; no back reflections observed. [b] Acknowledgment is made to Professor P. M. Harris and Mr. A. L. Foster for assistance in obtaining these data. [c] Interplanar spacings. [d] Relative intensity, estimated visually; 10, strongest band; 1, weakest band.

Experimental

α-D,α-L-Glucose.—Crystalline α-L-glucose (0.5000 g.) was prepared according to the method of Sowden and Fischer[3] and in admixture with a like amount of α-D-glu-

(1) E. Fischer, *Ber.*, **23**, 2620 (1890).
(2) H. Saha and K. N. Choudhury, *J. Chem. Soc.*, **121**, 1044 (1922).
(3) J. C. Sowden and H. O. L. Fischer, THIS JOURNAL, **69**, 1963 (1947).
(4) C. S. Hudson, *ibid.*, **65**, 1239 (1943).
(5) H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **69**, 1145 (1947).
(6) O. L. Sponsler and W. H. Dore, *ibid.*, **53**, 1639 (1931).
(7) R. Behrend and P. Roth, *Ann.*, **331**, 359 (1904).

cose was dissolved in 100 ml. of warm, absolute methanol. Crystallization was effected on slow solvent removal in a desiccator over sulfuric acid. Pure material was obtained on recrystallization (or elution) from methanol or ethanol and drying was effected under reduced pressure over phosphorus pentoxide at 56°; m. p. 112–113.5°, $[\alpha]^{20}D$ 0° (no mutarotation). It crystallized as fine needles.

Anal. Calcd. for $C_6H_{12}O_6$: C, 40.00; H, 6.66. Found: C, 39.90; H, 6.72.

α-D,α-L-Glucopyranose Pentaacetate.—α-D,α-L-Glucose (0.200 g.) and 2 ml. of anhydrous pyridine were cooled to 0° and 1.4 ml. of acetic anhydride was added slowly under mechanical stirring while maintaining the same temperature. The suspension was stirred at 0° for twenty hours after which time the solution was poured slowly into 10 ml. of ice and water. The crystalline material was removed by filtration, washed with water and recrystallized from 95% ethanol; yield 0.258 g. (61%), m. p. 140–140.5°. The substance formed complex rhombic crystals.

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.22; H, 5.68. Found: C, 49.21; H, 5.75.

This product showed the same X-ray powder diffraction diagram (Table I) as that obtained by recrystallizing equal amounts (0.2000 g.) of the α-D and the below-described α-L-glucose pentaacetate from 95% ethanol; m. p. 141–141.5°, mixed melting point unchanged; m. p. 113–115° on admixture with the below-described β-D,β-L-pentaacetate of m. p. 125–126°.

α-L-Glucopyranose Pentaacetate.—α-L-Glucose[3] (0.40 g.) was acetylated as described above for the α-D,α-L isomer and the crude crystalline product (0.77 g., 89%, m. p. 108–110°) was recrystallized from ethanol–water; m. p. 112–113°, $[\alpha]^{25}D$ −101° (*c* 4.4, chloroform) in agreement (opposite sign) with those cited by Hudson and Dale[8] for α-D-glucose pentaacetate.

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.22; H, 5.68. Found: C, 49.29; H, 5.30.

(8) C. S. Hudson and J. K. Dale, THIS JOURNAL, **37**, 1264 (1915).

β-L-Glucopyranose Pentaacetate.—α-L-Glucose[3] (0.20 g.) was heated on a steam-bath with freshly fused sodium acetate (0.12 g.) and acetic anhydride (2.0 ml.) and heating was maintained for two hours after solution, which required about thirty minutes. The crystalline material (0.38 g., 88%, m. p. 130–131°) obtained on pouring the reaction mixture into 20 ml. of ice and water, was recrystallized from 95% ethanol; m. p. 131–132°, $[\alpha]^{25}D$ −3.9° (*c* 2.9, chloroform) in agreement (opposite sign) with those cited by Hudson and Dale[8] for β-D-glucose pentaacetate.

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.22; H, 5.68. Found: C, 49.30; H, 5.32.

β-D,β-L-Glucopyranose Pentaacetate.—Equal amounts (0.1000 g.) of β-D- and β-L-glucose pentaacetate were recrystallized from 95% ethanol; m. p. 125–126°, needles.

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.22; H, 5.68. Found: C, 49.60; H, 5.43.

Summary

1. A crystalline form of racemic glucose has been prepared.

2. The crystalline pyranoid pentaacetates of α-L-, β-L-, α-D,α-L- and β-D,β-L-glucose are described.

3. X-Ray powder diffraction diagrams of the above compounds have been obtained.

4. Mild acetylation of the racemic glucose produces α-D,α-L-glucopyranose pentaacetate.

5. The D,L-glucose (m. p. 112–113.5°) described is a racemic mixture of the α-D and α-L forms of glucose, probably pyranoid.

6. The described pyranoid pentaacetates of α-D,α-L- and β-D,β-L-glucose are true racemic compounds.

COLUMBUS, OHIO RECEIVED APRIL 29, 1949

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Liquid–Vapor Equilibrium of Ethanol–Methylcyclohexane Solutions

BY CARL B. KRETSCHMER AND RICHARD WIEBE

In two recent publications results on the liquid–vapor equilibria of ethanol–isoöctane[2] and ethanol–toluene[3] solutions were described. The work has now been extended to solutions of ethanol in methylcyclohexane. The only previous measurements on this system are those of Isii,[4] who measured the total vapor pressure at 0 to 30°.

Experimental

The apparatus, method and purification of the ethanol have been described fully in previous articles.[2,3] A commercial grade of methylcyclohexane was fractionally distilled in an efficient column and percolated through a column of silica gel. Facilities for a determination of the freezing point were not available but the physical properties, d^{25}_4 0.76496, $n^{25}D$ 1.42059, are in satisfactory agreement with the values given by Forziati[5] for a sample containing 0.10 mole per cent. impurity, *viz.*: d^{25}_4 0.76501, $n^{25}D$ 1.42056.

Since the densities of the two liquids differ by only 0.02, solutions were analyzed by means of their refractive indices for the green mercury line (5461 Å.). A Bausch and Lomb precision refractometer was used. In order to establish the relation between composition and index of refraction, solutions were made up by weight as previously described.[2] Because of the theoretical and practical interest in the change of volume on mixing, the densities of these solutions were measured as well as their refractive indices. Table I gives the resulting values. The volume changes are all positive and are remarkably close to the values for

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) C. B. Kretschmer, J. Nowakowska and R. Wiebe, THIS JOURNAL, **70**, 1785 (1948).

(3) C. B. Kretschmer and R. Wiebe, *ibid.*, **71**, 1793 (1949).

(4) N. Isii, *J. Soc. Chem. Ind. Japan*, **38**, Sup. Binding, 659 (1935).

(5) A. F. Forziati, A. R. Glasgow, C. B. Willingham and F. D. Rossini, *J. Res. Nat. Bur. Standards*, **36**, 129 (1946).

ethanol–isoöctane solutions at the same temperature. Compositions of the liquid and vapor samples were calculated from their indices of refraction with the aid of the indices listed in Table I. The accuracy of such analyses is believed to be about 0.1 unit in the percentage by weight.

TABLE I

DENSITIES AND REFRACTIVE INDICES OF ETHANOL–METHYLCYCLOHEXANE SOLUTIONS AT 25°

Ethanol Wt. fract.	Ethanol Mole fract.	n^{25}_{5461}	d^{25}_4	$10^5\ \Delta v$, ml./g.
0.0000	0.0000	1.42240	0.76496	0
.0327	.0671	1.41987	.76457	176
.0882	.1709	1.41605	.76484	316
.1586	.2866	1.41133	.76562	418
.3366	.5196	1.40002	.76836	547
.5376	.7125	1.38755	.77226	562
.5639	.7337	1.38600	.77284	553
.5662	.7356	1.38587	.77288	554
.6610	.8060	1.38021	.77508	504
.8018	.8961	1.37195	.77877	364
.8518	.9245	1.36904	.78024	290
1.0000	1.0000	1.36073	.78505	0

The results of the liquid–vapor equilibrium measurements at 35 and 55° are given in Table II. The vapor pressures for pure ethanol were taken from our previous work[3]; those for methylcyclohexane were calculated from the equation published by Willingham and co-workers.[6] Since the vapor pressure curves for this system are similar to those for the other systems studied, they are not reproduced here.

TABLE II

LIQUID–VAPOR EQUILIBRIUM OF ETHANOL–METHYLCYCLOHEXANE SOLUTIONS AT 35 AND 55°

Mole fract. ethanol Liquid, x	Vapor, y	p, mm.	Δy[a]	Log γ_1	Log γ_2
		35°			
0.0000	0.0000	73.62	.....	....	0.0000
.0526	.4645	135.40	0.0027	1.0634	.0120
.1446	.5118	146.97	− .0008	0.7016	.0509
.2878	.5362	151.27	.0024	.4353	.1204
.4052	.5471	152.36	.0018	.2986	.1913
.5403	.5575	152.93	− .0025	.1834	.2947
.6914	.5817	152.22	− .0042	.0927	.4414
.8450	.6423	145.73	− .0042	.0299	.6541
.9676	.8369	120.04	.0048	.0024	.9106
1.0000	1.0000	103.14	.....	.0000	....
		55°			
0.0000	0.0000	168.10	.....	....	0.0000
.0528	.4835	319.83	0.0012	1.0189	.0072
.1251	.5375	352.80	− .0026	0.7322	.0345
.2205	.5645	368.00	.0008	.5255	.0758
.3621	.5846	376.34	.0028	.3347	.1517
.5071	.5988	379.83	.0009	.2028	.2524
.6832	.6244	380.06	− .0024	.0918	.4160
.7792	.6528	375.78	− .0027	.0492	.5340
.9347	.7879	337.52	.0038	.0060	.8046
1.0000	1.0000	279.89	.....	.0000	....

[a] Observed values minus those calculated from equation (1).

(6) C. B. Willingham, W. J. Taylor, J. M. Pignocco and F. D. Rossini, *J. Res. Nat. Bur. Standards*, **35**, 219 (1945).

Discussion

The vapor compositions were fitted by the empirical equation previously used[3]

$$y(1 - x)/[x(1 - y)] = \alpha = (A - Bx)/[(x + C)(1 - 2C + Cx)] \quad (1)$$

where x and y are the mole fractions of ethanol in liquid and vapor, respectively. The following values of the constants were found to represent the data for ethanol–methylcyclohexane solutions: at 35°, $A = 1.131$, $B = 1.003$, $C = 0.020$; at 55°, $A = 1.339$, $B = 1.179$, $C = 0.028$. That the fit is satisfactory is shown by the deviations listed in Table II. Fig. 1 illustrates the method of fitting this equation. The quantity $q = \alpha(x + C)(1 - 2C + Cx)$ is plotted against x for various values of C, and that value of C is chosen which makes the points lie closest to a straight line, bearing in mind that the points must be given weights proportional to $y(1 - y)/q$ if all the values of y are assumed equally accurate.

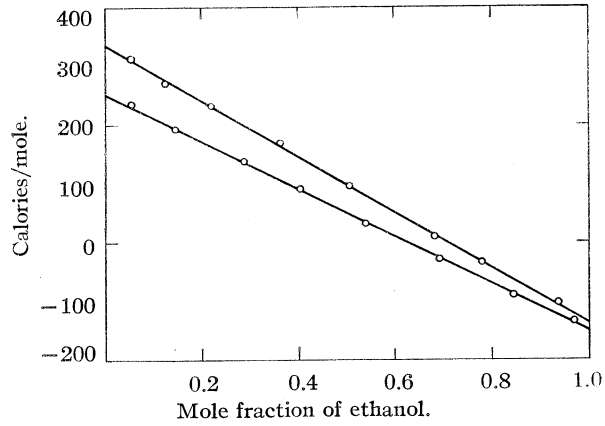


Fig. 1.—Relative volatilities of ethanol–methylcyclohexane solutions: upper curve, 55°, $C = 0.028$; lower curve, 35°, $C = 0.020$.

Equation (1) was substituted into the Gibbs–Duhem relation in the form given as equation (3) of our previous paper,[3] and used to calculate the vapor pressure at mole fractions of 0.5 and 1, for both temperatures. The liquid molal volumes and second virial coefficients for ethanol were the same as used previously.[3] For methylcyclohexane, the critical constants given by Kay,[7] were used with the equation of state of Keyes, Smith and Gerry in the form used by Scatchard and Raymond,[8] to give the following values of the second virial coefficient: at 35°, −3361; at 55°, −2592 cc./mole. Liquid molal volumes were calculated from the density equation of Massart.[9] The calculated vapor pressures differ from observed values by

(7) W. B. Kay, THIS JOURNAL, **69**, 1273 (1947).
(8) G. Scatchard and C. L. Raymond, *ibid*, **60**, 1278 (1938).
(9) L. Massart, *Bull. soc. chim. Belg.*, **45**, 76 (1936).

0.8% or less. This result may be taken to indicate a satisfactory degree of thermodynamic consistency in our data.

Redlich and Kister[10] have developed the following equation to represent the behavior of solutions containing an associating component such as an alcohol.

$$\log(\gamma_1/\gamma_2) = A'(K,x) + B'(1-2x) + C'[6x(1-x)-1] \quad (2)$$

Here γ_1 and γ_2 are the activity coefficients of alcohol and hydrocarbon, respectively. We have used primes to distinguish the notation from that of equation (1). A' is a function of x and of K, the equilibrium constant for the association reaction $ROH + (ROH)_n \rightleftarrows (ROH)_{n+1}$. The form of the function $A'(K,x)$ is given in reference (10b), equation (20). In equation (2) above, the terms in A' and B' are odd functions of $(1-2x)$, while the term in C' is, of course, an even function.

To test the applicability of equation (2) to the present data, the values of $\log \gamma_1$ and $\log \gamma_2$ listed in Table II were calculated from the experimental data by use of the relation

$$\log \gamma_i = \log(y_i p/x_i p_i) + (1/2.303RT)(\beta_i - v_i)(p - p_i) \quad (3)$$

Here x_i and y_i are the mole fractions of component i in liquid and vapor; p_i, β_i and v_i are the vapor pressure, second virial coefficient, and liquid molal volume of component i, and p is the vapor pressure of the solution. Values of $\log(\gamma_1/\gamma_2)$ were plotted against x, and the resulting curve was resolved into odd and even functions of $(1-2x)$ by means of the relation

$$f(x) = \tfrac{1}{2}[f(x) - f(1-x)] + \tfrac{1}{2}[f(x) + f(1-x)] \quad (4)$$

It was found that the odd function could be represented quite accurately by the odd terms of equation (2). However, the even function is represented poorly by the term $C'[6x(1-x)-1]$. This is shown in Fig. 2, where the plotted points have been taken from the experimental curve of $\log(\gamma_1/\gamma_2)$ *vs.* x, and the curve is calculated for $C' = -0.111$. The deviations represent errors in y of up to 0.015 mole fraction. The following values of the parameters were found for ethanol–methylcyclohexane solutions: at 35°, $K = 16$, $B' = 1.350$, $C' = -0.111$; at 55°, $K = 16$, $B' = 1.331$, $C' = -0.111$. The ethanol–toluene system[3] at 35° can be represented by $K = 6$, $B' = 0.994$, $C' = -0.130$, with deviations very similar to those shown in Fig. 2. The above values of K are anomalous in that one would reasonably expect K to decrease appreciably between 35 and 55°. Furthermore, the theory behind equation (2) requires that K have the same value for solutions of the same alcohol in different hydrocarbons at the same temperature. However, it has been emphasized[10] that K is very sensitive to experimental errors, and also, we might add, to deviations from the simplifying assumptions necessarily introduced in deriving equation (2).

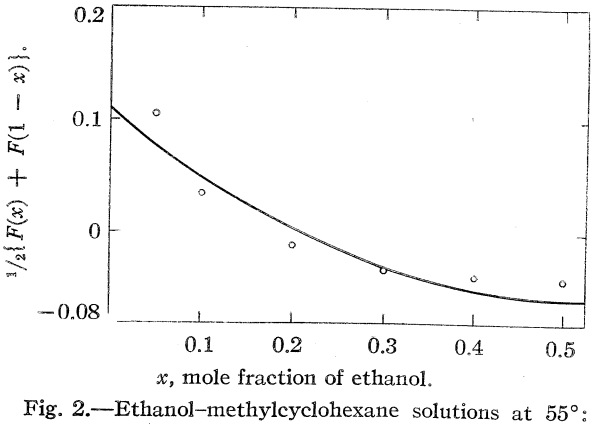


Fig. 2.—Ethanol–methylcyclohexane solutions at 55°: points, even component of $\log(\gamma_1/\gamma_2)$; curve, $0.111[1 - 6x(1-x)]$.

TABLE III

EXCESS THERMODYNAMIC FUNCTIONS OF ETHANOL–METHYLCYCLOHEXANE SOLUTIONS IN CALORIES/MOLE

Mole fract. ethanol	G^E, 35°	G^E, 55°	TS^E, 35°	H^M
0.0528	95	91	79	174
.1251	186	183	42	228
.2205	263	263	− 9	254
.3621	323	327	−62	261
.5071	334	341	−92	242
.6832	287	292	−95	192
.7792	231	235	−79	152
.9347	86	87	−29	57

The excess thermodynamic functions in Table III and Fig. 3 were calculated from the experimental values of y and p by the usual method.[3] The behavior is similar to that of the ethanol–toluene system, as well as various systems containing methanol which have been studied and discussed by Scatchard and co-workers.[11] Little

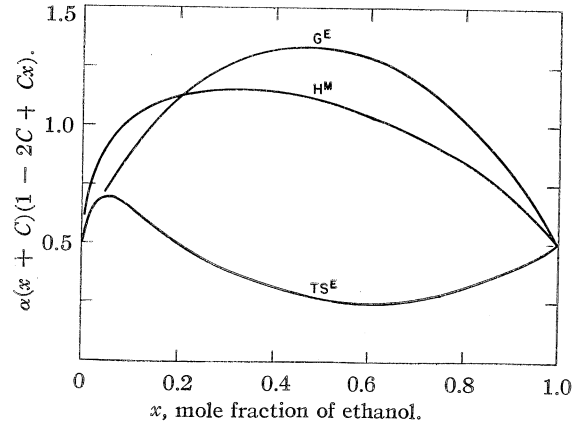


Fig. 3.—Excess thermodynamic functions of ethanol-methylcyclohexane solutions at 35°.

(10) (a) O. Redlich and A. T. Kister, *J. Chem. Phys.*, **15**, 849 (1947); (b) *Ind. Eng. Chem.*, **40**, 345 (1948).

(11) G. Scatchard, S. E. Wood and J. M. Mochel, THIS JOURNAL, **68**, 1957, 1960 (1946); S. E. Wood, *ibid.*, **68**, 1963 (1946); *J. Chem. Phys.*, **15**, 358 (1947).

can be added to their discussion except to say that a completely satisfying theory of the behavior of such solutions is not yet possible, and to emphasize again the fact that interactions between the unlike molecules are involved, in addition to the type of association of the alcohol postulated by Redlich and Kister.[10]

Summary

For the system ethanol–methylcyclohexane, densities and refractive indices have been measured at 25°. Total and partial vapor pressures have been determined at 35 and 55°. Thermodynamic consistency of the data was found to be satisfactory.

Vapor compositions are represented by the empirical equation previously developed by the authors, to within 0.005 mole fraction. They can be represented by an equation developed by Redlich and Kister, with somewhat less accuracy, and with rather anomalous values of the equilibrium constant involved.

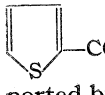
The excess free energy, entropy and enthalpy have been calculated from the data, and exhibit a similar behavior to that of other alcohol–hydrocarbon systems.

PEORIA 5, ILLINOIS RECEIVED MARCH 24, 1949

[CONTRIBUTION FROM THE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA]

The Fractional Separation of Zirconium and Hafnium by Extraction with Thenoyltrifluoroacetone[1]

BY E. H. HUFFMAN AND L. J. BEAUFAIT

The synthesis of thenoyltrifluoroacetone,  —CO—CH_2—CO—CF_3, has recently been reported by Reid and Calvin[2] and a study of the extraction of its zirconium chelate into benzene has been reported by Connick and McVey.[3] The work reported in this paper on the separation of zirconium and hafnium by means of this β-diketone was undertaken at the suggestion of M. Calvin and G. T. Seaborg. A study has been made of some differences in the extractions of zirconium and hafnium by benzene solutions of thenoyltrifluoroacetone (referred to as HT in equations and tables) from aqueous 2 *M* perchloric acid and the results applied to separations of these elements.

Zirconium is generally regarded as being in the form of ZrO^{++} in acid solutions. The complexing of zirconium by the diketone is negligible in the aqueous phase and the only important species in the benzene phase is ZrT_4.[3] The reaction then is expressed by the equation

$$ZrO^{+2} + 4HT = ZrT_4 + H_2O + 2H^+$$

and, assuming constant acid concentration, the equilibrium constant by

$$\log K = \log [ZrT_4]/[ZrO^{+2}] - 4 \log [HT] = \log R - 4 \log [HT]$$

where *R* is the extraction coefficient. If the zirconium is in the form of the simple Zr^{+4} ion in 2 *M* perchloric acid, as recently reported,[4] the expression for the equilibrium constant is not changed, providing that the zirconium ion is monomeric. Values for *R* and *K* have previously been determined[3] for zirconium using trace amounts of radioactive Zr^{95}.

The close similarity of zirconium and hafnium in chemical behavior makes it logical to assume that the above equations apply to both elements. The determination of values for *R* and *K* for both zirconium and hafnium, using macro quantities and concentrations for which the zirconium ions has been shown to be a monomer in 2.0 *M* perchloric acid,[4] has been carried out in this work in the thenoyltrifluoroacetone concentration range of 4×10^{-3} to 3×10^{-2} for zirconium and 10^{-2} to 7×10^{-2} for hafnium.

Experimental

Materials.—Thenoyltrifluoroacetone of 99.5% purity was obtained from M. W. Davis and H. R. Lehman of this Laboratory. Weighed amounts were dissolved in reagent thiophene-free benzene to give solutions of the desired concentrations.

Zirconium solutions were prepared in a manner similar to that of Connick and McVey.[3] Recrystallized $ZrOCl_2 \cdot 8H_2O$ was dissolved in 2.0 *M* perchloric acid to prepare a stock solution of approximately 0.09 *M* zirconium.

Tracer zirconium solutions were prepared from carrier-free Zr^{95} in 5% oxalic acid which was received from the Isotopes Branch, United States Atomic Energy Commission. This solution was made about 10 *M* in nitric acid and carrier zirconium added from the above stock solution. The solution was purified by the following treatment.[3] A small amount of 0.1 *N* potassium permanganate was added to precipitate manganese dioxide which carries the radioactive columbium but not zirconium. This precipitation was carried out three times to remove both oxalic acid and columbium. The zirconium solution was then diluted to about 1 *M* nitric acid and extracted with 0.02 *M* thenoyltrifluoroacetone in benzene, and the benzene phase washed twice with 2 *M* perchloric acid. The benzene solution was removed to a platinum dish and fumed with sulfuric acid with the addition of small amounts of 30% hydrogen peroxide to destroy organic matter. It was then diluted and zirconium hydroxide precipitated with ammonium hydroxide. The precipitate was dissolved in hydrochloric acid and the

(1) This paper is based on work done under the auspices of the Atomic Energy Commission.

(2) J. C. Reid and M. Calvin, MDDC-1405(BC-75), August 13, 1947.

(3) R. E. Connick and W. H. McVey, The Aqueous Chemistry of Zirconium, UCRL-101, March 1, 1948.

(4) W. H. Reas, Thesis, University of California, 1948.

TABLE I

ZIRCONIUM

$(HT)_B$ added	$(\mu g\ Zr/ml.)_B$	$(\mu g\ Zr/ml.)_W$	Act. coef. of HT and of ZrT_4	Activity of HT in benzene [HT]	Dist. ratio R	K
0.004900	6.50	181	0.999	0.00450	0.0359	8.8×10^7
.007950	21.5	144	.998	.00682	0.149	6.9
.00980	37.0	80.0	.997	.00795	0.461	11.5
.00980	43[a]	136[a]	.997	.00768	0.316	9.1
.01470	81.0	56.7	.995	.01081	1.42	10.4
.01470	86.8	75.3	.995	.01056	1.14	9.2
.01960	101	19.3	.991	.01465	5.18	11.3
.01960	115	39.5	.992	.01407	2.89	7.4
.01960	35.7	5.00	.988	.01735	7.05	7.8
.01960	104	41.0	.991	.01452	2.53	5.7
.01960	178	123	.994	.01142	1.44	8.5
.01960	224	235	.996	.00949	0.949	11.7
.01960	135[a]	44[a]	.992	.01321	3.04	10.0
.02485	162	21.2	.988	.01708	7.55	8.9
.02940	126	5.33	.983	.02238	23.2	9.3
.03430	173	3.42	.979	.02550	49.7	11.7
.03920	120	0.940	.974	.03220	125	11.6

[a] Analysis by tracer Zr^{95}.

zirconium hydroxide precipitated twice more to remove sulfate. Concentrated hydrochloric acid was then used to dissolve the hydroxide and this solution diluted to 6–7 *M* hydrochloric acid to precipitate $ZrOCl_2 \cdot 8H_2O$. A weighed amount of this salt was then dissolved in 2 *M* perchloric acid to give a stock solution approximately 0.003 *M* in zirconium.

Hafnium solutions were prepared from hafnium dioxide which contained 0.4% zirconium. This material was prepared from a commercial product, containing 5% zirconium, during preliminary extractions with 0.02 *M* thenoyltrifluoroacetone to explore the possibilities of the separation method. The zirconium content before and after purification was based on spectrographic analyses, as reported below. A weighed amount of the dioxide was warmed with concentrated nitric acid and a small amount of 48% hydrofluoric acid in a platinum dish until a clear solution was obtained which was then evaporated to near dryness. About 0.5 ml. of concentrated sulfuric acid was added and fumed for five to ten minutes. The preparation of $HfOCl_2 \cdot 8H_2O$ then followed the method given above for tracer $ZrOCl_2 \cdot 8H_2O$, beginning with dilution of the sulfuric acid solution. Tracer Hf^{181} solutions were prepared in the same way, using hafnium dioxide obtained from the Isotopes Branch, United States Atomic Energy Commission.

Analysis.—Colorimetric analyses were made with a Beckman spectrophotometer by G. Iddings who adapted the following method from that of Liebhafsky and Winslow[5] to correct for the effects of the organic substances and perchloric acid present. One-half ml. of saturated alizarin is added to a 25 ml. volumetric flask and then, in order, 10 ml. of 95% ethanol, 4 ml. of 2 *M* perchloric acid including that to be added from the sample, 1.0 ml. of 0.02 *M* thenoyltrifluoroacetone in benzene including that to be added from the sample, benzene or aqueous phase sample containing 25–90 μg of Zr or 25–125 μg of Hf, and 1 ml. of 2 *M* hydrochloric acid. After mixing, ammonium hydroxide is added carefully until the red color just appears and the mixture allowed to stand for five minutes. One normal hydrochloric acid is added until the red color disappears and then 0.10 ml. of 7 *M* hydrochloric acid is added in excess. The volume is made to 25 ml. with 95% ethanol and the mixture allowed to stand for four hours before the spectrophotometer reading is taken. Standard curves prepared by this procedure show that the zirconium and hafnium are colorimetrically equivalent, on a mole basis, in contrast to previous results.[5] The difference is probably due to the variation in the method of forming the lakes.

Radioactive analyses of zirconium were made using micropipets to obtain samples containing 500–1500 counts per minute. The samples were evaporated on platinum discs under an infrared lamp and counted in a Geiger counter, first with an aluminum absorber of 30 mg./sq. cm. and then with one of 150 mg./sq. cm. The differences in the two counts give that of the zirconium alone without the count of the active columbium which had grown in. The ratio of count to weight was obtained by evaporating a larger sample of the stock solution, igniting to zirconium dioxide and weighing. Hafnium radioactive analyses were made in a similar manner but counted without absorbers.

For the determination of extraction coefficients micropipets were used to obtain approximate weights of zirconium or hafnium from the stock solutions and the volume made to 5 ml. with 2 *M* perchloric acid. Five ml. of a benzene solution of thenoyltrifluoroacetone was then added and the mixture shaken for eighty minutes, although equilibrium was found to be reached within forty minutes for these amounts. Aliquots of the benzene and aqueous phases were then taken for analysis.

Results

Table I gives the results found for zirconium on the distribution ratios and equilibrium constant. Columns one, two and three give, respectively, the molar concentrations of diketone added, the micrograms per ml. of zirconium in the benzene phase and the micrograms per ml. in the aqueous phase at equilibrium. The free diketone concentration, not allowing for solubility in the aqueous phase, is obtained by multiplying the molar concentration of zirconium found in the benzene phase by four and subtracting the product from the molar concentration of diketone added. This answer is then multiplied by 0.974 to correct for solubility in 2 *M* perchloric acid[4] and to obtain the diketone concentration in the benzene phase. In column four are given the activity coefficients for these cor-

(5) H. Liebhafsky and E. Winslow, THIS JOURNAL, **60**, 1776 (1938).

rected diketone concentrations.[6] These also represent the activity coefficients of the chelate.[3] Column five gives the diketone activities found by multiplying the corrected concentrations by the corresponding activity coefficients. The distribution ratios in column six are obtained by multiplying the ratios of values from columns two and three by the activity coefficients of column four. Table II gives similar results for hafnium.

TABLE II

HAFNIUM

$(HT)_B$ added	$(\mu g$ Hf/ml$)_B$	$(\mu g$ Hf/ml$)_W$	Act. coef. of HT and of HfT_4	Activity of HT in benzene [HT]	Dist. ratio R	K
0.00980	15.0	296	0.997	0.00916	0.0505	7.2×10^6
.01470	41.0	234	.993	.01333	0.174	5.5
.01491	45.0	280	.993	.01345	0.160	4.9
.01960	73.8	212	.988	.01727	0.344	3.9
.01960	83.0	202	.988	.01707	0.406	4.8
.01960	89.0	282	.988	.01694	0.312	3.8
.01960	70[a]	270[a]	.988	.01735	0.258	2.9
.02450	132	148	.985	.02067	0.879	4.8
.02940	184	90.5	.981	.02415	1.99	5.9
.02940	221	128	.982	.02338	1.70	5.7
.02940	205[a]	135[a]	.982	.02373	1.49	4.7
.03920	238	31.8	.973	.03210	7.29	6.9
.03920	272	66.7	.974	.03141	3.97	4.1
.03920	261[a]	79[a]	.974	.03164	3.22	3.2
.04473	277	46.5	.969	.03637	5.78	3.3
.04900	233	19.0	.965	.04115	11.9	4.2
.04900	266	19.0	.966	.04049	13.5	5.0
.04900	260	19.0	.966	.04063	13.2	4.9
.05880	320	20.0	.958	.04818	15.3	2.8
.05880	272	9.67	.958	.04918	26.9	4.6
.05880	292	13.3	.958	.04876	21.1	3.7
.05880	324	15.0	.958	.04809	20.7	3.9
.05880	321[a]	19	.958	.04816	16.1	3.0
.07840	263	2.16	.945	.06674	115	5.8

[a] Analysis by tracer Hf^{181}.

The dependence of the extraction coefficients on the diketone activities for zirconium and hafnium are given in the figure. The straight lines are drawn with a slope of four and corresponding to the average values found for the equilibrium constants.

A good separation of hafnium was carried out on a solution in 2 *M* perchloric acid containing 22.9 mg. of hafnium and 13.6 mg. of zirconium in 150 ml. Two extractions were made with 150-ml. portions of 0.025 *M* thenoyltrifluoroacetone and 6.31 mg. of hafnium was recovered in the aqueous phase, as determined by tracer count. The zirconium present in the aqueous phase was then too small to be determined by a combination of colorimetric and tracer Hf^{181} analysis. Spectrographic analysis, made on the perchloric acid solution, showed the presence of less than 1.2% zirconium based on the hafnium present. Calculations from the curves show that about 1% zirconium should be present.

In another separation, carried out before the data for the curves were obtained, 78.6 mg. of hafnium and 3.93 mg. of zirconium, from a commercial hafnium dioxide, were dissolved in 300 ml. of 2 *M* perchloric acid. This solution was then extracted with three 300-ml. portions of 0.02 *M* thenoyltrifluoroacetone. Precipitation and ignition of the oxide from the aqueous solution gave a recovery of 39.4 mg. of hafnium. Spectrographic analysis of a hydrofluoric acid solution of this product showed a 0.4% zirconium content, which is the value calculated from the curves. This is the material which was used in preparing hafnium solutions to obtain the data for the curve. Spectrographic analyses were made by J. Conway and M. Moore of this Laboratory who report that such analyses are more sensitive when carried out on hydrofluoric acid solutions than when on perchloric acid solutions.

(6) E. L. King and W. H. Reas, UCRL BC-69, July, 1947.

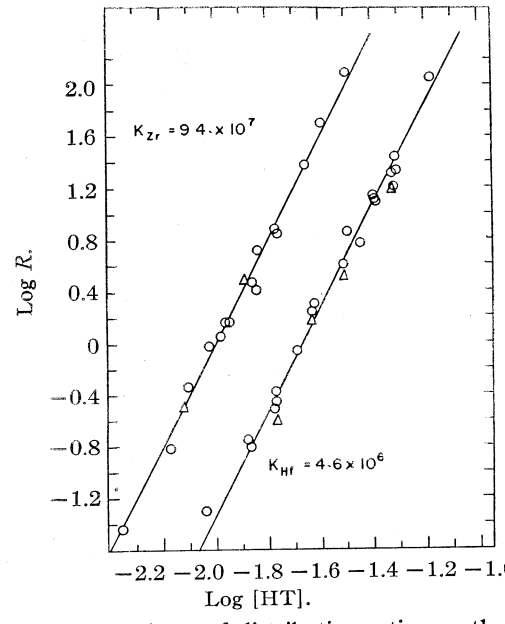


Fig. 1.—Dependence of distribution ratios on thenoyltrifluoroacetone activities: upper curve, zirconium; lower curve, hafnium; O, colorimetric analysis; △, radioactive tracer analysis.

The similarity of zirconium and hafnium makes it unlikely that better separations would be attained at other acidities and temperatures, but it is possible that higher concentrations could be worked with at higher acidities where the monomeric state is retained.

Summary

Distribution ratios for zirconium and hafnium have been found for extraction from 2 *M* perchloric acid with benzene solutions of thenoyltrifluoroacetone of varying concentration. The equilibrium constants for the zirconium and hafnium extractions were found to be 9.4×10^7 and 4.6×10^6, respectively, at this acidity.

Two extractions with 0.025 *M* thenoyltrifluoroacetone of a solution containing 59% as much zirconium as hafnium yielded 27% of the original hafnium with a content of less than 1.2% zir-

conium. Three extractions with 0.02 *M* thenoyltrifluoroacetone of a solution containing 5.0% zirconium, based on the hafnium content, gave a recovery of 50% of the hafnium with zirconium content of 0.4%.

RECEIVED NOVEMBER 22, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

The Aqueous Chemistry of Zirconium[1]

BY ROBERT E. CONNICK AND WILLIAM H. MCVEY[2]

Although the chemistry of zirconium has been the subject of numerous investigations since its discovery in 1789, practically nothing is known about the species existing in aqueous solutions of its salts. Typical is the fact that not even the formula of the uncomplexed zirconium(IV) ion, present in perchloric acid solutions, has been identified. The formulas of several complex ions in aqueous solutions such as $ZrO(SO_4)_2^{=}$ [3] and $ZrOCl_4^{=}$ [4] have been reported but the data could be interpreted equally well by assuming other species. From a search of the literature we have been forced to the conclusion that the formula of not a single aqueous zirconium(IV) species has been unambiguously identified up to the present time.

The existing information on the chemistry of zirconium was collected in 1921 by Venable[5] and more recently by Pascal.[6] Nearly all of this work, as well as that published since 1931, deals with the identification of solid phases rather than the study of ions in solution.

The purpose of the present research was to determine the formulas of the zirconium species existing in acidic aqueous solutions and to study the complexing of zirconium(IV) by a number of the more common anions

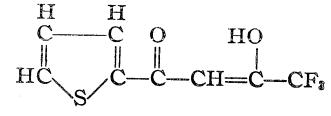
Experimental Method

The usual procedures for the determination of the formulas of species in solution, such as cell measurements, freezing point lowering, spectrophotometric analysis, *p*H determinations, solubility studies, etc., are not readily applicable in the case of zirconium because of the great tendency for hydrolysis to take place except in quite acidic solutions.

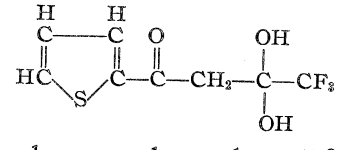
The experimental method employed involves the measurement of an equilibrium in which zirconium(IV) is distributed between the aqueous phase being investigated and an organic phase containing a chelating agent. The zirconium is inappreciably complexed by the chelating agent when in the aqueous phase, yet forms a chelate which is soluble in the organic phase and which is in equilibrium with whatever species exist in the aqueous phase. Any complexing of species in the aqueous phase is quantitatively reflected in a decrease of the extraction of the zirconium into the organic phase.

The method used in the present study is clearly a powerful one and it should find application in the study of many similar systems.

Calvin[7] has investigated the complexing properties of several chelating agents and the particular chelating agent used in this work, thenoyltrifluoroacetone was one prepared by Calvin and Reid.[8] This compound, hereafter referred to as TTA, is a weak acid having the following structure in the enol form



When TTA is equilibrated between dilute acid and benzene, the principal species in the aqueous phase is the hydrate[9]



while in the benzene phase, about 15% occurs in the hydrate form and 85% in the enol form. The keto form apparently is not an important species in this system. In aqueous solution TTA is a weak acid with an ionization constant[10] of 6.7×10^{-7}.

The distribution coefficient of TTA between benzene and a dilute acidic, aqueous phase favors the benzene phase, *i. e.*, at low TTA concentrations

$$(TTA)_b/(TTA)_{aq} = 40$$

The activity coefficient of TTA in benzene has been measured by King and Reas[9] who found it to decrease significantly below unity at TTA concentrations above 0.01 *M* in the benzene phase.

(1) This research was carried out in the Radiation Laboratory and the Chemistry Department of the University of California under the auspices of the United States Atomic Energy Commission.

(2) Present address, General Electric Co., Hanford Engineer Works, Richland, Wash.

(3) R. Ruer, *Z. anorg. allgem. Chem.*, **42**, 87 (1904); **46**, 449 (1905).

(4) W. Pauli and M. Adolf, *Kolloid-Z.*, **29**, 173 (1921).

(5) Francis P. Venable, "Zirconium and Its Compounds," American Chemical Society Monograph Series, New York, N. Y., 1921.

(6) P. Pascal, "Traité de Chimie Minerale," Masson and Company, Paris, 1931–1932.

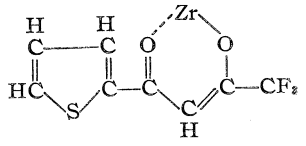
(7) M. Calvin, Manhattan Project Report, CN-2486, Dec. 1, 1944.

(8) J. C. Reid and M. Calvin, MDDC-1405, Aug. 13, 1947.

(9) E. L. King and W. H. Reas, "Atomic Energy Commission Report," BC-69, July, 1947.

(10) E. Zebroski, Atomic Energy Commission Report, BC-63, July 1, 1947.

The zirconium chelate species which is extracted into the benzene phase is a neutral molecule consisting of a zirconium ion bonded to four TTA ions. Presumably each TTA ion is attached by two oxygens in the following manner



with the two double bonds in the zirconium ring capable of resonating between the two carbon–oxygen and carbon–carbon bonds.

Materials and Analytical Procedures.—In most of the experiments carrier-free, radioactive Zr^{95} tracer was employed. In some experiments macro concentrations of inactive zirconium were used and in a few of the runs both radioactive and macro amounts of inactive zirconium were present. The inactive zirconium was obtained from City Chemical Corporation as $ZrOCl_2 \cdot 8H_2O$ and was recrystallized several times from concentrated hydrochloric acid in the form of large crystalline needles of $ZrOCl_2 \cdot 8H_2O$. This solid was dissolved in 1.00 *M* perchloric acid to give a 0.1 *M* solution of zirconium(IV) containing 0.2 *M* chloride ion. The solution was clear except for a slight Tyndall beam and remained so over a period of many months.

The Zr^{95} tracer, which was obtained from Oak Ridge, decays[11] with a 65 day half-life to Cb^{95} by emission of a beta particle and gamma rays. The columbium in turn decays with a 35 day half-life to stable Mo^{95} with the emission of a beta particle and a gamma ray. A small fraction of the columbium appears to be formed in an excited state, which drops to the ground state with a 90 hour half-life.

The zirconium tracer, containing radioactive columbium, was received in a 5% oxalic acid solution. The solution was made 10 *M* in nitric acid and a small amount of 0.1 *N* potassium permanganate added to precipitate manganese dioxide, which was removed by centrifugation. This process was repeated several times, the potassium permanganate being reduced by water in the later precipitations. The purification served the dual purpose of eliminating the oxalic acid and the radioactive columbium, which is carried by manganese dioxide. Further purification from columbium and removal of nitric acid were achieved by extracting the zirconium into a benzene–TTA solution and washing the benzene phase repeatedly with 2.0 *M* perchloric acid. Columbium is not as readily extracted into the organic phase as is zirconium. Finally the benzene phase was diluted ten-fold with benzene, to lower the TTA concentration, and the zirconium was re-extracted into a small volume of 2.00 *M* perchloric acid.

In the analysis for radioactive zirconium, aliquots from both phases, usually 0.100 ml. in size, were mounted on 22-mm. square glass cover slides and counted, either using a Geiger counter with a mica-window tube or an ionization chamber attached to a vibrating reed electrometer. The reproducibility of these analyses was generally of the order of 2 to 3%. The samples were counted through an approximately 10 mg. per sq. cm. aluminum absorber in an effort to minimize the activity from columbium, which grows into the samples from the decay of zirconium; the columbium beta particles are considerably less energetic than those of zirconium. The activity and counting times were such as to give a probable counting error of approximately 0.7% in those experiments where the extraction coefficient was about unity.

A colorimetric method, developed by Liebhafsky and Winslow[12] and capable of determining quantitatively a few micrograms of zirconium, was used for the analysis of macro amounts of zirconium. The reproducibility of the analysis was fairly good, *i. e.*, of the order of 3%; however, the process of lake formation was greatly slowed down in the presence of TTA. The apparent concentration of zirconium increased slowly over a period of several hours. Attempts to improve the analysis by destruction of the TTA with bromine, chlorine and sodium hydroxide were unsuccessful. The spectrophotometer reading used for calculating the zirconium concentration was the nearly constant value obtained after the solution had stood for several hours.

Perchloric acid solutions were prepared by diluting G. Frederick Smith double vacuum distilled perchloric acid with conductivity water. The solutions were standardized by the mercuric oxide–potassium iodide method. Lithium perchlorate, used in the hydrolysis experiments to maintain constant ionic strength, was purified by recrystallizing G. Frederick Smith $LiClO_4 \cdot 3H_2O$ from water. The solution was analyzed by evaporating aliquots with sulfuric acid, igniting and weighing as anhydrous lithium sulfate. Pure, vacuum distilled TTA was kindly furnished by Dr. James C. Reid. The benzene was thiophene-free. All other chemicals were of reagent or C. P. grade and were used without further purification.

The experiments were carried out by mixing 25-ml. portions of the two phases, aqueous and benzene, in 100-ml. volumetric flasks. A mechanical shaker was so arranged that the flask was immersed in a water thermostat at 25.00 ± 0.05°. The shaking was vigorous, the flasks going through 1520 up and down movements per minute with a stroke of 2.5 cm.

All concentrations are expressed in moles per liter of solution, designated by the symbol *M*.

Nature of Extraction Equilibrium

Formula of Zirconium Chelate and Evidence for Non-complexing of Zirconium by TTA in Aqueous Phase.—Before the zirconium chelate extraction equilibrium can be used in the study of zirconium species in aqueous solutions, it is necessary to determine the formula of the chelate compound extracted into benzene and to establish that there is no appreciable complexing of zirconium by TTA in the aqueous phase. These facts may be ascertained from a study of the extraction coefficient as a function of the TTA concentration at constant acidity.

One possible equation for the extraction of zirconium is

$$Zr^{+4}(aq) + 4HK(b) = ZrK_4(b) + 4H^+(aq) \quad (1)$$

where HK has been used to represent TTA. However, the zirconium in the aqueous phase may be hydrolyzed and complexed by TTA, and the chelate in the benzene phase may contain hydroxide as well as TTA groups. To include all possibilities we write the general equation for the reaction

$$Zr(OH)_nK_m^{+4-n-m} + (p - m)HK = Zr(OH)_{4-p}K_p + (4 - m - n)H^+ + (n + p - 4)H_2O \quad (2)$$

and we may define the equilibrium constants

$$K_{m,n,p} = \frac{[Zr(OH)_{4-p}K_p][H^+]^{4-m-n}[H_2O]^{n+p-4}}{[Zr(OH)_nK_m^{+4-n-m}][HK]^{p-m}} \quad (3)$$

Brackets have been used to represent activities of the enclosed species. (Parentheses will be used to indicate concentrations.) The designation of the phase in which each species exists has been omitted to simplify the writing of the equation. The spe-

(11) G. T. Seaborg and I. Perlman, "Table of the Isotopes," Department of Chemistry and Radiation Laboratory, University of California, Report UCRL-179, August, 1948.

(12) H. Liebhafsky and E. Winslow, THIS JOURNAL, **60**, 1776 (1938).

cies $Zr(OH)_nK_m^{+4-n-m}$ and H^+ occur in the aqueous phase while the species $Zr(OH)_{4-p}K_p$ and HK are components of the benzene phase. All species in the benzene phase have been assumed to be neutral molecules because of the low dielectric constant of this solvent. The letter K has been used to indicate both an equilibrium constant and the ion of TTA; however, there should be no confusion as in the latter case it will always appear within brackets.

An extraction coefficient expressed in terms of activities is defined as the sum of the activities of zirconium species in the benzene phase divided by the sum of the activities of zirconium species in the aqueous phase, *i. e.*

$$E_a = \frac{\sum_p [Zr(OH)_{4-p}K_p]}{\sum_n \sum_m [Zr(OH)_nK_m^{+4-n-m}]} \quad (4)$$

From equation (3) the relationship holds

$$[Zr(OH)_nK_m^{+4-n-m}] = \frac{[ZrK_4][H^+]^{4-m-n}[H_2O]^n}{K_{m,n,4}[HK]^{4-m}} \quad (5)$$

From equations (3) and (5)

$$\frac{[ZrK_4][H^+]^{4-m-n}[H_2O]^n}{K_{m,n,4}[HK]^{4-m}} = \frac{[Zr(OH)_{4-p}K_p][H^+]^{4-m-n}[H_2O]^{n+p-4}}{K_{m,n,p}[HK]^{p-m}} \quad (6)$$

Solving for the activity of the general species in the benzene phase

$$[Zr(OH)_{4-p}K_p] = \frac{[ZrK_4][H_2O]^{4-p}K_{m,n,p}}{[HK]^{4-p}K_{m,n,4}} \quad (7)$$

Since this equation holds for any set of values of m and n, we shall for simplicity choose m and n to be zero. Then

$$[Zr(OH)_{4-p}K_p] = \frac{[ZrK_4][H_2O]^{4-p}K_{o,o,p}}{[HK]^{4-p}K_{o,o,4}} \quad (8)$$

Substituting equations (8) and (5) into equation (4), one obtains

$$E_a = \frac{\sum_p \frac{[ZrK_4][H_2O]^{4-p}K_{o,o,p}}{[HK]^{4-p}K_{o,o,4}}}{\sum_m \sum_n \frac{[ZrK_4][H^+]^{4-m-n}[H_2O]^n}{K_{m,n,4}[HK]^{4-m}}} \quad (9)$$

The factor $[ZrK_4]$ cancels completely between the numerator and denominator. Taking the partial derivative of the logarithm of E_a with respect to the logarithm of the activity of HK and substituting from equations (8) and (5) gives

$$\frac{\partial \ln E_a}{\partial \ln [HK]} = \frac{\sum_p (p-4)[Zr(OH)_{4-p}K_p]}{\sum_p [Zr(OH)_{4-p}K_p]} - \frac{\sum_m \sum_n (m-4)[Zr(OH)_nK_m^{+4-m-n}]}{\sum_m \sum_n [Zr(OH)_nK_m^{+4-m-n}]} \quad (10)$$

Limits may be placed on the values of m and p on the basis of the size of the zirconium ion. It is found both theoretically and experimentally that the maximum coördination number of Zr^{+4} for oxygens does not exceed eight.[13] Assigning two coördination positions to each chelate group then limits the maximum possible number values of m and p to four. With this assumption equation (10) may be rewritten in the form

$$\partial \ln E_a / \partial \ln [HK] = -4f_0 - 3f_1 - 2f_2 - f_3 + 4f_0' + 3f_1' + 2f_2' + f_3' \quad (11)$$

where each f is the fraction of the total activity of that phase contributed by species containing the indicated number of chelate groups. The unprimed f's refer to the benzene phase and the primed f's to the aqueous phase. It should be pointed out that in performing the differentiation leading to equation (11) it was necessary that the activity of water and of hydrogen ion remained constant.

An equation having exactly the same form as (11) may be derived on the basis of an extraction coefficient, E', defined as the ratio of the sum of the activities of the zirconium species in the benzene phase to the total concentration of zirconium in the aqueous phase. The f's represent fractions of the total zirconium activity in the benzene phase and the f''s fractions of the total zirconium concentration in the aqueous phase. An additional restriction is imposed on the differentiation, *i. e.*, that the activity coefficients of all species in the aqueous phase remain constant.

This equation corresponds to the experimental conditions used in the determination of the dependence of the extraction coefficient on TTA activity, but unfortunately only E_c, the extraction coefficient expressed in concentrations, and not E' can be determined experimentally.

The activity coefficients of the individual zirconium chelate species in the benzene phase as a function of the TTA concentration are not known. For simplicity it will be assumed that they all behave like γ_{ZrK_4}, the activity coefficient of ZrK_4, and that this in turn is equal to γ_{UK_4} measured by Reas.[14] No appreciable error should be introduced by these assumptions since γ_{UK_4} varies little over the range of TTA concentration used. On this basis $E' = E_c\gamma_{ZrK_4}$.

From the slope of the line obtained by plotting the logarithm of the extraction coefficient E' *versus* the logarithm of the activity of TTA (see equation (11)), one should be able to determine the number of TTA groups present in the zirconium species in the benzene phase and in the aqueous phase. (Experiments in which only the TTA activity is varied provide no information about the number of hydroxide groups or other anions associated with the various zirconium species.) For any slope less than four, a number of combinations of the various f's and f''s would fit the data. The important point is that, should the slope be four, there is only one combination which will fit the

(13) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939.

(14) W. H. Reas, unpublished work, this Laboratory.

data and that is for all of the f's to be zero, and all of the f''s to be zero except f_0' which must be unity, *i. e.*, $p = 4$ and $m = 0$. Then the equation for the reaction must be written

$$Zr(OH)_n^{+4-n} + 4HK = ZrK_4 + (4 - n)H^+ + nH_2O \quad (12)$$

Experimental Results

The experiments designed to test the dependence of the extraction coefficient on the TTA concentration were carried out in 2.00 M perchloric acid. The conditions and results are presented in Table I.

TABLE I

DEPENDENCE OF EXTRACTION COEFFICIENT ON TTA ACTIVITY

Trace Concentrations of Zirconium, 2.00 M $HClO_4$, 25°

(HK)$_b$	$\gamma_{HK} = \gamma_{ZrK_4}$	E_c	[HK]	E'	log [HK]	log E'
.00506	0.999	0.046	0.00505	0.046	−2.2966	−1.337
.00583	.998	.090	.00582	.0898	−2.2351	−1.047
.00778	.997	.258	.00776	.257	−2.1101	−0.590
.00972	.996	.65	.00968	.647	−2.0141	− .189
.01361	.992	2.19	.01350	2.17	−1.8697	.337
.01673	.988	4.45	.01653	4.40	−1.7817	.644
.01945	.986	6.8	.01918	6.70	−1.7172	.826
.02918	.977	14.3	.02851	14.0	−1.5450	1.146
.02839	.977	45.0[a]	.02774	44.0	−1.5569	1.644[a]

[a] Value obtained when new aqueous phase was equilibrated with benzene phase of previous experiment, in order to eliminate columbium; see text.

In the first column is given the TTA concentration (moles per liter) in the benzene phase at equilibrium, calculated from the known concentration of TTA added and a distribution ratio of 35 for TTA between the benzene phase and the aqueous phase. (The distribution coefficient decreases from 40 in 0.1 M hydrochloric acid[9] to 35 in 2 M perchloric acid relative to benzene.) In column two is listed the value of the activity coefficient of TTA[9] corresponding to the concentration in column one. Reas[14] found that the activity coefficient of uranium(IV) chelate in benzene at various TTA concentrations was, within experimental error, the same as for TTA itself, hence the values of column two also represent γ_{ZrK_4} in benzene. In column three is given the ratio of the concentrations of zirconium in the benzene and aqueous phases as determined from the zirconium radioactivity. In columns four and five are listed the values of the activity of TTA and E', calculated from the relationships [HK] = (HK)γ_{HK} and $E' = E_c\gamma_{ZrK_4}$, respectively. The logarithms of the values of the activity of TTA and E', given in columns six and seven, are plotted in Fig. 1. In the experiments of Table I and all following experiments, both phases were analyzed as a function of time in order to make certain that equilibrium had been established.

The straight line in Fig. 1 has been drawn with a slope of four. It can be seen that the experimental points, indicated by solid circles fit this slope within experimental error up to a TTA activity of 10^{-2}, but, from there on, the points appear to fall off to a smaller slope. That this effect is not real, but arises from radioactive columbium impurity in the stock tracer, is shown by the point at highest TTA activity (designated by an open circle in Fig. 1) which falls on the line of slope four. In this experiment columbium was eliminated by reëquilibrating the benzene phase of the experiment at 0.02918 M TTA with a fresh aqueous phase. The columbium was removed along with the first aqueous phase as it is not extracted appreciably into benzene under these conditions. Presumably the other points which deviate would also be brought into line if the columbium were eliminated. No attempt was made to calculate a correction for these experiments because columbium is radio-colloidal in such solutions and probably does not behave reproducibly. The correction for columbium becomes small, *i. e.*, of the order of magnitude of the experimental accuracy in the experiments where the extraction coefficient is low.

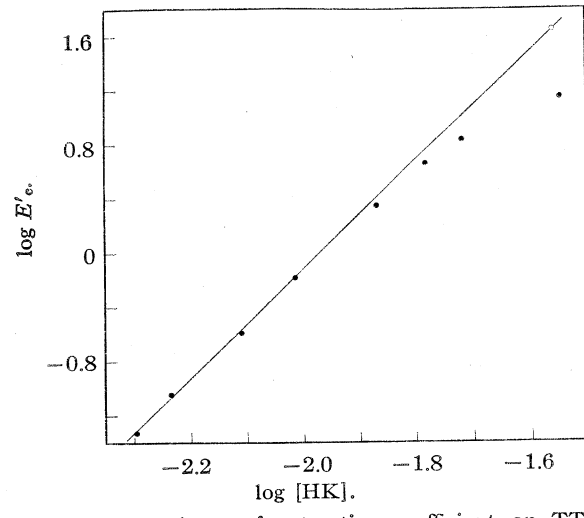


Fig. 1.—Dependence of extraction coefficient on TTA activity.

From the above results the extraction coefficient appears to follow a fourth power dependence on TTA activity within the accuracy of the measurements. Therefore the zirconium species in the aqueous phase are not appreciably complexed by TTA, and the only important species in the benzene phase is ZrK_4.

Comparison of Extraction Coefficients of Trace and Macro Amounts of Zirconium.—Experiments performed with macro amounts of zirconium to check the trace results gave somewhat greater coefficients, as shown in Table II. The concentration of TTA in column 2 has been corrected for that used up in forming the chelate. The extraction coefficients, corrected to the same TTA concentration as in the first experiment, are given in the last column as $E_{cor.}$

The increase in the extraction coefficient at macro zirconium concentrations seems best explained by assuming the presence of a small

TABLE II

EXTRACTION COEFFICIENT AT VARIOUS CONCENTRATIONS OF ZIRCONIUM(IV)

2.00 M $HClO_4$, 25°, 0.0100 M total TTA

$(Zr(IV))_{(aq)}$ at equil.	$(HK)_b$	E_c	$E_{cor.}$
Trace	0.00972	0.58	0.58
4.7×10^{-5} M	.00964	.70	.74
5.1×10^{-4} M	.00861	.56	.91

amount of impurity which partially complexed the trace zirconium. At high zirconium concentrations the effect would become small if the total amount of impurity were small compared to the total zirconium. If it is assumed that the amount of impurity was the same in each experiment, certain deductions may be made. Since the extraction coefficient of the second experiment is greater than for the trace experiment, an appreciable part of the impurity must have been tied up in the second experiment. The relatively small change in extraction coefficient for a ten-fold increase in zirconium concentration in going from the second to the third experiment indicates that nearly all of the impurity must be complexed by zirconium in the third experiment. Therefore the concentration of the impurity must be of the order of 10^{-4} to 10^{-5} M. Further, it may be concluded that the extraction coefficient in the last experiment is near the value that would be obtained in the absence of the impurity and that about 40% of the zirconium(IV) in the aqueous phase is complexed by the impurity in the first experiment.

A strenuous effort was made to eliminate the impurity. Different sources of all reagents were tried. The magnitude of the effect varied somewhat but in no case was the effect eliminated. It was shown by a study of their complexing power that none of the substances listed in Table VI were responsible.

Impurities in the radioactive tracer were not interfering as experiments with and without tracer gave the same results and the radioactive analysis agreed with the colorimetric analysis.

Radio-colloid formation did not appear to be a likely explanation since addition of 0.01 M silicic acid did not decrease the extraction coefficient greatly (see Table VI). Polymer or true colloid formation would have caused a decrease in extraction coefficient with rising zirconium concentration.

At the present time neither the identity nor the source of the impurity is known. Its presence introduces an uncertainty into the interpretation of the data of the trace experiments. The identification of the various zirconium complexes present in the aqueous phase is believed to be correct, but the calculated stabilities of these species may be somewhat in error. It should be noted that the fourth power TTA dependence of the extraction coefficient is not affected provided the amount of impurity remained the same in all of the TTA dependence experiments.

Hydrolysis

In order to determine the degree of hydrolysis of zirconium the extraction coefficient was measured as a function of the hydrogen ion concentration. Ignoring for the moment the perturbing effect of the unknown impurity, the equation for the net reaction may be written

$$Zr(OH)_n^{+4-n} + 4HK = ZrK_4 + (4 - n)H^+ + nH_2O \quad (13)$$

assuming that perchlorate ion, in conformity with its general chemical behavior, does not complex zirconium. Equilibrium quotients expressed in concentrations may be written for equation (13)

$$K_n = \frac{(ZrK_4)(H^+)^{4-n}}{(Zr(OH)_n^{+4-n})(HK)^4} \quad (14)$$

An extraction coefficient is defined in terms of concentrations

$$E_c = \frac{(ZrK_4)}{\sum_n (Zr(OH)_n^{+4-n})} \quad (15)$$

Proceeding as before gives (for constant activity coefficient and TTA concentration)

$$\partial \ln E_c^0 / \partial \ln (H^+) = -4 + f_1 + 2f_2 + 3f_3 + \ldots \quad (16)$$

Each f is equal to that fraction of the total zirconium in the aqueous phase which has the number of hydroxide groups per zirconium indicated by the subscript. In the experiments, it was necessary to vary the TTA concentration as the acidity was varied in order to obtain measurable extraction coefficients. Therefore all measured values of E_c were corrected to a common basis, *i. e.*, the values the extraction coefficients would have had at unit activity of TTA and at $\gamma_{ZrK_4} = 1$. This quantity, E_c^0, is defined by the equation

$$E_c^0 = E_c \gamma_{ZrK_4} / (HK)^4 \gamma_{HK}^4 \quad (17)$$

It was assumed that the activity coefficients of all species in the aqueous phase remained essentially constant since the ionic strength was maintained at 2.0 by adding lithium perchlorate as the perchloric acid concentration was decreased. Some justification is obtained from the fact that the activity coefficient of hydrochloric acid in lithium chloride solutions does not change measurably from 10^{-3} M hydrochloric acid to 3 M hydrochloric acid at a total molality of 3 M.[15]

In equation (13) it has been assumed that there is no complexing of zirconium in the aqueous phase by TTA over the whole acidity range studied. This has already been shown to be the case at 2.0 M hydrogen ion. From the hydrolysis data it appears that complexing by hydroxide ion does occur to some extent in the 2 M hydrogen ion region and therefore the hydroxide ion has a stronger tendency than the chelate ion to complex zirconium under these conditions. Since the

(15) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corporation, New York, N. Y., 1943, p. 457.

ratio of chelate ion concentration to hydroxide ion concentration decreased in going to the experiments at lower acidity, it seems likely that no appreciable complexing by TTA occurred in any of the experiments.

In the trace experiments samples from the aqueous phase could not be evaporated directly for counting because of the self-absorption by lithium perchlorate. To circumvent this difficulty, the zirconium in samples from the aqueous phase was extracted completely into a benzene–TTA solution and aliquots of this phase were mounted to give plates free of solid. This procedure also served to eliminate any columbium impurity.

The experimental results are shown in Fig. 2 where log E_c^0 is plotted against log (H^+). According to equation (16) the average number of hydroxides per zirconium is the slope minus four. The two straight lines in Fig. 2 are drawn with slopes of -2 and -3 corresponding to $Zr(OH)_2^{++}$ and $ZrOH^{+3}$.

The three types of symbols in Fig. 2 represent experiments with trace amounts of zirconium in uncoated glass vessels, trace experiments in coated glass vessels and experiments with macro amounts of zirconium in uncoated glass vessels. In some of the experiments the glass was coated with "Dri-Film" to prevent the zirconium from sticking to the walls of the vessels at low acidity. "Dri-Film," which is $SiCl_2(CH_3)_2$, is hydrolyzed, by the thin film of water always present on a glass surface that has been air-dried, to give a hydrocarbon surface which is not wet by water. The coating was quite successful in preventing the sticking of zirconium to the glass but the possibility of radio-colloid formation on particles in solution was, of course, still present.

The extraction coefficients at low acidity did not fall on a smooth curve, which fact suggested the formation of a radio-colloid. This was confirmed by centrifuging experiments. Therefore the data of Fig. 2, for acidities below 0.1 *M*, should be regarded only as lower limits for the extraction coefficient.

The curve drawn through the points of the trace experiments was calculated assuming that the only important species were $ZrOH^{+3}$ and $Zr(OH)_2^{++}$. The significance of such a calculation is doubtful, however, because of the unknown effect of the impurity. If the impurity is the ion of a strong acid the break from slope -3 to -2 should have occurred at higher acidity than shown by the data. If the complexing impurity is the ion of a weak acid (which seems more likely since no ions of strong acids were found to complex zirconium strongly in 2 *M* perchloric acid), then the slope of the curve should be steeper everywhere, corresponding to less hydrolysis of the zirconium.

The macro experiments, which were run with approximately 3×10^{-4} *M* zirconium(IV) in the aqueous phase, all show higher extraction coefficients than the trace experiments. Presumably this arises from the complexing action of the impurity in the trace experiments. The two points at highest acidity in the macro runs give a slope between three and four, indicating a mixture of Zr^{+4} and $ZrOH^{+3}$. The falling off of the points for the macro experiments at low acidity may be caused by polymer formation. The discrepancy in the two points at log $(H^+) = 0.4$ may arise from the same cause, since the concentration of zirconium in the aqueous phase of the higher point was only 0.4 times that in the other experiment.

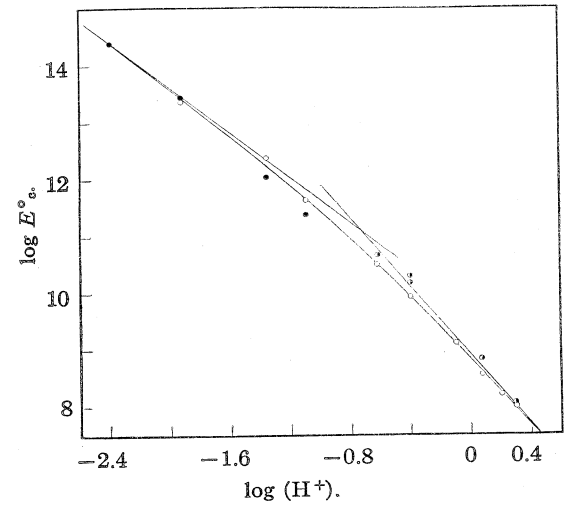


Fig. 2.—Dependence of extraction coefficient on hydrogen ion concentration: trace Zr(IV) in uncoated vessel, ○; trace Zr(IV) in "Dri-Film" coated vessel, ●; macro Zr(IV) in uncoated vessel, ◑.

From the results of the hydrolysis experiments it seems likely that at low zirconium concentrations the average zirconium species in 2 *M* perchloric acid has somewhere between zero and one hydroxide group attached, *i. e.*, lies between Zr^{+4} and $ZrOH^{+3}$.

Hydrolysis data reported in the literature give evidence of polymer formation at higher concentrations of zirconium and/or lower acidity.

Complexing

Sulfate Complexing.—The stability of the sulfate complexes of zirconium was determined by measuring the extraction coefficient as a function of sulfate concentration at constant acidity. The general equation may be written

$$Zr(OH)_n^{+4-n} + mHSO_4^- = Zr(OH)_x(SO_4)_m^{+4-x-2m} + (n-x)H_2O + (x-n+m)H^+ \quad (18)$$

The principle sulfate species in 2 *M* H^+ is HSO_4^-. Equilibrium quotients and an extraction coefficient are defined in terms of concentrations

$$K_{n,m,x} = \frac{(Zr(OH)_x(SO_4)_m^{+4-x-2m})(H^+)^{x-n+m}}{(Zr(OH)_n^{+4-n})(HSO_4^-)^m} \quad (19)$$

TABLE III

DEPENDENCE OF EXTRACTION COEFFICIENT ON BISULFATE CONCENTRATION. TRACE CONCENTRATIONS OF ZIRCONIUM, TOTAL ACIDITY 2.00 *M*, 25°

(HSO_4^-)	$(HK)_b$	$\gamma_{HK} = \gamma_{ZrK_4}$	$[HK]_b$	E_c	E_c^0	log (HSO_4^-)	log E_c^0
0.2726	0.0499	0.959	0.0478	0.692	1.40×10^5	−0.5645	5.146
.2396	.0499	.959	.0478	.831	1.68×10^5	− .6205	5.225
.1013	.0195	.986	.0192	.113	8.22×10^5	− .9945	5.915
.02921	.0195	.986	.0192	.850	6.18×10^6	−1.5345	6.791
.00974	.0167	.989	.0166	1.50	1.98×10^7	−2.0116	7.297
.003115	.0167	.989	.0166	3.28	4.34×10^7	−2.5065	7.637
.0000	.0195	.986	.0192	10.4	7.55×10^7	$-\infty$	7.878
.0000	.0167	.989	.0166	6.09	8.02×10^7	$-\infty$	7.904
				Av. of last two values	7.79×10^7	$-\infty$	7.891

$$E_c = \frac{(ZrK_4)}{\sum_m \sum_x (Zr(OH)_x(SO_4)_m^{+4-x-2m}) + \sum_n (Zr(OH)_n^{+4-n})} \quad (20)$$

Proceeding as before one obtains

$$\partial \ln E_c^0 / \partial \ln (HSO_4^-) = -f_1 - 2f_2 - 3f_3 \ldots \quad (21)$$

Each f in equation (21) is equal to the fraction of the total zirconium in the aqueous phase which is complexed by the number of sulfate groups indicated by the subscript numbers. The equations apply to conditions of constant hydrogen ion and TTA concentrations and constant values of all activity coefficients. When log E_c^0 is plotted against log (HSO_4^-) the slope of the curve gives the average number of sulfate groups per zirconium.

To obtain measurable extraction coefficients it was necessary to vary the TTA concentration. Therefore the measured extraction coefficients, E_c, were corrected to the value they would have had at unit activity of TTA and unit activity coefficient of ZrK_4, according to equation (17).

The aqueous solutions were prepared by mixing the appropriate volumes of 2.00 *M* perchloric acid and 1.95 *M* sulfuric acid, which gave solutions of essentially constant ionic strength. It was assumed that, over the range of mixtures studied, all activity coefficients of species in the aqueous phase remained constant.

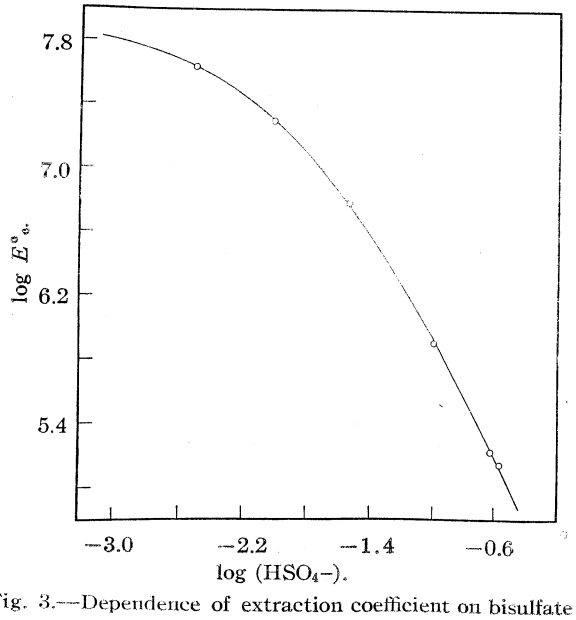


Fig. 3.—Dependence of extraction coefficient on bisulfate ion concentration.

The experimental data are presented in Table III and plotted in Fig. 3. From the slope of the curve it is found that there is an average of one sulfate per zirconium at 0.013 *M* HSO_4^- and an average of two sulfates at 0.3 *M* HSO_4^-. At neither of these points is just one species present, but rather several species, of which the predominant one is that with one and two sulfates, respectively. A mixture is obtained because the successive complexing constants do not differ greatly in magnitude.

It is not possible to determine from the data the number of hydroxide groups associated with each complex since the experiments were performed at constant acidity; however, some reasonable deductions may be made. The hydrolysis experiments indicated that zirconium in 2 *M* perchloric acid had between zero and one hydroxide groups attached, and therefore had little tendency to hold a second hydroxide when one was already present. It would be expected that, when a sulfate group is bonded to a zirconium ion, there would be little tendency for a hydroxide group to be attached in addition. Thus the sulfate complexes in 2 *M* hydrogen ion are not expected to contain hydroxide groups.

Further, it is believed that it is sulfate rather than bisulfate ion which is present in these complexes. The attachment of Zr^{+4} to a bisulfate ion should make the hydrogen ion readily ionizable, just as the attachment of one hydrogen ion in sulfuric acid makes the other hydrogen a strong acid.

The solid line drawn in Fig. 3 is a theoretical curve based on the equations

$$Zr^{+4} + HSO_4^- = ZrSO_4^{++} + H^+ \qquad K_1 = 4.6 \times 10^2$$
$$ZrSO_4^{++} + HSO_4^- = Zr(SO_4)_2 + H^+ \qquad K_2 = 53$$
$$Zr(SO_4)_2 + HSO_4^- = Zr(SO_4)_3^= + H^+ \qquad K_3 = 1$$

The equilibrium quotients were evaluated from the data by a modification of the method described

TABLE IV

DEPENDENCE OF EXTRACTION COEFFICIENT ON HYDROFLUORIC ACID CONCENTRATION

Trace Concentrations of Zirconium, 2.0 M $HClO_4$, 25°

(HF)	$(HF)_b$	$\gamma_{HK} = \gamma_{ZrK_4}$	$[HK]_b$	H^+ Correction[a]	E_c	E_c^0	log (HF)	log E_c
7.92×10^{-3}	0.3907	0.836	0.3266	0.986	1.30	9.47×10^1	−2.1013	1.976
3.98×10^{-3}	.1951	.887	.1731	.992	0.659	6.47×10^2	−2.4001	2.811
1.99×10^{-3}	.1462	.905	.1323	.990	1.40	4.09×10^3	−2.7011	3.611
9.94×10^{-4}	.0389	.966	.0385	.987	0.033	1.58×10^4	−3.0026	4.200
4.98×10^{-4}	.0487	.958	.0466	.991	.367	7.41×10^4	−3.3023	4.870
1.99×10^{-4}	.0389	.966	.0385	.994	.791	3.81×10^5	−3.7011	5.581
9.94×10^{-5}	.0292	.977	.0285	.982	.850	1.23×10^6	−4.0026	6.090
2.99×10^{-5}	.0195	.986	.0192	.990	.857	6.18×10^6	−4.5343	6.791
9.94×10^{-6}	.0167	.989	.0166	.982	1.32	1.71×10^7	−5.0026	7.233

[a] Factor by which E_c is to be multiplied to give the value it would have at 2.00 M H^+.

by Leden.[16] The first is almost certainly too small because of the impurity. Comparison of the last two experiments of Table III with the last experiment of Table II indicates this error to be about 30%. In addition, it was assumed that all of the uncomplexed zirconium was Zr^{+4} which, if not true, again causes the first equilibrium quotient to be low. The values of K_2 and K_3 should not be affected by the presence of the impurity and should be correct provided the right species have been chosen. The precision in determining K_2 is estimated to be ±8% while K_3 could be evaluated only approximately at the bisulfate concentrations used, and may be in error by a factor of two.

Fluoride Complexing.—Experiments similar to the sulfate series were performed to establish the zirconium species present in acidic solutions containing hydrofluoric acid. The following equation may be derived

$$\partial \log E_c^0 / \partial \log (HF) = -f_1 - 2f_2 - 3f_3 - \ldots \quad (22)$$

where each f represents the fraction of the zirconium which has the indicated number of fluoride ions attached.

The data are given in Table IV and plotted in Fig. 4. The solutions were prepared by adding small aliquots of a sodium fluoride solution to 2.00 M perchloric acid. A small acidity correction, for dilution of the perchloric acid and formation of HF, was applied (see column 5 of Table IV).

At the high concentrations of TTA used in some of the experiments there would probably be complexing of zirconium by TTA in the aqueous phase if there were no hydrofluoric acid present, and there is the possibility that the zirconium is complexed by both fluoride ion and TTA. However, in view of the extreme stability of the fluoride complexes, it seems unreasonable that there could be much competition by TTA for the zirconium in the presence of hydrofluoric acid, especially since the HF concentration was increased much more than the TTA concentration. To settle this point, it would be necessary to measure the TTA dependence in the presence of hydrofluoric acid. In the present experiments a fourth power TTA dependence was assumed in correcting the extraction coefficients to unit activity of TTA.

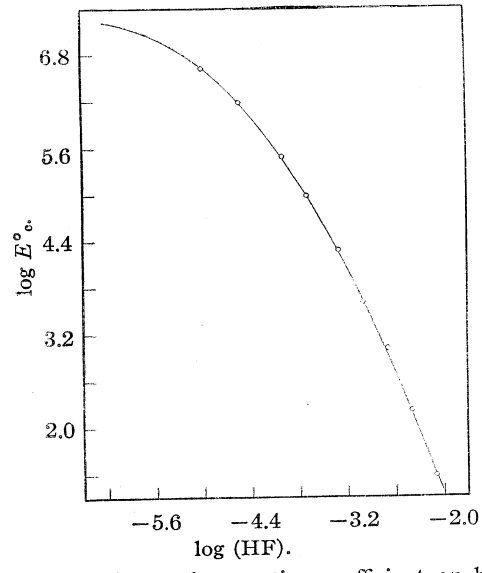


Fig. 4.—Dependence of extraction coefficient on hydrofluoric acid concentration.

The solid curve of Fig. 4 was plotted using the following values of the equilibrium quotients for the indicated equilibria

$$Zr^{+4} + HF = ZrF^{+3} + H^+ \qquad K_1 = 6.3 \times 10^5$$
$$ZrF^{+3} + HF = ZrF_2^{+2} + H^+ \qquad K_2 = 2.10 \times 10^4$$
$$ZrF_2^{+2} + HF = ZrF_3^{+} + H^+ \qquad K_3 = 6.7 \times 10^2$$

(16) I. Leden, *Z. physik. Chem.*, **188**, 160 (1941). The following modifications were made. The logarithm of the function on the left of Leden's equation (6) was plotted *versus* the logarithm of the HSO_4^- concentration. In the region where only the first and second complexes are important this curve has a universal shape, approaching a constant value at low HSO_4^- concentrations. This value is related to the first association constant and was determined by obtaining the best fit of the data to a theoretical plot. To get the second constant, the first constant was subtracted from the left side of (6) and this quantity divided by the HSO_4^- concentration. The logarithm of this quantity was plotted *versus* log (HSO_4^-) and now the same universal curve results, as long as complexes containing more than three sulfates are unimportant. The constant was determined as before. The process may be repeated to give higher constants.

The method of evaluating the equilibrium quotients was the same as in the preceding section; the estimated precision in evaluating K_1 and K_2 is $\pm 10\%$, while that for K_3 is $\pm 30\%$.

To illustrate the stability of the fluoride complexes, one calculates from the data of Table IV that in 10^{-5} M hydrofluoric acid, 78% of the zirconium is complexed by fluoride and that in 8×10^{-3} M hydrofluoric acid, all but 0.00012% of the zirconium is complexed. From the slope of the curve of Fig. 4 and equation (22) the average number of fluoride groups per zirconium ion is found to be one at 2×10^{-5} M hydrofluoric acid, two at 5×10^{-4} M hydrofluoric acid and three at 10^{-2} M hydrofluoric acid. The same considerations apply here as in the case of the sulfate complexes regarding the validity of the equations and the values of the equilibrium quotients. Again, the successive complexing constants differ so little that all solutions contain appreciable amounts of several species.

It was thought that hydrofluoric acid would attack the glass walls of the container and be converted to fluosilicate ion or some hydrolyzed form of this ion. Therefore all of the above experiments were run in vessels coated with "Dri-Film" to prevent the hydrofluoric acid from coming in contact with the glass. In no case was there any evidence of attack of the glass and the extraction appeared to come to equilibrium and remained steady thereafter. Several preliminary experiments were run in non-coated glass vessels, but even here there was no sign of attack, as the extraction coefficients were about the same as with the coated vessels. Apparently the hydrofluoric acid does not attack silica at this rather high acidity (2.0 M) and relatively low concentration of hydrofluoric acid.

Chloride and Nitrate Complexing.—The extraction coefficient of trace zirconium was measured in mixtures of hydrochloric and perchloric acids at a total hydrogen ion concentration of 2.00 M. Similar experiments were carried out with mixtures of nitric acid and perchloric acid. The data are given in Table V. The per cent. uncomplexed was assumed to be equal to the extraction coefficient for the given solution divided by the extraction coefficient in 2.00 M perchloric acid. This presumes that there are no significant differences in activity coefficients in the various solutions studied.

TABLE V

CHLORIDE AND NITRATE COMPLEXING AT 25° AND 2.00 M H^+

$HClO_4$ moles/l.	HCl, moles/l.	HNO_3, moles/l.	Fraction Zr uncomplexed
0.80	1.20	..	0.29
.00	2.00	..	.19
.80	..	1.20	.30
.00	..	2.00	.20

Without specifying the nature of the uncomplexed and complexed zirconium species, the following equations may be written

$$Zr(IV) + xCl^- = Zr(IV)Cl_x \quad (23)$$

$$K = (Zr(IV)Cl_x)/(Zr(IV))(Cl^-)^x \quad (24)$$

Equating the equilibrium quotients for two different chloride concentrations one obtains

$$\frac{(Cl^-)_1}{(Cl^-)_2^x} = \frac{(Zr(IV)Cl_x)_1(Zr(IV))_2}{(Zr(IV)Cl_x)_2(Zr(IV))_1} \quad (25)$$

Substituting the data of Table V, x is found to be 1.08 for chloride ion and 1.06 for nitrate ion, in the corresponding expression. Therefore there is approximately one chloride ion and one nitrate ion present in the respective complexes in the range of conditions studied. Assuming x to be 1.00 the value of the equilibrium quotient for equation (24) is 2.0 for both the nitrate and chloride complexes. Elimination of the impurity would tend to raise these values about 30%.

Miscellaneous Complexes.—Single extraction experiments were run in the presence of a number of substances to ascertain the order of magnitude of their complexing action on zirconium at trace concentration. From one experiment, it is of course impossible to identify the species present. The results are presented in Table VI. Data for sulfuric and hydrofluoric acid are included for comparison. The fraction of zirconium uncomplexed was again assumed to be equal to the measured extraction coefficient divided by the extraction coefficient in 2.00 M perchloric acid.

TABLE VI

COMPLEXING ABILITY OF VARIOUS SUBSTANCES FOR ZIRCONIUM

Trace Concentrations of Zirconium, 2.00 M $HClO_4$, 25°

Substance	Concn. M	% Zr uncomplexed
Bisulfate, ion, HSO_4^-	0.0031	56
Hydrofluoric acid, HF	10^{-5}	22
Oxalic acid, $H_2C_2O_4$	0.001	0.36
Malonic acid, HOOC—CH_2—COOH	0.01	100
Succinic acid, HOOC—$(CH_2)_2$—COOH	0.005	100
Glutaric acid, HOOC—$(CH_2)_3$—COOH	0.1	94
Fumaric acid, HC—COOH ‖ HOOC—CH	0.05	88
Maleic acid, HC—COOH ‖ HC—COOH	0.05	74
Orthophosphoric acid, H_3PO_4	0.012	68
Orthoboric acid, H_3BO_3	0.1	100
Metasilicic acid, H_2SiO_3	0.01	87
Acetic acid, CH_3COOH	1.0	100
Trifluoroacetic acid, CF_3COOH	0.11	51
Carbonic acid, H_2CO_3	1 atm. CO_2	90
Hydrogen peroxide, H_2O_2	0.015	63

The fluoride complex is by far the most stable studied. In the series of aliphatic dibasic acids

from oxalic to glutaric, only oxalic showed any strong complexing tendency. The apparent value of 6% of the zirconium complexed by glutaric acid may not be significant. Oxalic acid has a much greater complexing power relative to the other members of the series than can be accounted for simply by comparison of the acid dissociation constants. Geometry considerations cannot be too important since the carboxyl groups of all the acids are able to assume very nearly the same relative configuration. The explanation for the great difference in complexing ability must lie in more complicated effects.

The two unsaturated dibasic acids, fumaric and maleic, seem to have some complexing tendencies, with the *cis* configuration showing a slightly greater complexing power. The result of the experiment with phosphoric acid probably has little significance since there was a continual decrease with time in the zirconium concentration; the per cent. zirconium uncomplexed, given in this table, was one determined early in the experiment.

There was no indication of any complexing by either 0.1 *M* boric acid or 1 *M* acetic acid. Trifluoroacetic acid complexed approximately half of the zirconium when present at a concentration of 0.11 *M*. It should be pointed out that the presence of a very small amount of hydrofluoric acid in the trifluoroacetic acid could account for the observed results. The experiment with the silicic acid solution, which was very cloudy, probably does not indicate complexing but rather the formation of a small amount of radio-colloid. It is believed that little significance should be attached to the apparent value of 10% complexing when carbon dioxide gas was present in the extraction flask at a pressure of one atmosphere.

It has been observed[17] that plutonium(IV) at macro concentrations forms complexes with hydrogen peroxide involving two plutonium atoms in the complex ion. Zirconium at trace concentrations apparently forms a complex with hydrogen peroxide, which must certainly contain only one zirconium atom in the complex ion. It would be interesting to study the zirconium peroxide complexes at higher concentrations of zirconium, to see if peroxy complexes containing two zirconium ions are formed.

A correlation of the stability of the various zirconium complexes will be presented in a later paper.

(17) R. E. Connick and W. H. McVey, THIS JOURNAL, **71**, 1534 (1949).

Summary

The nature of the zirconium(IV) species existing in aqueous solutions has been investigated by means of a two phase distribution equilibrium. The zirconium is partially extracted into benzene as the neutral chelate of thenoyltrifluoroacetone and the formulas of the zirconium species in the aqueous phase are deduced from the quantitative variation of the extraction coefficient as a function of the aqueous solution composition.

In 2 *M* perchloric acid at 25° and low zirconium concentrations, the average number of hydroxide ions attached to each zirconium ion lies between zero and one. The composition is not known precisely because of the interference in the experiments of an unidentified impurity.

The stabilities of several of the complexes formed with sulfate and fluoride ions were measured in 2 *M* perchloric acid solution. At bisulfate concentrations of 10^{-2} and 0.3 *M* there are on the average one and two sulfate groups in the complex, respectively. At hydrofluoric acid concentrations of 2×10^{-5}, 5×10^{-4} and 10^{-2} *M* the average number of fluorides per zirconium ion is one, two and three, respectively. In both cases the equilibrium constants for the formation of the successive complexes are so close together that any solution always contains appreciable amounts of several complexes.

Chloride and nitrate ions form only weak complexes of about the same stability in 2 *M* perchloric acid. Peroxide forms a moderately stable complex under the same conditions. The oxalate complex is very stable, while the next three members of the aliphatic, dibasic acid series show little tendency towards complex formation.

BERKELEY 4, CALIFORNIA RECEIVED DECEMBER 1, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

An Example of the Difficulty in Obtaining Equilibrium Corresponding to a Macrocrystalline Non-volatile Phase. The Reaction $Mg(OH)_2 \rightleftarrows MgO + H_2O(g)$

BY W. F. GIAUQUE

Recently Torgeson and Sahama[1] measured the heat of solution of magnesium hydroxide in hydrochloric acid solution. They selected conditions of experiment, including final concentrations, to correspond to the work of Shomate and Huffman,[2] on the heat of solution of magnesium oxide.

Combining the results they obtain

$$Mg(OH)_2(c) = MgO(c) + H_2O(l)$$
$$\Delta H_{298.16^\circ K} = 8850 \pm 25 \text{ cal. mole}^{-1}$$

Torgeson and Sahama prepared their $Mg(OH)_2$ by reaction of MgO with steam(saturated) at 150 p. s. i. Shomate and Huffman prepared MgO by heating $Mg(OH)_2$ in a silica flask for one hundred hours, during which the temperature was raised from 400 to 1000°. Torgeson and Sahama consider both substances to have been crystalline and we see little reason to doubt that they were approximately macrocrystalline with respect to their properties.

Giauque and Archibald[3] measured the heats of solution of $Mg(OH)_2$ and MgO in hydrochloric acid solution and obtained a result of $\Delta H_{298.16} = 9739 \pm 25$ cal. mole.$^{-1}$ for Reaction 1, however, with the MgO in a different physical state.

They prepared crystals of $Mg(OH)_2$ with an average diameter of 0.2 mm. by slowly cooling a solution of $MgCl_2$ in concentrated potassium hydroxide from 210°. There is no reason for believing that the $Mg(OH)_2$ used by Torgeson and Sahama was appreciably different in its macroscopic properties from the visible crystals used by Giauque and Archibald.

The MgO prepared by Giauque and Archibald was made by dehydrating the above $Mg(OH)_2$ crystals, *in vacuo*, at a relatively low temperature. Decomposition was attempted at 200°, but was so slow that the temperature was raised to 300°, and for a short period to 350° at the end of ten days of heating *in vacuo*. This treatment decomposed 95% of the material, which was in the form of a fine powder. The above data lead to the result

$$MgO(\text{crystalline}) = MgO \text{ (finely divided)} \quad (2)$$
$$\Delta H_{298.16} = 888 \text{ cal. mole}^{-1}$$

Giauque and Archibald[3] were not primarily interested in the properties of either MgO or $Mg(OH)_2$ and were using these substances only as a means of determining the entropy of $H_2O(g)$ by use of the third law of thermodynamics and the decomposition equilibrium

$$Mg(OH)_2 = MgO + H_2O(g)$$

For this reason they considered it desirable to prepare and investigate the heat content and heat capacity of MgO under approximately the same conditions as those existing during their study of the decomposition pressures.

The heat capacity of the finely divided MgO was found to be higher than that of the crystalline material, which had been investigated by Parks and Kelley.[4] ΔC_p was about 1% at ordinary temperatures and this increased to about 6% at 90°K.

Giauque and Archibald were aware that the heat content of the powder should be somewhat higher than that of large crystals, due to increased surface energy, but had no idea that the difference would be a large quantity such as 888 cal. mole.$^{-1}$ We believe that it would be proper to describe the MgO powder prepared at about 300° as colloidal.

Our attention has been called to an equivalent result of Taylor and Wells[5] who decomposed $Mg(OH)_2$ at various temperatures, with a heating period of two and one-half hours.

Taking the heat of solution results at their lowest and highest temperatures

$$MgO_{(\text{formed at } 1425^\circ)} = MgO_{(\text{formed at } 450^\circ)} \quad (3)$$
$$\Delta H_{298.1^\circ K} = (36{,}670 \pm 70) - (35{,}720 \pm 30) = 950 \text{ cal. mole}^{-1}$$

This value and the 888 cal. mole.$^{-1}$ value given above agree within the limits of error of the measurements. Taylor and Wells[5] made X-ray diffraction patterns of their various samples and found no change in crystal structure. They ascribed their results as due "mainly to differences in surface."

The Decomposition Pressure of $Mg(OH)_2$.—The principal purpose of this paper is to ask the following question: How often have experimenters recorded equilibrium data which did not correspond to the macrocrystalline properties of the phases present?

Giauque and Archibald[3] studied the decomposition pressure of $Mg(OH)_2$ with unusual care at 463.1 and 485.0°K., waiting as long as two weeks for equilibrium. The equilibrium pressures at these temperatures were approached from both below and above, with results which were identical to an unusually high degree of accuracy. Moreover, there can be no reasonable doubt that they obtained an equilibrium value for the phases present, since the entropy of $H_2O(g)$ calculated from their calorimetric and equilibrium data, and the third law of thermodynamics, agrees very closely

(1) Torgeson and Sahama, THIS JOURNAL, **70**, 2156 (1948).
(2) Shomate and Huffman, *ibid.*, **65**, 1625 (1943).
(3) Giauque and Archibald, *ibid.*, **59**, 561 (1937).
(4) Parks and Kelley, *J. Phys. Chem.*, **30**, 47 (1926).
(5) Taylor and Wells, *Bur. Standards J. Res.*, **21**, 133 (1938), R. P. 1121.

with the result which is known accurately from band spectroscopy.

Let us assume that the results of Torgeson and Sahama[1] had been available to Giauque and Archibald, and that the entropy of crystalline MgO had been used in their calculations, the resultant free energy would have differed by the following amount

$$\text{MgO(crystals)} = \text{MgO(fine powder)}$$
$$\Delta F = \Delta H - T\Delta S \qquad (4)$$
$$\Delta F_{474^\circ K} = (\sim 900) - 474 \times (\sim 0.2)$$
$$= 800 \text{ cal. mole}^{-1}$$

where F, H and S refer to free energy, heat content and entropy.

We have used 474°K. as the average temperature of the experimental results and have estimated roughly that the finely divided MgO had a larger entropy by about 0.2 cal. deg.$^{-1}$ mole.$^{-1}$

This means, that had the pressure of H_2O been calculated from the calorimetric results on the macroscopic MgO, decomposition pressures greater by some 130%, than the values which were observed with a reproducibility of 0.1%, would have been expected.

Discussion of the Results—The above facts cannot be explained by assuming that the H_2O was in equilibrium with surface material on particles, which had macroscopic thermodynamic properties inside, since all of the material was dissolved when the heat of solution was measured. Similarly the $\int_0^T C_p \, d \ln T$ corresponds to the average entropy per mole of interior and surface material.

We conclude that the MgO came to complete equilibrium throughout the particles and thus had the same free energy per mole in the interior as on the surface.

It is often assumed that the excess of some property such as heat content, heat capacity or entropy of a system with considerable surface can be allocated to the surface. This idea is based on the assumption that the substance in the interior has retained the properties of the substance in bulk. This assumption would certainly not hold in the present case. Strictly speaking it is never possible to consider the properties within a particle as separable from those of the surface material. If such an approximation is made, as a matter of convenience, the equilibrium proved in the present case implies that

$$F = H(\text{inside}) - TS(\text{inside}) = H(\text{surface}) - TS(\text{surface}) \qquad (5)$$

By a thermodynamic artifice it is possible to obtain an approximate value for the free energy of small drops of liquid. In this case consideration of the increase in free energy of the interior material due to pressure caused by the surface tension, leads to the well known formula, $dF = 2V\,d(\gamma/r)$ which gives the change of free energy with size.[6] V represents the molal volume, and r and γ are the radius and surface tension, respectively, of the drop.

A similar consideration may be applied roughly to the MgO particles leading to the equation

$$\Delta F(\text{in calories}) \times 4.8 \times 10^7 = 2\gamma V \text{ ergs}/r$$
$$V = 11.1 \text{ cm.}^3 \text{ mole}^{-1}$$

from which

$$\frac{2\gamma}{r} = \frac{800 \times 4.8 \times 10^7}{11.1}$$
$$= 35 \times 10^8 \text{ dynes cm.}^{-2}$$

If one assumes spherical particles, this is equivalent to an inside pressure of 3500 atmospheres. We have no information concerning either γ or r of the finely divided material obtained in the equilibrium measurements. A search was made for a sample of the material used but it was probably discarded. It would have been interesting to obtain an electron-microscopic photograph of the material. If the particles were large enough to be seen in an ordinary microscope, they would have to possess some open type of structure, such as a loose aggregation of small units. It is difficult to see how such a reversible equilibrium, as that observed, could have been reached unless the unit particles had assumed something approximating a spherical shape.

It is, however, not any exact knowledge of particle dimensions which interests us here, but rather the fact that the usual tests of attainment in a chemical equilibrium are no guarantee that it corresponds, even approximately, to the thermodynamic properties of macroscopic phases.

It is not difficult to see why the dehydration of crystalline $Mg(OH)_2$ should produce particles of MgO which become detached before they reach macroscopic dimensions, and it is difficult to escape the conclusion that this is a fairly commonplace occurrence in other cases, although usually in lesser degree.

For example it seems probable that anhydrous salts, or the lower hydrates of salts, formed by the decomposition of multihydrated forms, in the absence of a solution, can be expected to produce finely divided material. The higher free energies of substances in this form should give lower decomposition pressures than do macroscopic phases.

(6) *E. g.*, "Thermodynamics and the Free Energy of Chemical Substances," Lewis and Randall, McGraw-Hill Book Co., Inc., New York, N. Y., 1923, p. 252. Lewis and Randall make an impractical statement on p. 248 with respect to surface effects as follows: "If we start with a given amount of liquid and increase its surface, the molal free energy in the body of the liquid does not necessarily change, and if we maintain equilibrium the total free energy in the surface formed must be the same as in the body of the liquid. Therefore the molal free energy multiplied by the total number of moles remains constant, but the total free energy is increased by $\gamma d\sigma$." We believe that it is impossible to devise a procedure in which the surface, and thus the surface energy, of a system is changed, under equilibrium conditions, without an equivalent change in the free energy of the substance or substances of which the system is composed. The total free energy of any system at equilibrium is always equal to the free energy per mole times the number of moles, summed over all components.

When the equilibrium decomposition pressure is sufficiently close to the saturation pressure, so that adsorption is considerable, equilibrium may be facilitated among solid phases. However, when the dissociation pressure of water is very small compared to that of the saturated solution, the attainment of macroscopic equilibrium may be excessively slow, and a rather definite metastable equilibrium can exist as a consequence.

When very fine particles are themselves nonvolatile, and lack a reconstituting mechanism, such as some equilibrium volatile compound which can transport material from them, they can only be expected to give equilibrium results consistent with their own free energy. At sufficiently high temperatures, sintering will produce macroscopic properties but the $Mg(OH)_2$ dissociation pressure would reach considerable values at temperatures below those required to sinter the MgO produced. We conclude that many measurements on systems involving equilibrium between gases and dry solid phases should be accepted with considerable caution in correlating thermodynamic data.

Summary

It is shown that the true dissociation pressure in the reaction $Mg(OH)_2$(cry.) = MgO(cry.) + H_2O(g), as determined from the third law of thermodynamics, is some 130% higher than accurately measured values which were reproducible to 0.1%.

The above result is attributed to the colloidal nature of the magnesium oxide produced under equilibrium conditions.

Giauque and Archibald have shown previously that the third law gives accurate agreement with the measured equilibrium pressures, when the entropy and heat content are measured on the actual finely divided magnesium oxide in equilibrium. Thus the colloidal particles approached essentially zero entropy at very low temperatures and evidently approximated a perfect crystalline structure.

For the finely divided material obtained during equilibrium dissociation, MgO(cry.) = MgO (finely divided); $\Delta H_{25} = 888$ cal. mole.$^{-1}$

It is concluded that neither reproducibility of equilibrium measurements based on approach from each side nor agreement with the third law of thermodynamics, can be accepted as proof that an equilibrium corresponds to the thermodynamic properties of macrocrystalline phases.

It seems impossible to escape the conclusion that many equilibrium measurements involving gases and finely divided dry solid phases, produced by the evolution of gases, or formed by reaction with gases, do not correspond to the properties of macroscopic materials.

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[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY, HARVARD UNIVERSITY, AND THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Infrared Spectrum of Dimethylcadmium

BY H. S. GUTOWSKY[1]

In a previous publication,[2] the infrared and Raman spectra of dimethylmercury and dimethylzinc were presented and interpreted as supporting a linear C–M–C structure of D_{3h}' symmetry, with essentially free internal rotation of the methyl groups. Similar data for dimethylcadmium are of interest in verifying this interpretation and in providing force constants which, with those for mercury and zinc, afford a basis for relating molecular properties to atomic parameters of the Group IIb metals.

Experimental

Preparation of Sample.—Attempts to produce dimethylcadmium by heating dimethylmercury with cadmium metal were unsuccessful. The sample used was prepared by Mr. A. R. Bader, under the direction of Professor E. G. Rochow, from cadmium iodide and methylmagnesium bromide in ether solution. Their coöperation in furnishing the sample is gratefully acknowledged. It was purified by bulb to bulb distillation in a vacuum system until it was infrared spectroscopically free from ether.

Infrared Spectrum.—The region from 430 to 650 cm.$^{-1}$ was observed with a KRS-5 prism in conjunction with a lithium fluoride mirror using the Harvard spectrometer.[3] The gaseous sample of dimethylcadmium was at its room temperature vapor pressure of 3.6 cm., in a 30-cm. cell with potassium bromide windows. The region from 625 to 5000 cm.$^{-1}$ was run at the same pressure in a 5-cm. sodium chloride cell on a Baird Associates spectrometer. The observed spectrum is summarrized in Table I. Its general appearance is similar to that of dimethylzinc,[2] with the exception that the structure of the bands at 1140 and 1305 cm.$^{-1}$ in dimethylcadmium is not nearly as distinct as the corresponding bands in dimethyl zinc.

Frequency Assignment

A generally satisfactory frequency assignment has been made, using D_{3h}' symmetry. The Raman data of Fehér, Kolb and Leverenz[4] are in-

(1) Present address: Department of Chemistry, University of Illinois, Urbana, Illinois.

(2) H. S. Gutowsky, *J. Chem. Phys.*, **17**, 128 (1949).

(3) For a detailed listing of pertinent literature and the general methods used in this investigation see ref. (2).

(4) F. Fehér, W. Kolb and L. Leverenz, *Z. Naturforsch.*, **2a**, 454 (1947).

TABLE I

INFRARED AND RAMAN SPECTRA OF DIMETHYLCADMIUM AND THE ASSIGNMENT OF VIBRATIONAL FREQUENCIES[a]

Infrared (g), ν cm.$^{-1}$	Raman[4] (l), $\Delta\nu$ cm.$^{-1}$	Assignment	Species for combinations	Calcd. freq. of combinations, ν cm.$^{-1}$
	150 (1/2?)	ν_{11}		
	464 (20b), 468 (2?) } 0.29	ν_3		
	520 (1/2 b)	? (ν_7)		
538 (8)		ν_7		
	642 (3sb, 0.77)	ν_{14}		
705 (10)		ν_{10}		
	934 (00)	$2\nu_3$	A_1'	930
	1129 (8sb, 0.32)	ν_2		
1140 (5)		ν_6		
1305 (6)		$\nu_2 + \nu_{11}$; $2\nu_{14}$	E′; $A_1' + A_2' + E'$	1279, 1284
1325 (4)		$\nu_3 + \nu_{10} + \nu_{11}$	$A_1' + A_2' + E'$	1320
1350 (2)		$\nu_{10} + \nu_{14}$	$A_1'' + A_2'' + E''$	1347
	1384 (00b)	ν_{13}		
1435 (1)	1448 (00)	ν_9		
1620 (1)		$\nu_3 + \nu_6$	A_2''	1605
	2103 (1/2)	$\nu_{10} + \nu_{13}$	$A_1'' + A_2'' + E''$	2089
2230 (2)	2218 (1/2)	$\nu_{10} + \nu_{11} + \nu_{13}$	$A_1'' + A_2'' + 3E''$	2239
	2658 (00)	$\nu_2 + \nu_{11} + \nu_{13}$	$A_1' + A_2' + E'$	2663
	2691 (00)	$\nu_7 + \nu_9 + \nu_{10}$	$A_1'' + A_2'' + E''$	2684
2840 (6)		$\nu_9 + \nu_{13}$	$A_1'' + A_2'' + E''$	2832
(2895)	2876 (3)	ν_8		
2900 (9)		ν_8; P branch ν_5		
	2904 (4, pol.)	ν_1		
(2920)		ν_5		
2940 (7)		R branch ν_5		
	2963 (1/2)	ν_{12}		
3530 (0)		$\nu_8 + \nu_{14}$	$A_1'' + A_2'' + E''$	3517

[a] The numbers after the band frequencies are relative apparent intensities. The appearance and polarization are indicated for the Raman lines by the letters s (scharf), b (breit) and a second set of numbers.

cluded in Table I as well as the infrared observations and the details of the frequency assignment. The infrared band intensities listed are merely relative values. The numerals in parentheses after the Raman line frequencies are intensity and polarization, respectively. The assignment of fundamental frequencies is summarized in Table II.

The Raman active A_1' fundamental frequencies are readily assigned as the three strongest lines which are polarized. The infrared active A_2'' fundamentals ν_6 and ν_7 are obtained by comparison with the corresponding A_1' frequencies. The E″ Raman active fundamentals are selected from the remaining unassigned lines. 2963 cm.$^{-1}$ is assigned as ν_{12} since it does not overlap the C–H stretching frequencies in the infrared spectrum. In the CH_3 deformation region the Raman line at 1448 cm.$^{-1}$ coincides with the infrared band at 1435 cm.$^{-1}$ so they are assigned as ν_9, which leaves the 1384 cm.$^{-1}$ line as ν_{13}. ν_{14} is taken to be the Raman line at 642 cm.$^{-1}$ as this value is intermediate between the corresponding values for dimethylmercury and dimethyl zinc. Moreover, there are no other unassigned lines in the expected frequency range. The polarization value of 0.77 given for this line is sufficiently close to the depolarized value that this assignment is not precluded. The E′ fundamentals are both infrared and Raman active and ν_8 is assigned as the coincidence in frequencies at about 2885 cm.$^{-1}$. The intense infrared band at 705 cm.$^{-1}$ is undoubtedly ν_{10}, and the only observed frequency low enough to be the C–Cd–C bending frequency, ν_{11}, is the doubtful 150 cm.$^{-1}$ line reported by Kolb and Leverenz.[4]

The remaining bands are interpretable as combinations or overtones with the exception of the weak Raman line at 520 cm.$^{-1}$. Assuming this line to be real, it might be the asymmetric skeletal stretching frequency, ν_7, the selection rule prohibiting its appearance in the Raman spectrum being relaxed by Coriolis interaction with the skeletal bending ν_{11}. The relatively high intensity of the infrared bands at 1305 and 1325 cm.$^{-1}$ is a bit surprising for combinations but their assignment as fundamental frequencies is not supported by any other considerations.

Normal Coördinate Analysis and Force Constants

Valence-type force constants have been determined from the above frequency assignment following the symmetry coördinate methods of Wilson[5] and using the G and diagonal F matrices

(5) E. B. Wilson, Jr., *J. Chem. Phys.*, **7**, 1047 (1949); **9**, 76 (1941).

TABLE II

FUNDAMENTAL FREQUENCIES AND FORCE CONSTANTS OF DIMETHYLCADMIUM

	D_{3h}'		Obs.	Comp.	% Dev.	F_{ii}
A_1'	C–H stretching	ν_1	2904 cm.$^{-1}$	2882 cm.$^{-1}$	−0.76	4.79×10^5
	CH_3 bending	ν_2	1129	1131	[a]	0.36×10^{-11}
	C–Cd–C R, P stretching	ν_3	465	470	+1.06	2.05×10^5
A_1''	Torsion	ν_4	..	..	....	.....
A_2''	C–H stretching	ν_5	(2920)	2886	−1.15	4.79×10^5
	CH_3 deformation	ν_6	1140	1140	[a]	0.375×10^{-11}
IR, ∥	C–Cd–C stretching	ν_7	538	535	[a]	2.05×10^5
E′	C–H stretching	ν_8	2885	2922	+1.29	4.55×10^5
R	CH_3 deformation	ν_9	1441	1441	[a]	0.549×10^{-11}
IR, ⊥	CH_3 rocking	ν_{10}	705	705	[a]	0.334×10^{-11}
	C–Cd–C bending	ν_{11}	150	150	[a]	0.368×10^{-11}
E″	C–H stretching	ν_{12}	2963	2921	−1.42	4.55×10^5
	CH_3 deformation	ν_{13}	1384	1384	[a]	0.505×10^{-11}
R	CH_3 rocking	ν_{14}	642	642	[a]	0.277×10^{-11}

[a] Used in computing force constants.

FORCE CONSTANTS DERIVED FROM F_{ii}

f_r	4.63×10^5 dynes/cm.	$d^2f_{\alpha\alpha}$	$0.003 + 10^{-11}$ dyne cm./radian
f_{rr}	0.08	$d^2f_{\beta\beta}$	− .036
f_η	2.05	$d^2(f_{\alpha\alpha_2} + f_{\beta\beta_2})$	.029
d^2f_α	0.530×10^{-11} dyne cm./radian	$d^2(f_{\alpha\alpha_2} - f_{\alpha\alpha'_2})$	.022
d^2f_β	0.270	$d^2(f_{\beta\beta_2} - f_{\beta\beta'_2})$	.029
D^2f_γ	0.368		

given previously[2] for a linear CH_3–M–CH_3 molecule. These force constants, as given in Table II, are in terms of the internal coördinates α, β, γ, r and η which are defined as small displacements in the H–C–H, H–C–Cd, C–Cd–C bond angles and the C–H, C–Cd bond lengths, respectively. In the computations, tetrahedral angles were assumed for the methyl groups and 1.10 Å. was adopted as the C–H bond distance, *d*. No measurement of the C–Cd bond distance, *D*, appears to be available, so a value estimated from the covalent radii to be 2.15 Å. was used.

The F_{ii} values in Table II are the numerical values used in the diagonal *F* matrices for the various factors in computing the frequency of the corresponding vibration. No attempt was made to introduce off-diagonal terms in the *F* matrix. The values of the force constants given in terms of the internal coördinates are derived from F_{ii} using the relations previously reported[2]; the numerical values for the C–H stretching, f_r and f_{rr}, and the H–C–H angle distortion, d^2f_α, are also adopted from the previous work.

Discussion

Configuration and Internal Rotation.—On the basis of the evidence reported herein for dimethyl cadmium and the earlier data[2] for dimethylmercury and dimethylzinc, it appears that the dimethyl compounds of the group IIb metals have a linear C–M–C skeleton. Moreover, there are sufficient coincidences between the infrared and Raman frequencies assigned as E′ fundamentals to confirm the nonexistence of the staggered orientation of the methyl groups; such a D_{3d} configuration would have a center of symmetry and the fundamentals could be active only in either the infrared *or* Raman spectrum. The simplest interpretation of all the spectral data is in terms of either an eclipsed D_{3h} orientation of the methyl groups or a D_{3h}' model in which the methyl groups are free to rotate internally about the C–M bonds. Inasmuch as the staggered configuration is generally considered[6,7] to be the stable form when there is hindrance to internal rotation, it appears that a more or less free internal rotation exists in these dimethyl compounds. The application of an empirical inverse fifth power law[6] to the potential restricting the internal rotation suggests the barrier to such rotation is of the order of 15 cal./mole. The theoretical calculations of Lassettre and Dean[7] give a value of 31 cal./mole for the barrier to internal rotation in dimethyl acetylene; this indicates the possibility of a somewhat higher barrier in the metal alkyls than the 15 cal./mole from the empirical calculation. In any event, the spectral results are in general accord with the calculated barriers; both suggest that hindrance to internal rotation in these compounds is slight at most.

Force Constants and Electronegativities of the Group IIb Metals.—In Table III there are summarized the force constants directly related to the C–M bonds in the Group IIb dimethyl alkyls. A number of more or less empirical expressions have been proposed, relating bond stretching force constants, bond lengths, position in the periodic table, type of compound, and similar parameters. In this connection, it is of some

(6) J. G. Aston, S. Iserow, G. J. Szasz and R. M. Kennedy, *J. Chem. Phys.*, **12**, 336 (1944).

(7) E. N. Lassettre and L. B. Dean, Jr., *ibid.*, **17**, 317 (1949).

TABLE III

C-M FORCE CONSTANTS FOR THE GROUP IIb DIMETHYL ALKYLS

	$Zn(CH_3)_2$	$Cd(CH_3)_2$	$Hg(CH_3)_2$	
f_η	2.39×10^5	2.05×10^5	2.45×10^5	dynes/cm.
d^2f_β	0.274×10^{-11}	0.270×10^{-11}	0.359×10^{-11}	dyne cm/radian
D^2f_γ	0.276×10^{-11}	0.368×10^{-11}	0.457×10^{-11}	dyne cm/radian

interest to consider the recent extensive discussion by Gordy[8] who proposed the equation $k = aN(X_AX_B/d^2)^{3/4} + b$. k is the bond stretching force constant in 10^5 dynes/cm.; a and b are empirical constants with the values 1.67 and 0.30 for stable molecules in their normal covalent state; N is the bond order; X_A and X_B are the electronegativities of the bonded atoms; and d is the bond length in angstroms. Electronegativities are given in Table IV for zinc, cadmium and mercury, computed with this equation using the $f\eta$ force constants in Table II and also the force constants of the dihalides from their Raman spectra in solution.[9,10] Included for comparison are the electronegativities proposed by Gordy[8] from the force constants in the diatomic hydrides and also values suggested by Haissinsky[11] from thermal data. While some of the differences between the computed electronegativities may result from the approximation of several of the bond lengths, the differences between the values from the alkyls and those from the halides and hydrides are too large not to be real.

TABLE IV

ELECTRONEGATIVITIES OF ZINC, CADMIUM AND MERCURY COMPUTED FROM THE BOND STRETCHING FORCE CONSTANTS IN THE DIMETHYL ALKYLS AND THE DIHALIDES

A/B	Zn		Cd		Hg		
	d^a_{Zn-A}	X_{Zn}	d^a_{Cd-A}	X_{Cd}	d_{Hg-A}	X_{Hg}	X^S_A
C, Å	2.05	2.22	2.15	1.93	[b]2.20	2.66	2.55
Cl	2.13	1.14	2.23	0.72	[c]2.28	2.24	2.97
Br	2.23	1.08	2.33	0.89	[c]2.38	2.13	2.75
I	2.40	..	2.50	0.91	[c]2.55	1.73	2.45
Gordy[8]		1.2		1.1		1.0	
Haissinsky[11]		1.5		1.5		1.9	

[a] Bond lengths are estimated from convalent radii by comparison with the corresponding compounds of mercury. [b] L. O. Brockway and H. O. Jenkins, THIS JOURNAL, **58**, 2036 (1936). [c] H. Braune and S. Knoke, *Z. physik. Chem.*, **B23**, 163 (1933).

(8) W. Gordy, *J. Chem. Phys.*, **14**, 305 (1946). Citations of earlier work are given in this reference.

(9) S. Venkateswaran, *Proc. Ind. Acad. Sci.*, **1**, 851 (1935).

(10) K. W. F. Kohlrausch, "Ramanspectren," Edwards Brothers, Inc., Ann Arbor, Michigan, 1945, p. 75.

Part of the disagreement may lie in the bond order. For the alkyls, hyperconjugation of the methyl groups could increase the bond order from 1.0 to perhaps as high as 1.2. This is still inadequate to bring the corresponding electronegativities into agreement with the values from the halides and hydrides. The thermal electronegativities of Haissinsky[11] differ from the alkyl values by a fairly narrow range, from 0.43 to 0.76 indicating the force constants could be fitted fairly well by Gordy's equation, with a different value of b or else a bond order of about 1.4. However, it is particularly difficult to reconcile the very wide scatter of electronegativity values for mercury without introducing an excessive number of new empirical constants.

Summary

1. The infrared spectrum of dimethylcadmium is reported and a frequency assignment proposed. Valence-type force constants are computed from a normal coördinate analysis. The results support a linear C–Cd–C structure of D_{3h}' symmetry with free internal rotation of the methyl groups, consistent with similar conclusions made previously for dimethylzinc and dimethylmercury.

2. A comparison of electronegativity values computed from the bond stretching force constants in the dimethyl alkyls and dihalides of the Group IIb metals, using an empirical relation proposed by Gordy, suggests the difficulty of applying the relation to additional types of compounds.

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(11) M. Haissinsky, *J. phys. radium.*, **7**, 7 (1946).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Conversion of Fibrinogen to Fibrin. I. Influence of Hydroxyl Compounds on Clotting Time and Clot Opacity[1]

BY JOHN D. FERRY AND SIDNEY SHULMAN

The reaction between fibrinogen and thrombin to form a solid structure of fibrin is modified by the presence of glycerol or other hydroxyl compounds so that the clotting time is prolonged and the clot opacity, a measure of coarseness of structure, is markedly decreased.[2] It has been suggested that hydroxyl compounds reduce the attractive forces between fibrinogen molecules and diminish their tendency toward side-by-side association during clotting, resulting in a network of fine rather than coarse strands.

This phenomenon has now been further studied by examining the effects of a large number of hydroxyl compounds on clotting time and clot opacity. Correlations are drawn between molecular structure and effectiveness in modifying the clotting process, and tentative conclusions can be reached concerning the nature of the interactions involved.

Materials and Methods

Bovine fibrinogen (Fraction I[3]) and thrombin were furnished through the kindness of Dr. J. D. Porsche of Armour and Company, to whom we are deeply indebted for the gift of these materials. In Fraction I preparation C-185A the protein was 79% fibrinogen, as determined by the assay method of Morrison[4]; in preparation C-739, it was 65%. Thrombin preparation C-173B had an activity[5] of 4.7 units per mg.

Glycerol, mannitol, pentaerythritol, trimethylene glycol and pinacol were obtained from the Eastman Kodak Company; 2-methyl-1,3-pentanediol, 2-methyl-2,4-pentanediol, 1,3-butanediol, and bis-(2-hydroxyethyl) sulfide from Carbide and Carbon Chemicals Corporation[6]; pentamethylene glycol, hexamethylene glycol, and polyvinyl alcohol (Elvanol 72-51) from E. I. du Pont de Nemours and Co.; and tetrahydrofurfuryl alcohol from the Quaker Oats Co.[6] A sample of tetramethylene glycol was kindly given us by Professor Homer Adkins. The other compounds were commercial products of reagent grade. Most of the reagents were used without further purification. Trimethylene glycol, tetrahydrofurfuryl alcohol and pentamethylene glycol were redistilled.

Fibrinogen solutions were prepared by dissolving the stock powder (which had been dried from a frozen solution in citrate buffer) in water at a concentration of about 3% protein, dialyzing against a large volume of sodium chloride solution (usually 0.45 *M*) with several changes for twenty-four hours to remove citrate, and clarifying by filtration through filter pads. After filtration, each stock solution was assayed[4] for fibrinogen, and the *p*H was measured. Aliquots were then diluted to give samples with chosen concentrations of fibrinogen, salt, and added reagent. The reagents (hydroxyl compounds) were added in the form of moderately dilute solutions containing 0.45 *M* sodium chloride (the *p*H having been adjusted to 6.3 if necessary), to minimize possible injurious effects of local changes in composition. In every case, the *p*H of the mixture containing the highest concentration of reagent differed by not more than ±0.1 unit from the corresponding control with no reagent. Thrombin solutions were prepared by dissolving the stock powder in 0.45 *M* sodium chloride, usually at a concentration of 20 unit/cc.

Each sample, after addition of thrombin, had a volume of 5 cc. and contained 5 g./l. of fibrinogen, 1 unit/cc. of thrombin, and 0.45 *M* sodium chloride. The clotting time was taken as that required to develop a characteristic rigidity in a test-tube of 1.40 cm. i.d. The opacity,[2] or extinction coefficient, was measured in the same tube at a wave length of 6000 Å. with a Beckman spectrophotometer[7] at intervals, sometimes before as well as after the moment of clotting. The clots were kept at room temperature, which varied from 22 to 25°.

Results

Effect of *p*H and Ionic Strength.—Since previous studies[2] of the dependence of clot opacity and clotting time on reaction conditions had been made with human rather than bovine fibrinogen and thrombin, preliminary experiments were made to show that the effects of *p*H and ionic strength were qualitatively the same for both species. For the bovine, as for the human system, both opacity and clotting time decreased with increasing *p*H; with increasing ionic strength, clotting time increased and opacity passed through a minimum. However, at *p*H 6.3 and ionic strength 0.45, the bovine clotting time was roughly twice as long and the clot opacity twice as great as the human; a higher *p*H, and/or a higher salt concentration, was required for bovine than for human fibrinogen to effect the changes in properties representing the transition from coarse to fine structure.[2] This difference has also been noted by Edsall and Lever.[8]

Preliminary experiments showed that, with bovine as with human fibrinogen, addition of glycerol prolonged the clotting time and diminished clot opacity. These effects were observed at various values of *p*H and ionic strength. At the average unadjusted *p*H of our solutions, 6.3, the sensitivity of opacity to added glycerol was greatest near an ionic strength of 0.45, the value selected for all experiments with other reagents.

In various successive stock solutions prepared as described above, the clotting times without added reagent varied from six to nine minutes for

(1) This work was supported in part by the Research Committee of the Graduate School of the University of Wisconsin from funds supplied by the Wisconsin Alumni Research Foundation.

(2) J. D. Ferry and P. R. Morrison, THIS JOURNAL, **69**, 388 (1947).

(3) E. J. Cohn and others, *ibid.*, **68**, 459 (1946); J. B. Lesh and J. D. Porsche, reported at the 110th Meeting of the American Chemical Society, Chicago, Sept. 9–13, 1946.

(4) P. R. Morrison, THIS JOURNAL, **69**, 2723 (1947).

(5) Minimum requirements of the National Institute of Health for Dried Thrombin, Division of Biologics Control, National Institute of Health, Bethesda, Md., 3rd ed., 1946.

(6) We are grateful to those manufacturers who furnished complimentary samples of reagents.

(7) We are indebted to Professors V. W. Meloche and J. W. Williams for the use of their spectrophotometers, and to Mr. Meredith Miller for help in some of the measurements.

(8) J. T. Edsall and W. F. Lever, private communication.

preparation C-185A, and from eleven to fourteen minutes for C-739. The corresponding opacities (six hours after addition of thrombin) varied from 0.5 to 1.2 cm.$^{-1}$ for C-185A, and from 1.0 to 1.2 cm.$^{-1}$ for C-739. Most of the data reported here were obtained with the latter preparation, whose opacity was more nearly reproducible. In any case, the relative effects of different added reagents could be expressed independently of the variability of the stock solutions, by the methods of calculation described below.

Clotting Time.—Most of the hydroxyl compounds prolonged the clotting time (t_C); a plot of log t_C against concentration of reagent (c, in g./l.) gave a straight line at low concentrations (Fig. 1). At higher concentrations, the slope usually decreased somewhat. Two reagents—starch and polyvinyl alcohol—decreased the clotting time; here also log t_C was a linear function of c (Fig. 1).

TABLE I

EFFECT OF HYDROXYL COMPOUNDS ON CLOTTING TIME

Fraction I Preparation C-739 except where otherwise noted

Reagent	Expt.	d log t_C/dc (g./l.)$^{-1}$	d log t_C/dm (mole/l.)$^{-1}$
2-Methyl-1,3-pentanediol	49	0.083	9.8
Hexamethylene glycol	34	.078	9.2
	36	.082	9.7
	47	.075	8.9
Cyclohexanol	43	.080	8.2
Pinacol	32	.085	10.0
	46	.060	7.1
	51	.060	7.1
Trimethylene glycol	49	.070	5.3
Tetrahydrofurfuryl alcohol	45	.063	6.4
Mannitol[b]	33	.07	13
Pentaerythritol[b]	51	.06	8
Glucose[b]	51	.06	11
Sucrose[b]	51	.06	20
Pentamethylene glycol	45	.055	5.7
bis-(2-Hydroxyethyl) sulfide	47	.044	5.3
Propanol	37	.039	2.3
	40	.050	3.0
Butanol	37	.036	2.7
	40	.051	3.8
1,3-Butanediol	43	.043	3.9
Tetramethylene glycol	46	.040	3.6
2-Methyl-2,4-pentanediol	11[a]	.033	3.9
Propylene glycol	41	.020	1.5
Ethylene glycol	30	.018	1.1
Diethylene glycol	43	.017	1.8
Glycerol	7[a]	.009	0.9
	33	.012	1.1
	34	.013	1.2
	36	.010	1.0
	38	.016	1.5
	41	.014	1.3
Ethanol	6[a]	.008	0.35
	40	.010	0.46
Starch	39	− .050	−8.2[c]
Polyvinyl alcohol	51	− .14	−5.9[c]

[a] Fraction I Preparation C-185A. [b] No straight line; initial slope estimated. Slope falls off sharply above 4 g./l. [c] (moles monomer residue per liter)$^{-1}$.

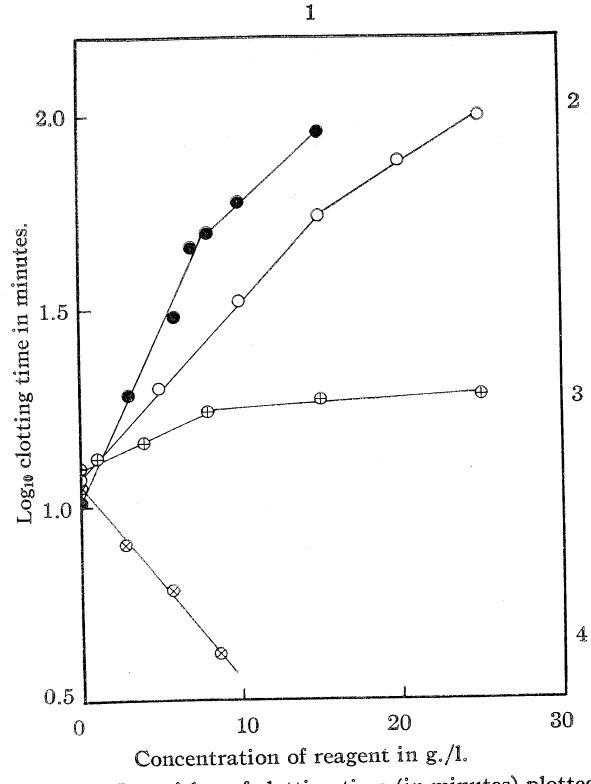


Fig. 1.—Logarithm of clotting time (in minutes) plotted against concentration of reagent in g./l.: 1, hexamethylene glycol; 2, 1,3-butanediol; 3, ethylene glycol; 4, starch.

The initial slopes of plots such as Fig. 1 were taken as measures of the effectiveness of the various reagents in altering the clotting time. They are summarized in Table I in decreasing order. Except where noted, only those experiments in which at least three points fell on a straight line are included; some other experiments, in which erratic results were obtained, have been omitted.

With the same reagent, different stock fibrinogen solutions usually gave lines with similar slopes, as shown by the fair agreement in values of d log t_C/dc in successive experiments. The slopes are recorded both as d log t_C/dc and d log t_C/dm, where m is the concentration in moles per liter. Since most of the compounds do not differ greatly in molecular weight, the order of decreasing values is about the same in both cases. The extremes represent rather marked effects; thus, hexamethylene glycol at a concentration of 5 g./l. prolongs the clotting time by a factor of 2.5, while polyvinyl alcohol at the same concentration shortens the clotting time by a factor of 3. At higher concentrations, beyond the linear range, far greater changes are observed; polyvinyl alcohol shortens t_C by as much as a factor of 10, and hexamethylene glycol prolongs it indefinitely. How-

ever, these larger effects are not so convenient for characterizing reagents.

Change of Clot Opacity with Time.—In the course of the conversion process, the opacity rises steadily before the moment of clotting and continues to rise for a long time thereafter.[2] Its increase with time is illustrated in Figs. 2 and 3 for systems containing varying amounts of 1,3-butanediol. In the early stages (Fig. 2) the opacity rises linearly with time; the moment of clotting, indicated by a cross, occurs during this linear increase.[9] In the later stages (Fig. 3) the opacity appears to approach a limiting value, but in the presence of higher concentrations of glycol the opacity is still rising after twenty-four hours.

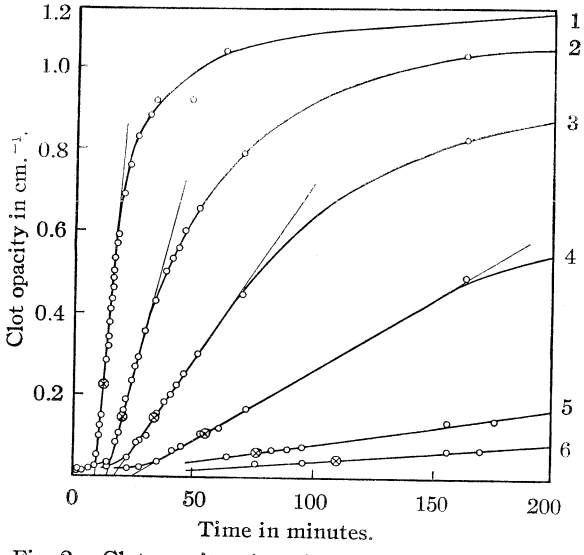


Fig. 2.—Clot opacity plotted against time, for different concentrations of 1,3-butanediol in g./l. as follows: 1, 0; 2, 5; 3, 10; 4, 15; 5, 20; 6, 25. The crosses denote clotting times.

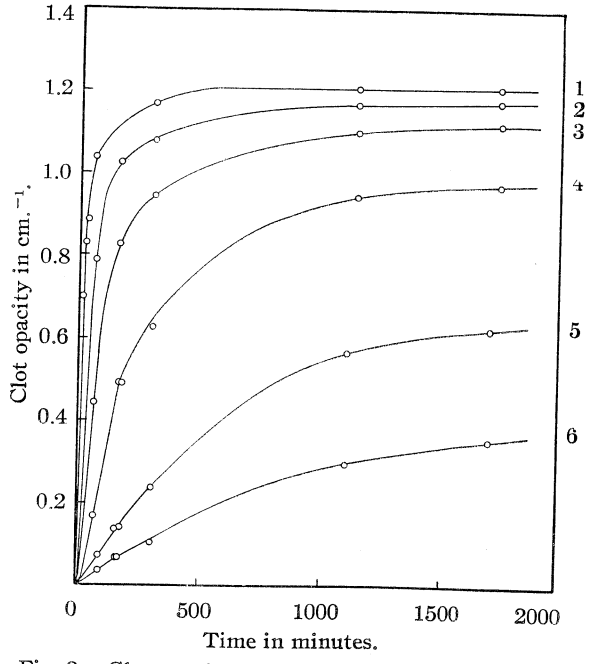


Fig. 3.—Clot opacity plotted against time, for different concentrations of 1,3-butanediol (for longer time periods). Key to curves same as in Fig. 2.

Change of Clot Opacity with Concentration of Added Reagent.—The butanediol decreases markedly the slope of the linear portion of the opacity–time curve, and it also decreases the opacity attained after a given time interval. This result may be partly attributed to a decrease in the rate of formation of the fibrin structure (as measured by the prolonged clotting time) and partly to a change in the character of the structure itself. We seek a measure of the latter effect alone. It could be provided by a comparison of the final opacity values after conversion is complete. However, it is difficult to ascertain when the opacity attains its maximum value; in the presence of relatively high concentrations of hydroxyl compounds, the rise may continue for several days, and it is undesirable to prolong experiments for such periods because of possible instability and bacterial action.

Accordingly, to gage the effect of added reagents on the clot structure, we have adopted the procedure of comparing opacities *at the clotting time*

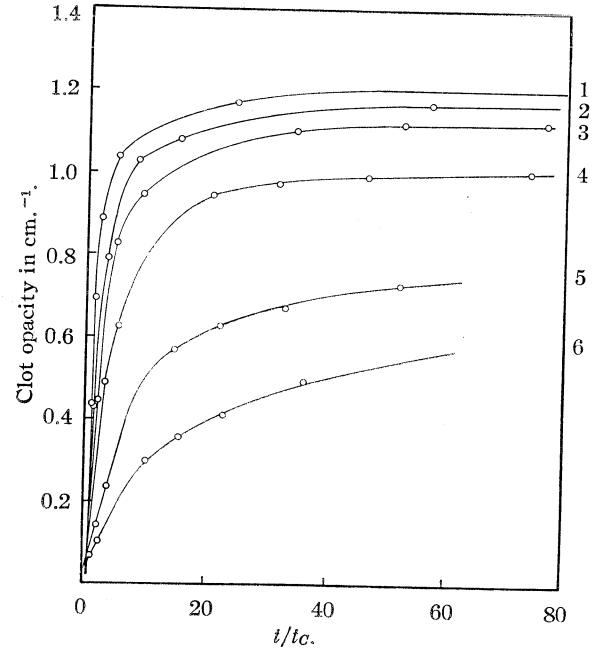


Fig. 4.—Clot opacity plotted against t/t_C for different concentrations of 1,3-butanediol. Key to curves same as in Fig. 2.

(9) Oster (*J. Colloid Sci.*, **2**, 291 (1947)) has shown that the opacity should increase linearly with time when molecules are growing by condensation polymerization, provided the molecular sizes are all small compared with the wave length of light. However, it cannot be inferred that the conversion of fibrinogen to fibrin is a condensation polymerization, because the above provision is not satisfied.

($t = t_C$) or at equal multiples thereof.[10] When the opacity data of Figs. 2 and 3 are plotted against t/t_C instead of t, the influence of the glycol appears less pronounced (Fig. 4). Here its effectiveness in decreasing coarseness of structure has been isolated, as a first approximation, from its effectiveness in decreasing the rate of the conversion process.

TABLE II

CONCENTRATION OF REAGENT REQUIRED TO REDUCE OPACITY BY ONE-HALF

Fraction I Preparation C-739 except where otherwise noted

Reagent	Expt.	c (g./l.) $t/t_C = 1$	c (g./l.) $t/t_C = 10$	m (mole/l.) $t/t_C = 1$	m (mole/l.) $t/t_C = 10$
bis-(2-Hydroxy-ethyl) sulfide	32	..	3	..	0.02
	47		2		.02
Pinacol	32	..	3	..	.03
	51		4		.03
Pentaerythritol	9[a]	..	6	..	.05
	33		4		.03
	51		4		.03
Pentamethylene glycol	45	..	5	..	.05
Cyclohexanol	42	4.0	6	0.04	.06
Hexamethylene glycol	10[a]	..	6	..	.05
	34	..	7	..	.06
	36	4.6	7	.04	.06
Trimethylene glycol	48	..	6	..	.08
	49		7		.09
Glucose	51	..	8	..	.04
Sucrose	51	..	8	..	.02
Tetrahydrofurfuryl alcohol	45	..	8	..	.08
2-Methyl-2,4-pentanediol	33	..	9	..	.08
Mannitol	33	..	10	..	.05
2-Methyl-1,3-pentanediol	49	..	11	..	.09
Butanol	40	13.5	12	.18	.16
Propanol	37	10.0	..	.17	..
	40	10.5	..	.17	..
1,3-Butanediol	43	14.5	19	.16	.21
Glycerol	7[a]	..	14	..	.15
	38	12.0	23	.13	.25
	41	..	21	..	.23
	42	11.7	18	.13	.20
Tetramethylene glycol	46	..	24	..	.27
Triethylene glycol	34	..	64	..	.43
Diethylene glycol	34	..	67	..	.63
	43	..	73	..	.69
Propylene glycol[b]					
Ethylene glycol[c]					
Dipropylene glycol[d]					

[a] Fraction I Preparation C-185A. [b] Depresses the opacity by 13% at $c = 25$ g./l. [c] Depresses the opacity by 11% at $c = 40$ g./l. [d] Depresses the opacity by 14% at $c = 40$ g./l.

(10) It would be preferable to compare opacities at equal extents of reaction, corresponding to times when a given proportion of fibrinogen had been converted to fibrin. However, this is impractical, if not impossible, to determine at present.

The effects of different concentrations at time intervals which are equal multiples of the clotting time are represented by intersections of the curves of Fig. 4 with vertical lines. Opacities obtained in this way are plotted against the concentration in Fig. 5 for $t/t_C = 1$, 10, 30 and 50. The sigmoid shape of the upper curves was characteristic of most of the other reagents studied.

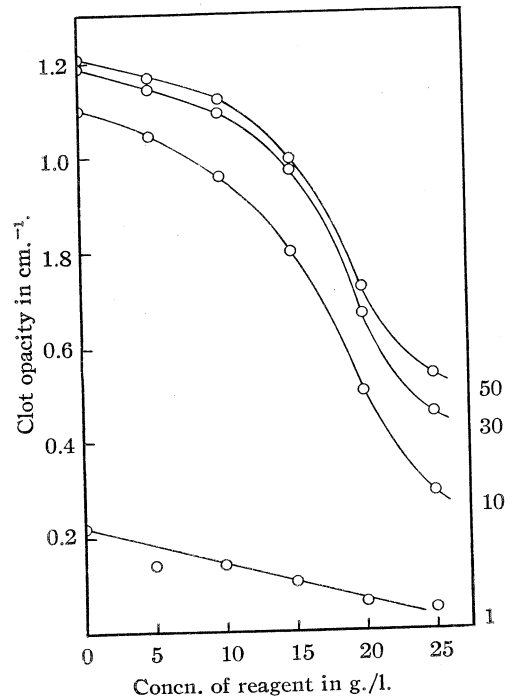


Fig. 5.—Opacity plotted against concentration of 1,3-butanediol, at various values of t/t_C as indicated.

Comparison of Reagents.—To provide a simple comparison, the concentrations of reagents in g./l. required to reduce the capacity to half the control value (with no added reagent) at $t/t_C = 1$ (*i.e.*, at the moment of clotting) and at $t/t_C = 10$ were interpolated from graphs of the type of Fig. 5. These results are given in Table II, together with the corresponding concentrations expressed as moles per liter. Fewer values are available at $t/t_C = 1$ because of the difficulty of making numerous opacity measurements in a short time interval in the vicinity of the clotting time. At $t/t_C = 10$, they range from 2 to 3 g./l. (0.02 *M*) for bis-(2-hydroxyethyl) sulfide to 70 g./l. (0.6 *M*) for diethylene glycol. This particular comparison is striking because the two molecules differ only in the central atom, which is oxygen and sulfur, respectively. Several compounds at the end of the table are so weakly effective that the opacity is not diminished to one-half the control value within the concentration range studied. In some cases the range was limited by solubility.

The two compounds of high molecular weight, starch and polyvinyl alcohol, which shorten the

clotting time, increase the opacity when compared at constant t but are without effect when compared at constant t/t_C.

Inhibition.—Several of the most effective reagents, at moderate concentrations, inhibit clotting altogether. These compounds can be characterized by the minimum inhibiting concentration required to prevent clotting for at least twenty-four hours (Table III); this is practically equivalent to inhibition indefinitely, since mixtures unclotted after one day have been observed to remain unclotted for weeks. It is surprising that these simple alcohols interfere so effectively with the reaction between fibrinogen and thrombin, while others at higher concentrations permit clotting within an hour or less: mannitol and glucose at 80 g./l., and ethylene glycol and glycerol at 200 g./l.

TABLE III

MINIMUM INHIBITING CONCENTRATIONS[a]

Reagent	c, g./l.	m, moles/l.
Hexamethylene glycol	32–43	0.27–0.36
Pentamethylene glycol	48–60	.46– .58
bis-(2-Hydroxyethyl) sulfide	61–81	.50– .66

[a] The first concentration is the highest observed that permits clotting, and the second is the lowest that prevents clotting for at 24 hours, at pH 6.2–6.4, ionic strength 0.45.

Reversibility of Effects of Hydroxyl Compounds.—The reagents studied do not appear to cause any irreversible changes in either fibrinogen or thrombin, as shown by the following experiments with several of the more powerful compounds. (*a*) Solutions of fibrinogen with the standard concentration, pH, and ionic strength, containing hexamethylene glycol, pentamethylene glycol, and bis-(2-hydroxyethyl) sulfide at concentrations somewhat above their minimum inhibiting levels, were allowed to stand six hours and then dialyzed against large volumes of sodium chloride–phosphate buffer of ionic strength 0.45. The dialyzed solutions showed no evidence of precipitation, and, upon addition of thrombin, clots of normal opacity and clotting time were obtained. (*b*) Similar solutions of fibrinogen were dialyzed against large volumes of 0.45 M sodium chloride without buffer. In this case, the pH fell to 5.5, (as did that of fibrinogen solution with no reagent present), and portions tested with thrombin did not clot; but, after the pH was readjusted to 6.2, clots of normal opacity and clotting time were obtained. (*c*) Solutions of thrombin (20 units/cc.) containing the above inhibitors at concentrations somewhat above their minimum inhibiting levels were allowed to stand twenty hours and then used to clot fresh fibrinogen solutions with the standard procedure. Since the concentration of reagent was reduced twenty-fold in mixing with the fibrinogen, its influence should have been slight unless the thrombin had been inactivated; clots of nearly normal opacity and clotting time were in fact obtained, showing that the thrombin had not been affected. (*d*) Mixtures of fibrinogen and thrombin containing the inhibitors which had been kept without clotting for as long as a month were dialyzed against 0.45 M sodium chloride. Clotting soon took place, although the opacity was of course lower than normal because the inhibitor had not been completely removed.

When opaque control clots, formed with the standard procedure in cellophane tubing, were dialyzed against 0.45 M sodium chloride containing pentamethylene and hexamethylene glycols at their minimum inhibiting concentrations, no changes in opacity were apparent, showing that once the coarse structure is established these reagents are powerless to alter it.

When transparent clots, formed in cellophane tubing from fibrinogen solutions containing slightly less than the minimum inhibiting concentrations of the above reagents, were dialyzed against 0.45 M sodium chloride, a gradual increase in opacity occurred after one or two days. It is not yet certain whether this represents a coarsening of the fine structure already established or a continued polymerization of smaller units which had remained unattached to the network structure.

Discussion

Interpretation of these results will be based on the concepts previously developed,[2] that the conversion of fibrinogen to fibrin is essentially a polymerization; that the rod-like fibrinogen molecules (about 35 × 700 Å.) enter the fibrin structure without any profound changes in their own shape; and that their end-to-end junction is accompanied by varying degrees of side-by-side association. The more lateral association, the coarser are the strands of the final network.

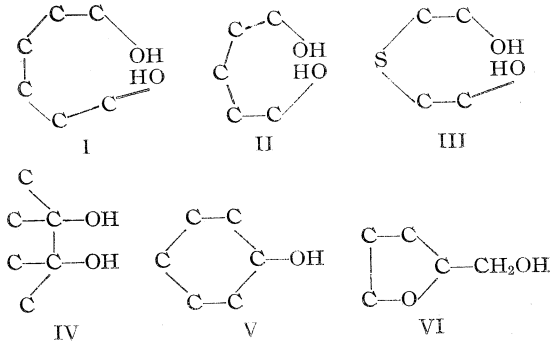
Since the hydroxyl compounds studied do not produce any irreversible change in fibrinogen or thrombin, it may be concluded that their effects on the clotting process are due to interaction involving van der Waals forces. This interaction might interfere with the primary reaction between fibrinogen and thrombin, or it might modify the normal interactions between fibrinogen molecules which determine the geometrical details of polymerization. In either case, the simplest assumption is that the volume of the reagent molecule prevents the two protein molecules from approaching closely enough for their normal combination to occur.

Modification of the geometry of polymerization would cause differences in structure, which are measured roughly by changes in opacity at constant t/t_C (Table II). Interference with the fibrinogen–thrombin reaction would affect the clotting time (Table I), but the latter could also be changed by differences in association geometry, so that both influences must be considered in interpreting the effects of reagents on the time of

clotting.[11] Actually, the orders of effectiveness in the two tables are rather similar.

Relation of Effectiveness to Structure.—As Pauling has emphasized,[13] in van der Waals interactions steric factors are overwhelmingly important; and it should be possible to correlate the observed effects with molecular shape and arrangement of hydroxyls. The most profound effect is complete inhibition by hexamethylene glycol (I), pentamethylene glycol (II), and bis-(2-hydroxyethyl) sulfide (III). Their similarity in structure is evident, with two terminal hydroxyls separated by a chain about 8 to 9 Å. long when fully extended.

The above three compounds appear near the top in Table I and Table II, together with pinacol (IV), cyclohexanol (V), and tetrahydrofurfuryl alcohol (VI). These six molecules present rather similar contours if the glycols are in the ring configuration with the hydroxyls aligned in a hydrogen bond



It seems probable that this is the configuration which interacts strongly with one of the proteins to impede clotting; it represents a bulky mass of paraffin material with either one hydroxyl or two associated hydroxyls at one side.

Near the bottom of each table appear ethylene and propylene glycol and glycerol, with other compounds containing a relatively high proportion of hydroxyl to carbon. From the relative inactivity of these reagents, it appears that the non-polar areas of the more powerful substances are essential to their interaction; it may be supposed that the site on the protein which is blocked involves both a non-polar side chain and a hydrogen bond-forming group.

The compounds mannitol, pentaerythritol, glucose, and sucrose, which are bulky but carry many hydroxyls, are anomalous in that they strongly decrease opacity but have relatively little effect on the clotting time except at quite low concentrations.

Interpretation of Opacity Changes.—Since most of the effective reagents not only prolong clotting but also decrease the opacity at constant t/t_C, it seems probable that they interact with fibrinogen rather than with thrombin, and moreover that they interfere with side-by-side association of fibrinogen molecules even more than with end-to-end junction.[14] It is easy to see how the existence of several sites for interaction with reagent could produce this result (Fig. 6); when a moderate proportion of sites is covered, the probability of finding an unimpeded side is less than that of finding an unimpeded end. The picture of Fig. 6 also explains qualitatively the shape of the curves of opacity against concentration (Fig. 5). If the interaction between sites and reagent can be expressed by an association constant k, then the probability of a free side (and hence the opportunity for association to give coarse network strands) is proportional to $1/(1 + kc)^n$, where c is the concentration and n the number of sites on a side. With increasing c, this fraction at first decreases slowly, and then falls rather rapidly toward zero.

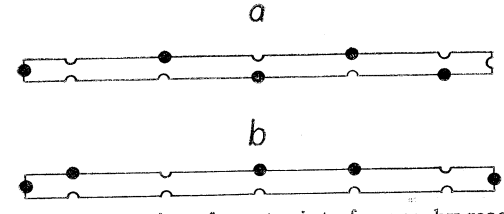


Fig. 6.—Illustration of greater interference, by reagents, with side-by-side than with end-to-end combination. If there are n interaction sites on each side of a fibrinogen molecule and 1 on each end, and a proportion p is blocked by reagents, the probability of a free end (a) is $1 - p$ but the probability of a free side (b) is $(1 - p)^n$.

Effect of Starch and Polyvinyl Alcohol.—The two reagents of high molecular weight are clearly in a class by themselves. Their effect in decreasing the clotting time is shared by a number of other macromolecules, termed "fibrinoplastic" by Ferguson.[15] No more detailed interpretation is offered than the possibility suggested previously[2] that the polymer molecules serve as additional cross-links which permit the network to be established at an earlier stage of the reaction.

Summary

1. The effects of twenty-five hydroxyl compounds on the conversion by thrombin of bovine fibrinogen to fibrin have been investigated by measurements of clotting time and clot opacity.

2. All the reagents except two prolong the

(11) This discussion implies that the extent of reaction at the moment of clotting or gel point[12]—*i. e.*, the proportion of fibrinogen which has been converted to fibrin, or the proportion reacted of whatever specific groups on the fibrinogen molecule are involved—does not depend greatly on the presence of modifying reagents. It is impossible to test the validity of this assumption at present; it probably does not invalidate any of the qualitative conclusions drawn here.

(12) P. J. Flory, *J. Phys. Chem.*, **46**, 132 (1942); *cf.* J. D. Ferry, "Advances in Protein Chemistry," Vol. IV, p. 60 ff.

(13) L. Pauling, in K. Landsteiner, "The Specificity of Serological Reactions," Cambridge, Mass., 1947, Chapter VIII.

(14) This conclusion is supported by preliminary electron micrographs of fibrinogen which has been allowed to react with thrombin in the presence of hexamethylene glycol; very long thin isolated fibers are observed.

(15) J. H. Ferguson, *Ann. N. Y. Acad. Sciences*, **49**, 486 (1948).

clotting time (t_C), and diminish the opacity both compared at constant time (t) after addition of thrombin and at constant t/t_C. The exceptions, starch and polyvinyl alcohol, shorten the clotting time.

3. The effectiveness in prolonging clotting time (expressed by d log t_C/dc, where c is concentration) and in diminishing opacity (expressed by the value of c at which opacity at constant t/t_C is one-half the control value) is generally greatest for compounds with one or two hydroxyls and several methylene or methyl groups, although specific characteristics are apparent.

4. Three reagents—hexamethylene glycol, pentamethylene glycol, and bis-(2-hydroxyethyl)-sulfide—prevent clotting entirely at moderate concentrations but cause no apparent irreversible changes in either fibrinogen or thrombin.

5. The results are interpreted as due to van der Waals association of the reagents with fibrinogen, and consequent steric interference with both end-to-end and side-by-side union of fibrinogen molecules.

MADISON, WISCONSIN RECEIVED APRIL 1, 1949

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Cyclization of α-Phenylglutaric Anhydride

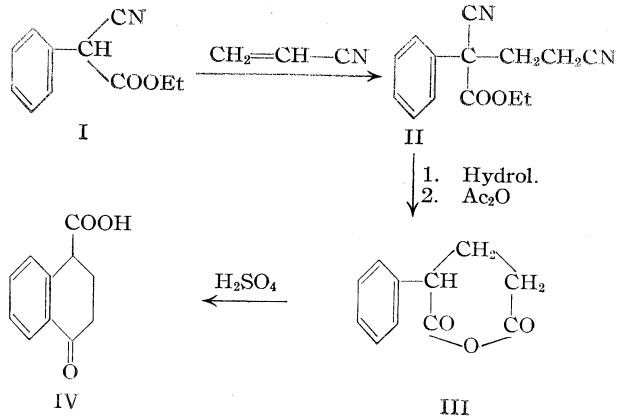
BY E. C. HORNING AND A. F. FINELLI[1]

From an extensive study by Attwood, Stevenson and Thorpe[2] on the cyclization of dicarboxylic acids derived from γ-phenylbutyric acid, the generalization was drawn that substitution in the β-position (with respect to the ring) was necessary for cyclization. For example, both β-benzylglutaric acid and α-benzylsuccinic acid gave tetralones on treatment with sulfuric acid; it was postulated that anhydride formation occurred first, and that cyclization then followed under the influence of concentrated acid. The effect of a β-substituent was not clearly defined, but since every instance in which cyclization occurred included this structural feature, the generalization seemed valid.

In the course of work on the synthesis of certain substituted tetralones, we have investigated the cyclization of α-phenylglutaric anhydride. This compound was prepared from phenylacetonitrile by the following steps. Carbethoxylation of phenylacetonitrile with diethyl carbonate by a modification of the usual method[3] gave ethyl phenylcyanoacetate (I). Addition of acrylonitrile to the latter compound provided α-phenyl-α-carbethoxyglutaronitrile (II); this was hydrolyzed and decarboxylated to the corresponding glutaric acid, which was then converted to the anhydride with acetic anhydride. Treatment of α-phenylglutaric anhydride (III) with sulfuric acid gave 4-keto-1,2,3,4-tetrahydro-1-naphthoic acid (IV) in 57% yield.

It was recognized by the English workers that α-phenylglutaric acid or its anhydride should be investigated as a simple test case for their generalization, but unfortunately the method of Fichter and Merckens[4] for the preparation of the acid could not be repeated. Since the original work, instances in which this generalization does not hold have been found; for example, Robinson[5] has described the cyclization of 5-carboxy-4-carboxymethyl-7-phenylheptanoic acid with sulfuric acid to the corresponding tetralone. The present method provides a satisfactory way of obtaining α-phenylglutaric anhydride, and its successful cyclization confirms the view that substitution in the β-position with respect to the ring is not a prerequisite for cyclization. At the same time, the conditions of cyclization may determine the nature of the product. When the anhydride was treated with aluminum bromide in benzene, an intermolecular reaction occurred with formation of α-phenyl-γ-benzoylbutyric acid. It has recently been demonstrated[6] that benzene is a suitable solvent for intramolecular Friedel–Crafts reactions, and this result indicates that sulfuric acid may give results different from those obtained under Friedel–Crafts conditions.

Acknowledgment.—We are indebted to the Research Corporation for a grant in support of this work, and to Mrs. Sarah M. Woods for the analytical data.



(1) Research Corporation Research Assistant, 1949.

(2) Attwood, Stevenson and Thorpe, *J. Chem. Soc.*, **123**, 1755 (1923).

(3) Wallingford, Jones and Homeyer, THIS JOURNAL, **64**, 576 (1942).

(4) Fichter and Merckens, *Ber.*, **34**, 4174 (1901).

(5) Robinson and Thompson, *J. Chem. Soc.*, 2009 (1938).

(6) Johnson and Glenn, THIS JOURNAL, **71**, 1092 (1949).

Experimental

All melting points are corrected.

Ethyl Phenylcyanoacetate.—Sodium ethoxide was prepared from 12.0 g. (0.52 mole) of sodium and 300 ml. of anhydrous ethanol in a 1-l. three-necked, round-bottomed flask fitted with a reflux condenser and drying tube. After the sodium dissolved, the excess ethanol was removed by heating the flask on a steam-bath while the system was maintained at the pressure obtained with an ordinary aspirator.

As rapidly as possible, after removal of the ethanol, the flask was fitted with a stirrer, a dropping funnel, a distilling head with thermometer, and a condenser arranged for distillation into a flask protected by a calcium chloride tube. There was added 300 ml. of dry diethyl carbonate, 80 ml. of dry toluene, and 58.5 g. (0.50 mole) of phenylacetonitrile. The flask was heated with good stirring and when distillation started, dry toluene was added dropwise at about the same rate as that of distillation. Approximately 200–250 ml. of toluene was added over a period of two hours while stirring and distillation was continued.

The mixture was cooled, transferred to a beaker, and after addition of 300 ml. of cold water, the aqueous phase was acidified with 35–40 ml. of acetic acid. The layers were separated, and the water solution was extracted with three 75-ml. portions of ether. The organic solutions were washed with 100 ml. of water, and then dried over magnesium sulfate. The low-boiling solvents were removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure through a short (15 cm.) Vigreux column. After a 1–5 g. forerun, the product was collected as a colorless liquid at 125–135° (3–5 mm.). The yield was 66–74 g. (71–79%), $n^{25}D$ 1.5012–5019.

α-Phenyl-α-carbethoxyglutaronitrile.—A solution of 57.0 g. (0.30 mole) of ethyl phenylcyanoacetate in 80 ml. of *t*-butyl alcohol was heated to 40°, and with stirring the dropwise addition of a solution of 33.0 g. (0.62 mole) of acrylonitrile in 30 ml. of *t*-butyl alcohol was started. After the addition of about 10–15 drops, 1.0 ml. of 30% methanolic potassium hydroxide was added, and the temperature was maintained at 40–45° by occasional external cooling while the remaining solution was added slowly. When about one-half of the acrylonitrile was added an additional 1.0 ml. of potassium hydroxide solution was added. When the temperature was no longer maintained above 40° by the exothermic reaction, a hot-water-bath was employed to keep the mixture at 40–45° for one hour and it was then allowed to stand overnight.

The solution was diluted with 250 ml. of water, and acidified with 10% hydrochloric acid (30–40 ml.). The product was separated with 100 ml. of ether, and the aqueous solution extracted with two 50-ml. portions of ether. The combined extracts were washed with 50 ml. of water and dried over magnesium sulfate. The ether was distilled at atmospheric pressure, and the residue was distilled under reduced pressure through a short (15-cm.) Vigreux column. After a forerun of a few grams, the product was collected as a colorless viscous oil at 157–167° (0.5–1 mm.). The yield was 50–61 g. (69–83%), $n^{25}D$ 1.5100–5103.

Anal. Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.82. Found: C, 69.59; H, 6.04.

α-Phenylglutaric Anhydride.—A mixture of 48.4 g. (0.20 mole) of α-phenyl-α-carbethoxyglutaronitrile, 225 ml. of hydrochloric acid (sp. gr. 1.19) and 50 ml. of acetic acid was heated under reflux for ten hours. After cooling, the solution was diluted with 300 ml. of water. The α-phenylglutaric acid was extracted with five 100-ml. portions of ether–ethyl acetate (1:1). The extracts were combined and dried over magnesium sulfate. The solvents were removed as completely as possible by heating on a steam-bath, and the residue was transferred to a 200-ml. flask. Acetic anhydride (50 ml.) was added, and the solution was heated under gentle reflux for one hour. The excess acetic anhydride was removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure through a short (15 cm.) Vigreux column. The product was collected at 178–188° (0.5–1 mm.). The yield was 32.7 g. (86%); m. p. 90–94°.

This material was recrystallized from ethyl acetate–hexane to give a colorless crystalline product, m. p. 95–96°. The acid and its anhydride have been reported by Fichter and Merckens.[4]

α-Phenyl-γ-benzoylbutyric Acid.—To a solution of 14.4 g. (0.06 mole) of anhydrous aluminum bromide in 30 ml. of dry benzene there was added a solution of 3.8 g. (0.02 mole) of α-phenylglutaric anhydride dissolved (with warming) in 20 ml. of dry benzene. After the ensuing exothermic reaction the mixture was refluxed for twenty minutes and allowed to stand overnight.

The solution was decomposed with ice and concentrated hydrochloric acid. Approximately 30 ml. of ether was added to aid in the separation. The aqueous layer was extracted with three 30-ml. portions of ether. The combined organic extracts were washed with water. The organic layer was filtered and extracted with six 25-ml. portions of 10% sodium carbonate solution. The alkaline extract was filtered and acidified with hydrochloric acid (10%) to precipitate the organic acid. The mixture was chilled for two hours, filtered, and the product washed with cold water and dried at room temperature to yield 3.6 g. (67%) of crude colorless acid; m. p. 119–125°. Recrystallization from benzene–cyclohexane gave the acid as colorless needles, m. p. 130–131°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.00; H, 6.09.

4-Keto-1,2,3,4-tetrahydro-1-naphthoic Acid.—α-Phenylglutaric anhydride (4.0 g.) was dissolved with slight warming in 25 ml. of concentrated sulfuric acid, and the solution was kept at 60–70° for thirty minutes. This was allowed to stand overnight at room temperature. The solution was poured on chopped ice and allowed to stand until separation of the colorless solid product was complete. The crude material was removed by filtration and dried to yield 2.3 g. (57%); m. p. 91–92°. Recrystallization from ethyl acetate–pentane gave colorless needles, m. p. 93–95°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30; neut. equiv., 190. Found: C, 69.57; H, 5.40; neut. equiv., 192.

The colorless **semicarbazone** melted at 237° (dec.).

Anal. Calcd. for $C_{12}H_{13}O_3N_3$: C, 58.29; H, 5.30. Found: C, 58.46; H, 5.20.

The orange **2,4-dinitrophenylhydrazone** was recrystallized from benzene; m. p. 255–256 (dec.).

Anal. Calcd. for $C_{17}H_{14}O_6N_4$: C, 55.13; H, 3.81. Found: C, 55.12; H, 3.68.

Summary

The preparation and cyclization of α-phenylglutaric anhydride to 4-keto-1,2,3,4-tetrahydro-1-naphthoic acid is described.

PHILADELPHIA 4, PENNSYLVANIA RECEIVED MAY 2, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Studies in the Indole Series. XI. The Reduction of Certain Oxindoles with Lithium Aluminum Hydride

BY PERCY L. JULIAN AND HELEN C. PRINTY

This investigation had its origin in the need for rather large quantities of N-methylyobyrine[1] and certain 5-ethoxylated indole derivatives. To secure the necessary starting materials, namely, 1-methylindole and 1-methyl-5-ethoxyindole, it seemed appropriate to study the reduction of the corresponding and very readily accessible oxindole analogs[2] with lithium aluminum hydride.[3] The method has been applied to several N-methylated oxindoles, and appears generally applicable for the reduction of these derivatives to indoles.

Even with the reverse addition of one mole of lithium aluminum hydride in ether to two moles of the oxindole suspended or dissolved in the same solvent, there always arose about 10–15% of the corresponding indoline. Easily removed from the indole by washing with dilute acid, its presence, nevertheless, gave another example of the reduction of isolated double bonds by lithium aluminum hydride.[4]

In view of the ease with which the reduction of N-substituted oxindoles and indoles took place, it was surprising that the reaction was an almost complete failure with unsubstituted oxindoles. Little or no indole could be obtained from oxindole even when the reaction was carried out at elevated temperatures in butyl ether, dioxane, or tetrahydrofuran. Likewise, unsubstituted indoles were not reduced to indolines by the reagent, a fact we have been able to utilize in the selective reduction of certain groups in more complex indole derivatives.[5]

Analogous results were noted in the behavior of dioxindoles: dioxindole was reduced to oxindole, with small amounts of indole resulting, whereas 1-methyldioxindole was reduced to 1-methylindole.

With ample quantities of 1-methylindole at our disposal, the preparation of 1-methyltryptamine was carried out according to the elegant method of Snyder and Eliel[6]; however, we were able to improve the yield by catalytic reduction[7] of the 1-methylindolylacetonitrile. N-Methylyobyrine was prepared from 1-methyltryptamine by the method already described for yobyrine.[8]

Experimental[9]

Reduction of 1-Methyloxindoles with Lithium Aluminum Hydride.—Twelve grams of lithium aluminum hydride in 600 ml. of anhydrous ether was added in forty minutes to a stirred suspension of 100 g. of 1-methyloxindole in 1 liter of anhydrous ether. The mixture was stirred another ten minutes, 250 ml. of water was added slowly, then 250 ml. of 4% hydrochloric acid. The reaction products were shaken out with ether, and the ether washed with 1 liter of 3% hydrochloric acid. The ether extract was concentrated, then steam-distilled until 4 liters of distillate was obtained. This was extracted with ether, dried over sodium sulfate, and the ether distilled. Fifty-five grams (61.8%) of 1-methylindole, a pale yellow oil, was obtained. This gave a red picrate, m. p. 146–147° dec. (lit.[10] 150°).

The residue from steam-distillation was extracted with ether, washed, dried and concentrated. Fourteen grams of 1-methyloxindole, m. p. 82–85°, was obtained.

The acid washes were treated with sodium hydroxide pellets until strongly alkaline, then steam-distilled until 1 liter of distillate was obtained. This was extracted with ether, which was dried over sodium sulfate, and the ether was distilled. Eleven grams (12%) of pale yellow oil was obtained. This oil distilled at 100–102° at 14 mm., and gave a picrate, shiny yellow plates, m. p. 171–172° dec. Carrasco[11] reports a melting point of 165° for 1-methylindoline picrate.

1,3-Dimethyloxindole was reduced by the metal hydride to 1,3-dimethylindole, b. p. 132–139° (16 mm.), picrate m. p. 141–142° dec., in 85.8% yield. A 13% yield of 1,3-dimethylindoline, a yellow oil, was also obtained. This gave a yellow picrate which crystallized from methanol, m. p. 111–112° dec.

Anal. Calcd. for $C_{16}H_{16}O_7N_4$: C, 51.06; H, 4.28. Found: C, 51.06; H, 4.15.

1-Methyl-5-ethoxyoxindole was reduced in 60% yield to 1-methyl-5-ethoxyindole; 6% of 1-methyl-5-ethoxyindoline was obtained, and 27% of 1-methyl-5-ethoxyoxindole, m. p. 88–90°,[12] recovered. 1-Methyl-5-ethoxyindole was, surprisingly, a higher-melting compound than we expected. It was obtained, on recrystallization from methanol, as shiny white plates, m. p. 86–87°.

Anal. Calcd. for $C_{11}H_{13}ON$: C, 75.39; H, 7.47. Found: C, 75.74; H, 7.70.

This compound gave a very soluble picrate which crystallized from methanol in fine red needles, m. p. 95–96° dec.

Anal. Calcd. for $C_{17}H_{16}O_8N_4$: C, 50.49; H, 3.98. Found: C, 50.90; H, 4.10.

For purposes of comparison, 1-methyl-5-ethoxyindole was prepared from pyruvic acid and *p*-ethoxyphenylmethylhydrazine.[13] The indole obtained this way was identical with that from 1-methyl-5-ethoxyoxindole.

1-Methyl-5-ethoxyindoline was an oil which was isolated as the picrate. This crystallized from methanol in shiny yellow plates, m. p. 142–144° dec.

Anal. Calcd. for $C_{17}H_{18}O_8N_4$: C, 50.24; H, 4.46. Found: C, 50.30; H, 4.61.

Dehydrogenation of the Indolines to Indoles.—This was effected by refluxing a solution of 4 g. of the indoline in 80 ml. of xylene with 7.5 g. of chloranil. The yields of indole were approximately 50%, the remainder of the material apparently forming a complex with chloranil.[14]

Reduction of Indoles with Lithium Aluminum Hydride.—A solution of 4.68 g. of indole in 50 ml. of anhydrous ether was added to a stirred suspension of 1.0 g. of lithium

(1) Woodward and Witkop, THIS JOURNAL, **71**, 379 (1949).

(2) Stollé, *J. prakt. Chem.*, **128**, 1 (1930); Julian, Pikl and Boggess, THIS JOURNAL, **56**, 1797 (1934).

(3) Nystrom and Brown, *ibid.*, **69**, 1197 (1947).

(4) Hochstein and Brown, *ibid.*, **70**, 3484 (1948).

(5) Julian and Magnani, *ibid.*, **71**, 3207 (1949).

(6) Snyder and Eliel, *ibid.*, **70**, 1703 (1948).

(7) *Cf.* Fluchaire and Chambret, *Bull. soc. chim.*, **11**, 22 (1944).

(8) (a) Clemo and Swan, *J. Chem. Soc.*, 617 (1946); (b) Julian, Karpel, Magnani and Meyer, THIS JOURNAL, **70**, 180 (1948).

(9) Carbon-hydrogen analyses by Mr. C. W. Beazley of Micro-Tech Laboratories, Skokie, Illinois.

(10) Fischer and Hess, *Ber.*, **17**, 562 (1884).

(11) Carrasco, *Gazz. chim. ital.*, **38**, 306 (1908).

(12) Julian, Pikl and Wantz, THIS JOURNAL, **57**, 2026 (1935).

(13) Stedman, *J. Chem. Soc.*, 1373 (1924).

(14) *Cf.* Weitz and Schmidt, *J. prakt. Chem.*, **158**, 211–232 (1941).

aluminum hydride in 50 ml. of ether, and stirred for one and one-half hours. Water was added, the aluminum hydroxide dissolved in 3% hydrochloric acid, and the ether layer washed, concentrated and steam-distilled. From the steam-distillate, 4.3 g. of indole was recovered. No indoline was formed. Under these same conditions both 1-methylindole and 1,3-dimethylindole were converted to the respective indolines in 25–30% yields.

Reduction of Dioxindoles.—From 3.72 g. of dioxindole, treated in essentially the same manner, 2.05 g. of oxindole, and, surprisingly, 0.41 g. of indole were obtained. On the other hand, 3.2 g. of 1-methyldioxindole on reduction yielded 1.2 g. of 1-methylindole and 0.5 g. of the oxindole.

Preparation of N-Methylyobyrine.—The following compounds were prepared as previously described.[8b]

***o*-Tolylacetyl-1-methyltryptamine** crystallized from ether in creamy white plates, m. p. 103.5°.

Anal. Calcd. for $C_{20}H_{22}ON_2$: C, 78.39; H, 7.23. Found: C, 78.52; H, 6.97.

N-Methyldihydroyobyrine picrate, crystallized in yellow needles from benzene, m. p. 205–206° dec.

Anal. Calcd. for $C_{26}H_{23}O_7N_5$: C, 60.34; H, 4.48. Found: C, 60.72; H, 4.47.

N-Methylyobyrine (picrate, m. p. 233° dec.) crystallized from ether–methanol as shiny white needles, m. p. 106°.[1]

Anal. Calcd. for $C_{20}H_{18}N_2$: C, 83.88; H, 6.33; N, 9.78. Found: C, 83.72; H, 6.30; N, 9.85.

The over-all yield, in large (4 g.) runs of N-methylyobyrine from *o*-tolylacetyl-1-methyltryptamine, was 30%.

Summary

1-Methyloxindoles are reduced in good yields to the corresponding indoles with lithium aluminum hydride.

The preparation of N-methylyobyrine is described.

CHICAGO, ILLINOIS RECEIVED MARCH 2, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Studies in the Indole Series. XII. Yohimbine (Part 3). A Novel Synthesis of the Yohimbine Ring Structure

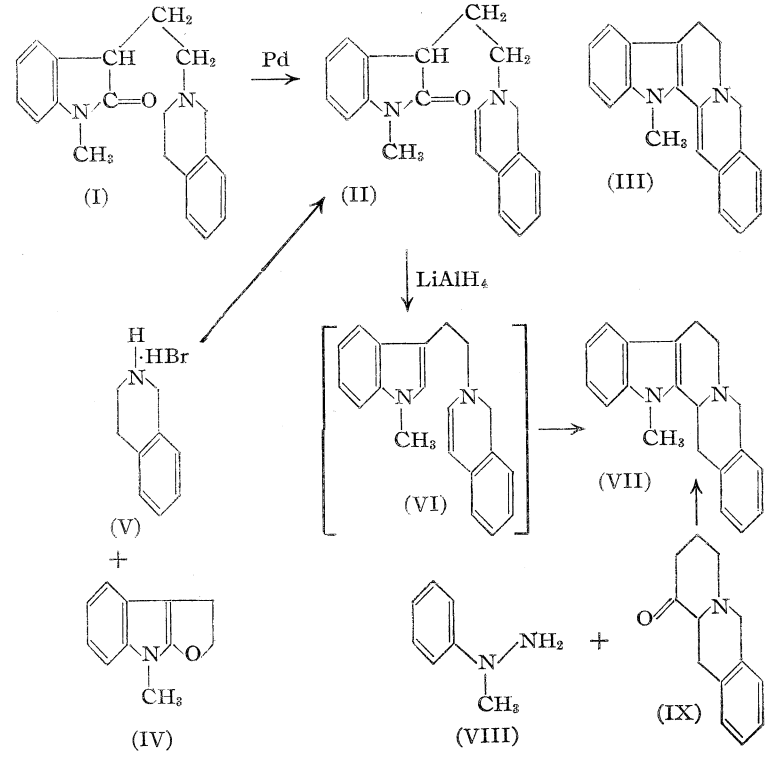
BY PERCY L. JULIAN AND ARTHUR MAGNANI

In an earlier communication dealing with the preparation and properties of 3-(N-tetrahydroisoquinolylethyl)-1-methyloxindole (I),[1] it was shown that dehydrogenation of I with palladium black yielded a 182° melting compound which could not be cyclicized, with the usual dehydrating agents, to III, a substance possessing the basic ring structure of yohimbine.

Largely because of this failure at ring closure, and also because of the difficulties hitherto experienced by various workers in attempts to prepare 1,2-dihydroisoquinolines like II, we expressed the opinion that our dehydrogenation product did not have the constitution II, despite the correct analyses and molecular weight. Certainly its preparation from the dihydrofuroindole (IV) and tetrahydroisoquinoline hydrobromide (V) was, to say the least, not a comfortable basis for ascribing to it the constitution II.

Our subsequent investigations, however, have shown that failure to secure ring closure represents no criterion for or against structure II, and further that the 182° melting dehydrogenation product of I actually does have the structure II, despite the considerations recorded above and in an earlier communication.[1]

Moreover, reduction of II with lithium aluminum hydride, a procedure which we have demonstrated converts 1-alkyl oxindoles smoothly to the corresponding indoles,[2] resulted in spontaneous cyclization of the intermediate (VI) to VII, a compound possessing the basic ring structure of



(1) Julian, Magnani, Pikl and Karpel, THIS JOURNAL, **70**, 174 (1948).

(2) Julian and Printy, *ibid.*, **71**, 3206 (1949).

yohimbine. Thus a novel synthesis of this structure is revealed, the potential usefulness of which is far-reaching.

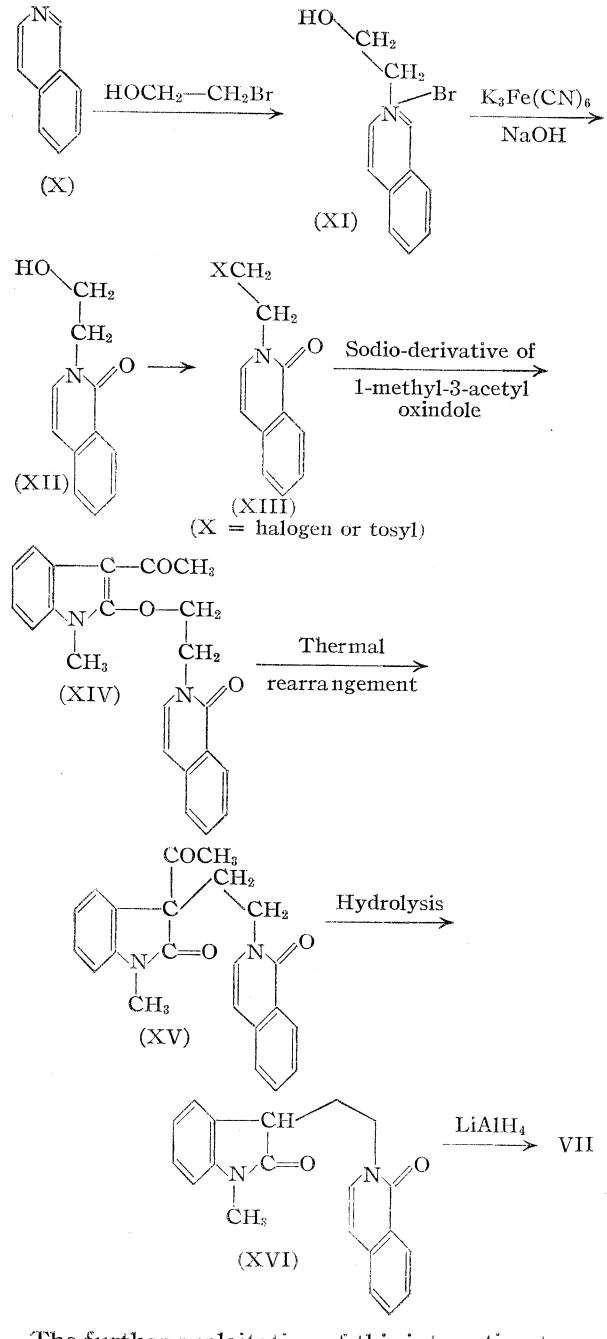
The structure of VII was demonstrated in several ways. First of all it was synthesized quite readily from VIII and IX by a procedure suggested by Clemo and Swan.[3]

The second verification of the structure of VII, demonstrated further the usefulness of this novel method of ring closure to yohimbine derivatives and afforded, in addition, some new insight into the 3-alkylation of oxindoles.[4] In an attempt to prepare compounds of the type represented by II and which indisputably possessed a double bond in the 3,4-position of the isoquinoline nucleus, we prepared the isoquinolone (XVI). All attempts to close the ring here through dehydration, involving enolization of the hydrogen atom in the 3-position of the oxindole, failed as had similar attempts on compound II. On reduction, however, with lithium aluminum hydride, XVI was readily converted into VII, the oxindole carbonyl being reduced as well as the carbonyl group of the isoquinolone.

Further verification of the structure of VII was obtained by its conversion to N-methylyobyrine[2] by treatment with palladium black, a reaction now well identified with compounds containing the yohimbine ring skeleton.[5]

As stated above, the preparation of XVI gave us our first insight into the mechanism of 3-alkylation of 1-methyl-3-acetyloxindole, a type of alkylation we have frequently employed over the past several years.[1,4] The quaternary adduct from ethylene bromohydrin and isoquinoline was converted in good yield with alkaline potassium ferricyanide to the isoquinolone alcohol (XII). The tosylate of the latter or the corresponding chlor-compound (XIII) reacted with the sodio-derivative of 1-methyl-3-acetyloxindole to yield a readily crystallizable O-alkyl derivative, to which we tentatively ascribe formula XIV. The experimental basis for this structure is diffuse and will be the subject of a separate communication. Suffice it to say that structure XIV has been chosen primarily on the basis of analogy in ultraviolet spectrum and other properties to the 1-methyl-2-methoxy-3-formyl indole prepared several years ago.[6]

Thermal rearrangement of this O-alkyl derivative (XIV) yields a C-alkyl acetyl derivative (XV), which could not be induced to crystallize, but which on hydrolysis gave the crystalline 1-methyl-3-(1-oxo-isoquinolylethyl)-oxindole (XVI). Thus we have one of the relatively rare cases where the O-alkyl intermediate in C-alkylation of 1,3-dicarbonyl compounds can be cleanly isolated and thermally rearranged into its C-alkyl isomer.



The further exploitation of this interesting type of ring closure for the simplest type of synthesis of the yohimbine ring structure yet reported, involving the addition of β-indolylethyl bromide and β-N-methylindolylethyl bromide to isoquinoline, is being studied and will be reported in another communication.

Experimental

Reduction of 1-Methyl-3-[2-N-(1,2-dihydroisoquinolylethyl)]-oxindole (II) to the Yohimbine Ring Skeleton (VII) with $LiAlH_4$.—The dihydroisoquinolylethyloxindole (II) was obtained by dehydrogenating the tetrahydroisoquinolylethyloxindole (I) with palladium black.[1] The

(3) Clemo and Swan, *J. Chem. Soc.*, 617 (1946).
(4) Julian, Pikl and Wantz, THIS JOURNAL, **57**, 2026 (1935).
(5) Clemo and Swan, ref. 3; Prelog, *Helv. Chim. Acta*, **31**, 588 (1948); Woodward and Witkop, THIS JOURNAL, **71**, 379 (1949).
(6) Julian, Pikl and Boggess, THIS JOURNAL, **56**, 1797 (1934).

dihydroisoquinolylethyloxindole (0.45 g., m. p. 180–182°) was dissolved in 5 ml. of dry dioxane and diluted with 30 ml. of absolute ether. Over a five-minute period with agitation there was added a solution of 70 mg. of lithium aluminum hydride in 25 ml. of absolute ether. The reaction mixture was allowed to stand for one hour at room temperature, cautiously decomposed by the addition of water, and then acidified with dilute acid. The aqueous acidic solution was extracted with ether to remove any non-basic material. The basic fraction (0.4 g.) obtained by basifying and extracting with ether was distilled. The fraction distilling as a yellow oil at 180–185° bath temperature (0.008 mm.) was collected and amounted to 0.3 g. Upon treatment in methanol with picric acid, there was obtained 0.25 g. of orange picrate, m. p. 198–202° dec. It was identical with the picrate of the base VII obtained from the Fischer indole synthesis involving the ketone IX, and after crystallization from methanol melted at 205–207° dec. The picrate (0.18 g.) upon decomposition with alkali yielded the base VII (85 mg.) melting at 132–135°. By heating 60 mg. of the base with palladium black as described below, N-methylyobyrine was isolated as the picrate (44 mg., m. p. 230–233° dec.).

Fischer Indole Synthesis of the Base VII.—The method and procedure used were essentially those described by Clemo and Swan.[3] The hydrazone prepared from α-methylphenylhydrazine (VIII) and the ketone (IX) was crystallized from aqueous methanol as yellow plates, m. p. 93°.

Anal. Calcd. for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.83; H, 7.47; N, 13.45.

The phenylhydrazone (0.44 g.) was ring closed by heating for twenty minutes on the steam-bath with 15 ml. of 5% sulfuric acid. The red aqueous solution was diluted with water, made alkaline, and extracted several times with ether. The ethereal solution was washed with water, dried over sodium sulfate, and the solvent removed. The residual reddish oil could not be crystallized at this point. It was dissolved in methanol, treated with a methanolic solution of 0.30 g. of picric acid, and concentrated on the steam-bath until crystallization of the picrate began. After cooling, the picrate was filtered and washed with methanol. There was obtained 0.32 g. of the picrate of the ring-closed-base VII, m. p. 206–208° dec. Recrystallization from methanol gave yellow needles, m. p. 209° dec.

Anal. Calcd. for $C_{26}H_{23}N_5O_7$: C, 60.34; H, 4.48; N, 13.54. Found: C, 60.40; H, 4.37; N, 13.26.

The free base VII was obtained from the picrate (0.3 g.) by shaking a suspension of it in ether with alkali until complete solution resulted. The ethereal solution was washed well with water, dried over sodium sulfate, and the solvent removed. The partially crystalline residue (0.14 g.) was distilled as a yellow oil (0.11 g.) collected at 0.002 mm. and 165–170° bath temperature. Slow crystallization from warm aqueous methanol gave the base VII as white plates; yield 88 mg., m. p. 135°.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.72. Found: C, 83.20; H, 6.92; N, 9.66.

The base VII (30 mg.) was heated with 30 mg. of palladium black for twenty minutes at 215 to 225° and at 10–15 mm. pressure. The product was extracted with hot methanol and treated with norite. The methanol solution, upon treatment with 25 mg. of picric acid, yielded, on concentration, 25 mg. of the yellow picrate of N-methylyobyrine, m. p. 230–232° dec. After decomposition of the picrate with alkali, N-methylyobyrine (10 mg.) was readily obtained by crystallization from a concentrated solution in ether–petroleum ether as white rods, m. p. 105–106°. When this product was mixed with an authentic sample of N-methylyobyrine[2] (m. p. 105–106°), there was no depression of the melting point.

β-Hydroxyethyl-isoquinolinium Bromide (XI).—A mixture of 17.7 g. of ethylene bromohydrin and 20 g. of isoquinoline was heated on the steam-bath until an exothermic reaction darkened the solution and rapidly raised the temperature of the mixture to 190°. When allowed to cool slowly the reddish liquid set to a mass of crystals which was digested with acetone and filtered. The isoquinolinium bromide (34 g.) was dissolved in 34 ml. of hot methanol and crystallized by adding 340 ml. of hot acetone. There was obtained 26.2 g. of the isoquinolinium bromide, m. p. 154–156°. Further crystallizations raised the melting point to 157°.

Anal. Calcd. for $C_{11}H_{12}ONBr$: C, 51.99; H, 4.76; N, 5.51. Found: C, 51.86; H, 4.70; N, 5.42.

2-β-Hydroxyethyl-1-isoquinolone (XII).—The isoquinolinium bromide was oxidized to the isoquinolone in 60% yield with potassium ferricyanide by the method of Elpern and Hamilton.[7] The crude isoquinolone was isolated by filtration or by chloroform extraction and distilled. From 26 g. of the isoquinolinium bromide there was obtained 14.2 g. of a yellow oil which crystallized readily, b. p. 190–200°, bath temperature (2.5 mm.). The isoquinolone was dissolved in 10 ml. of methanol, 50 ml. of warm benzene was added and the solution concentrated to a volume of 35 ml. It crystallized as white plates; yield 11.8 g.; m. p. 114–116°. For analysis it was recrystallized from benzene, m. p. 116°.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.73; H, 5.54; N, 7.31.

Tosylate of 2-β-Hydroxyethyl-1-isoquinolone (XIII).—The tosylate of the isoquinolone was best prepared by employing a large excess of tosyl chloride. To a suspension of 2.85 g. of the isoquinolone (finely divided) in 25 ml. of benzene was added 3.0 g. of tosyl chloride. The mixture was cooled in an ice-bath, and with vigorous agitation there was added 10 ml. of 30% sodium hydroxide over a period of five minutes. This mixture was agitated for five minutes, and the addition of tosyl chloride and sodium hydroxide was repeated twice. The slightly gummy precipitate of the tosylate changed to a finely divided precipitate which was collected on a filter and washed well with water and ether. There was obtained 4.0 g. of the tosylate, m. p. 160–164°. It is sparingly soluble in ether or benzene. For recrystallization, it was dissolved in a small amount of chloroform, diluted with hot benzene, and then concentrated until crystallization began, m. p. 166°.

Anal. Calcd. for $C_{18}H_{17}O_4NS$: C, 62.96; H, 4.99; N, 4.08. Found: C, 63.06; H, 4.96; N, 4.14.

2-β-Chloroethyl-1-isoquinolone (XIII).—Thionyl chloride (4 ml.) was cautiously added to 2.1 g. of the hydroxyethylisoquinolone covered with 6 ml. of petroleum ether (30 to 60°) and the resulting yellow layers allowed to stand for twenty minutes. This mixture was heated on the steam-bath until a homogeneous solution resulted, and the remaining petroleum ether and excess thionyl chloride were removed *in vacuo*. The residual yellow oil was dissolved in ether, and the solution washed with dilute alkali and water. The chloroethylisoquinolone was crystallized from ether–petroleum ether; yield 2.2 g., m. p. 102–105°. Recrystallization from the same solvents gave white needles, m. p. 109°.

Anal. Calcd. for $C_{11}H_{10}ONCl$: C, 63.62; H, 4.85; N, 6.74. Found: C, 63.88; H, 4.77; N, 6.62.

The same chloroethylisoquinolone was prepared from the tosylate. To 250 mg. of the tosylate in 10 ml. of dry alcohol-free acetone 50 mg. of lithium chloride was added and the mixture refluxed for one hour. The acetone was removed *in vacuo* and the residue was dissolved in ether and washed with water. The chloroethylisoquinolone (120 mg.) thus isolated melted at 107–109°.

2-β-Bromoethyl-1-isoquinolone (XIII).—Reaction of hydroxyethylisoquinolone with thionyl bromide yielded a mixture of products and very little of the bromoethylisoquinolone. The latter, however, was readily prepared from the tosylate as described for the chloroethylisoquinolone. From 0.5 g. of the tosylate and 0.5 g. of lithium bromide there was obtained 0.4 g. of the bromoethylisoquinolone, m. p. 109–110°. Recrystallization from ether–petroleum ether gave white needles, m. p. 112°.

(7) Elpern and Hamilton, THIS JOURNAL, 68, 1436 (1946).

Anal. Calcd. for $C_{11}H_{10}ONBr$: C, 52.40; H, 4.00. Found: C, 52.65; H, 4.10.

Reaction of Isoquinolones (XIII) with Sodio-derivative of 1-Methyl-3-acetyloxindole (a) with Tosylate of 2-β-Hydroxyethyl-1-isoquinolone.—A mixture of 2.5 g. of the tosylate and 2.1 g. of the sodium salt of the acetyloxindole in 50 ml. of alcohol-free acetone was refluxed vigorously for one hour under anhydrous conditions. The thick paste first formed was gradually replaced by a fine precipitate of the sodium salt of the sulfonic acid. This mixture was diluted with ether and washed with water. The reddish ethereal solution was concentrated and the last of the solvents removed *in vacuo*. The remaining oil was then crystallized from acetone–ether yielding 1.45 g. of the compound XIV resulting from O-alkylation of the acetyloxindole, m. p. 157–160°. Recrystallization from acetone–ether gave white needles, m. p. 161°.

Anal. Calcd. for $C_{22}H_{20}O_3N_2$: C, 73.31; H, 5.60; N, 7.77. Found: C, 73.37; H, 5.82; N, 7.40.

The compound XIV is sparingly soluble in ether and in the extraction described above will precipitate from the ethereal solution if all of the acetone is removed by washing.

(b) **With 2-β-Chloroethyl-1-isoquinolone.**—A mixture of 7.0 g. of the chloroethylisoquinolone, 14.0 g. of the sodio-derivative of 1-methyl-3-acetyloxindole, 1.0 g. of sodium iodide, and 70 ml. of dry dioxane was heated for 17 hours on the steam-bath with frequent shaking. The thick paste of solids slowly thinned as the reaction progressed. After cooling, water was added to dissolve the unchanged sodium salts and the mixture was extracted with ether. From the aqueous portion 5.6 g. of the acetyloxindole was recovered by acidification. The ethereal solution was washed free of alkali with water, small amounts of acetone being added to prevent precipitation of the sparingly soluble O-alkyl product. The product (XIV) was isolated and crystallized as previously described; yield, 3.1 g.; m. p. 158–160°.

(c) **With 2-β-Bromoethyl-1-isoquinolone.**—The same O-alkyl product (XIV) was obtained by refluxing 1.1 g. of the bromoethylisoquinolone, 2.2 g. of sodio-derivative of acetyloxindole, and 0.3 g. of sodium iodide in 25 ml. of dioxane for five hours. The work-up was the same as that described in (b); yield 0.35 g., m. p. 158–160°.

Hydrolysis of O-Alkyl Product (XIV).—Upon treatment of the O-alkyl product (XIV) with sodium ethoxide several products were obtained. To 1.45 g. of XIV in 10 ml. of ethanol a solution of 0.2 g. of sodium in 5 ml. of ethanol was added and the mixture heated for ten minutes on the steam-bath. The purple solution was diluted with ether and washed with water and dilute hydrochloric acid to remove most of the color. The ethereal solution was dried, concentrated, and taken to dryness. The residue (1.0 g.) crystallized readily from ether–petroleum ether to give 0.8 g. of crystals, m. p. 88–94°, which proved to be a mixture of two compounds. They were separated by fractional crystallization. One product crystallized as white plates, m. p. 116°, and proved to be 2-β-hydroxyethyl-1-isoquinolone. The other product crystallized as white rods, m. p. 110°, and by analysis appeared to be 2-β-ethoxyethyl-1-isoquinolone.

Anal. Calcd. for $C_{13}H_{15}O_2N$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.54; H, 6.77; N, 6.70.

Ether extraction of the acidified aqueous alkaline washes gave 1-methyl-3-acetyloxindole which crystallized as needles from aqueous methanol, m. p. 108–110°. By alkaline extraction of residues from the fractional crystallizations more of the acetyloxindole was obtained.

Thermal Rearrangement of the O-Alkyl Compound (XIV) and Hydrolysis to XVI.—The O-alkyl compound (1.3 g.) was heated in a metal-bath for ten minutes at 220–230° for the rearrangement. The red melt was allowed to cool and dissolved in ether but could not be induced to crystallize. By distillation (230–250° bath temperature, 0.5 mm.) there was obtained 1.1 g. of a red oil (XV) which again could not be obtained crystalline. It was dissolved in 5 ml. of ethanol and refluxed for ten minutes with a solution of 0.3 g. of sodium in 8 ml. of ethanol for deacetylation. After cooling and diluting with water, the product was extracted with ether and washed with water. Removal of the ether gave a reddish oil which crystallized readily from ether–petroleum ether yielding 0.7 g. of the 1-methyl-3-[2-N-(1-oxo-1,2-dihydroisoquinolylethyl)]-oxindole (XVI), m. p. 120–124°. Recrystallization gave fine white needles, m. p. 126°.

Anal. Calcd. for $C_{20}H_{18}O_2N_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.38; H, 5.76; N, 8.95.

Attempts to Ring Close 1-Methyl-3-[2-N-(1-oxo-1,2-dihydroisoquinolylethyl)]-oxindole (XVI).—A solution of 0.3 g. of the isoquinolylethyloxindole in 4 ml. of phosphorus oxychloride was refluxed for one hour. The oxychloride was removed *in vacuo* and the remaining viscous residue was dissolved by digestion with water. The acidic aqueous solution was rendered alkaline and extracted with ether. From the ethereal solution there was recovered 0.24 g. of the original compound, m. p. 121–124°. No other product was isolable. The same results were obtained when a longer refluxing time was used. Similarly, by using phosphorus pentoxide in xylene, the original compound was recovered. With phosphorus trichloride followed by treatment with aluminum chloride only the starting material was isolated from the halogen-containing products.

Reduction of 1-Methyl-3-[2-N-(1-oxo-1,2-dihydroisoquinolylethyl)]-oxindole (XVI) with $LiAlH_4$ to VII.—Two grams of the oxo-dihydroisoquinolylethyl oxindole was dissolved in 10 ml. of dioxane and diluted with 50 ml. of absolute ether. There was added with agitation a solution of 0.4 g. of lithium aluminum hydride in 50 ml. of absolute ether over a five-minute period. After standing for one hour the reaction mixture was worked up as described for the reaction with the dihydroisoquinolylethyloxindole (II). The crude basic fraction (1.5 g.) was purified by distillation. The fraction distilling at 180–210° bath temperature and at 0.01 mm. (0.8 g.) was redistilled and the pale yellow oil (0.55 g.) distilling at 180–190° at 0.01 mm. collected. Upon treating the oil in methanol with 0.45 g. of picric acid there was readily obtained 0.75 g. of crude picrate melting at 180–190° dec. After two crystallizations from methanol, the picrate (0.3 g.) melted at 205–207° dec. and gave no melting point depression when admixed with the picrate of the base VII obtained by the Fischer indole synthesis. Upon decomposition of 100 mg. of the picrate with alkali there was obtained 40 mg. of the base VII (m. p. 132–135°) which upon treatment with palladium black gave N-methylyobyrine, isolated as the picrate (29 mg., m. p. 232–234° dec.).

Summary

A novel synthesis of the yohimbine ring structure is reported which comprises the spontaneous ring closure of a 3-[2-N-(1,2-dihydroisoquinolylethyl)]-indole.

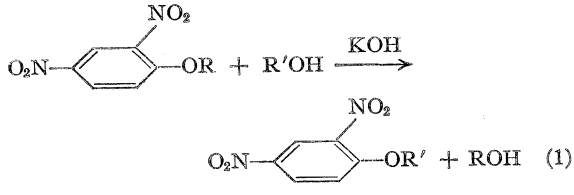
CHICAGO, ILLINOIS RECEIVED MARCH 2, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, THE FACULTY OF ENGINEERING, KYOTO UNIVERSITY]

Nucleophilic Substitution in Aromatic Ethers. I. Ethers in which Nucleophilic Substitution is Possible

BY YOSHIRO OGATA[1] AND MASAYA OKANO

Just like *p*-nitrochlorobenzene, *p*-nitroanisole is converted to *p*-nitrophenetole when boiled in ethyl alcohol in the presence of caustic alkali.[2] The substitution may be called an ether interchange. In an attempt to extend this reaction, we studied the interchange of *p*-nitroanisole with polyhydric alcohols and alcohols of the C_3–C_4 range. It was found that little or no reaction occurred. When an alkoxyl group was activated by the introduction of nitro groups into the 2 and 4 positions of anisole, however, substitution occurred readily



$$O_2N\text{—}C_6H_3(NO_2)\text{—}OR + R'OH \xrightarrow{KOH} O_2N\text{—}C_6H_3(NO_2)\text{—}OR' + ROH \quad (1)$$

In this paper a number of such substitution reactions are described.

The reaction was found to be reversible when the group R was alkyl but irreversible when R was aryl (Equation 1). In the same way, 2,4-dinitroanisole or 2,4-dinitrodiphenyl ether reacted with aniline, forming 2,4-dinitrodiphenylamine.[3] Benzyl methyl ether, benzhydryl methyl ether, anisole or anisoles substituted with electronegative groups other than nitro (*e.g.*, CH_3CO) were incapable of interchange.

Experimental

Ether Interchange.—The experiments summarized in Table I were carried out according to a standardized procedure which may be illustrated by the preparation of 2,4-dinitrophenyl isobutyl ether. In 30 cc. of isobutyl alcohol was dissolved 0.2 g. of potassium hydroxide by boiling. To this solution was added 3 g. of 2,4-dinitroanisole (m. p. 88°) and the mixture was boiled under a reflux condenser for ten hours. After removing the alcohols by distillation and evaporation, the residue was cooled and washed with water. The crude 2,4-dinitrophenyl isobutyl ether (m. p. 27–29°) weighed 2.8 g. (77%). It was recrystallized from ethanol to which a drop of concentrated hydrochloric acid was added. The product separated in the form of laminae, m. p. 34–35°, and recrystallization involved about a 10% loss of material.

Anal. Calcd. for $C_{10}H_{12}O_5N_2$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.58; H, 4.93; N, 10.9.

The same product (m. p. 33–35°) was isolated from the reaction of 2,4-dinitrochlorobenzene with sodium isobutoxide. A mixed melting point determination of this material with the product obtained from the ether interchange reaction showed no depression.[4]

Under approximately the same conditions anisole, *p*-acetylanisole, *p*-chloroanisole, 2,4,6-tribromoanisole and potassium *p*-methoxybenzenesulfonate did not react with ethanol. Similarly *p*-nitroanisole did not undergo interchange with isopropyl alcohol, isobutanol, allyl alcohol, ethylene glycol, or phenol. In boiling aniline solution, however, 2,4-dinitrodiphenyl ether and 2,4-dinitrophenyl β-naphthyl ether gave good yields (80 and 97%, respectively), of 2,4-dinitrodiphenylamine, m. p. 156–157°. 2,4-Dinitroanisole also reacted, but a large amount of amorphous material was formed. The yield of 2,4-dinitrodiphenylamine was less than 20%.

In the run in which glycerol was employed, the general procedure was modified to the extent that the reaction mixture was heated with stirring at 160–180° in an oil-bath.

TABLE I

ETHER INTERCHANGE OF SOME 2,4-DINITROPHENYL ALKYL OR ARYL ETHERS

R in Eq. 1	R′ in Eq. 1	Reaction time, hr.	Yield, %	Product, m. p., °C.
CH_3	*n*-C_3H_7	10	73	28–30[a]
CH_3	iso-C_3H_7	10	73	51–53[a]
CH_3	*n*-C_4H_9	10	70	Oil[a]
CH_3	iso-C_4H_9	10	77	34–35[b]
CH_3	CH_2=$CHCH_2$	10	0	
CH_3	C_6H_5	10	0	
CH_3	$C_6H_5CH_2$	10	0	
CH_3	*n*-$C_{15}H_{31}CH_2$	2	0	
CH_3	—CH_2CH_2—	2	69	109–110[c]
CH_3	—CH_2CHCH_2—	6	26	84–85
CH_2CH_2OH	CH_3 |	10	70	88–89
CH_2CH_2OH	iso-C_3H_7	10	64	51–53
C_6H_5	CH_3	10	82	87–89
C_6H_5	C_2H_5	10	73	84–86
C_6H_5	iso-C_3H_7	20	71	51–52
C_6H_5	—CH_2CH_2—	6	51	108–110[c]
C_6H_4Cl-*p*	CH_3	2	71	88–89
C_6H_4Cl-*p*	—CH_2CH_2—	2	66	109–110[c]
$C_6H_4NO_2$-*p*	CH_3	2	77	88–89
$C_6H_4NO_2$-*p*	—CH_2CH_2—	2	72	109–110[c]
$C_6H_4CH_3$-*p*	CH_3	10	82	88–89
$C_6H_4CH_3$-*o*	CH_3	10	76	88–89
$C_6H_4CH_3$-*m*	CH_3	10	84	88–89
$C_6H_4OCH_3$-*p*	CH_3	10	78	87–89
$C_{10}H_7$-α	CH_3	10	86	88–89
$C_{10}H_7$-β	CH_3	10	87	88–89

[a] Blanksma and van der Weyden, *Rec. trav. chim.*, **39**, 629 (1940). [b] New compound; see the Experimental part. [c] The melting point of this compound agrees with that of the monoglycol ether $(NO_2)_2C_6H_3OCH_2CH_2OH$, recently found by Blanksma and Fohr, *Rec. trav. chim.*, **65**, 706, 711 (1946); *cf. C. A.* **41**, 5484 (1947).

(1) Present address: Kyoto University, Yoshida, Kyoto, Japan.

(2) Oliverio, *C. A.*, **33**, 9302 (1939).

(3) For the reaction of 2,4-dinitroanisole with ammonia, see Salkowski, *Ber.*, **5**, 872 (1872).

(4) The tarry matter inevitable to the reaction of 2,4-dinitrochlorobenzene with sodium alkoxides is never produced in the ether interchange. It should therefore prove to be a better general method for the preparation of higher 2,4-dinitrophenyl ethers.

Summary

The methoxyl group of 2,4-dinitroanisole is convertible to another alkoxyl group, by boiling dinitroanisole in the presence of caustic alkali with polyhydric alcohols or alcohols of the C_2–C_4 range. Aniline leads to 2,4-dinitrodiphenylamine.

Similar reactions are possible with some other 2,4-dinitrophenyl alkyl or aryl ethers.

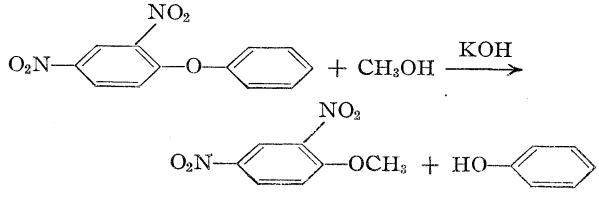
KYOTO, JAPAN RECEIVED FEBRUARY 28, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, THE FACULTY OF ENGINEERING, KYOTO UNIVERSITY]

Nucleophilic Substitution in Aromatic Ethers. II. Kinetics of the Methanolysis of 2,4-Dinitrodiphenyl Ethers

BY YOSHIRO OGATA AND MASAYA OKANO

In the preceding paper[1] it was shown that 2,4-dinitroanisole is formed irreversibly, when a solution of 2,4-dinitrodiphenyl ether is boiled in alkaline methanol



In the present paper, the rate of reaction and the effect of structure on the rate were studied. The rate was determined by taking out aliquots of the reaction mixture after suitable time intervals, and estimating the phenol produced iodometrically.

Experimental

Materials.—Methanol (b. p. 64.5–65°) was purified by repeated rectifications from calcium oxide and silver nitrate. The 2,4-dinitrodiphenyl ethers were prepared by the condensation of 2,4-dinitrochlorobenzene with the corresponding sodium phenolates. They were recrystallized (twice) slowly from acetone or, with the α- or β-naphthyl derivatives, from a mixture of acetone and methanol. Among them, the 4′-chlorophenyl, 4′-nitrophenyl, α-naphthyl and β-naphthyl ethers were prepared in methanol (many hours boiling was necessary in the case of the nitro or naphthyl derivatives). The melting points agreed with those in the literature[2] as follows. 2,4-Dinitrodiphenyl ether, 70–71°; 2′-methyl, 89–90°; 3′-methyl, 72–73.5°; 4′-methyl, 91–92.5°; 4′-chloro, 122–123.5°; 4′-nitro, 115–116°; α-naphthyl 127–128°; β-naphthyl, 93–94.5°.

Apparatus and Procedure.—About 0.0025 mole of one of the ethers was weighed out and dissolved in 200 cc. of methanol. The solution was poured into a four-necked flask and placed in a thermostat (20 ± 0.1°) until temperature equilibrium was established. The flask was fitted with a stirrer[3] in its central neck, and in the other three were placed a thermometer, a tube suitable for withdrawing samples, and a tube into which air could be blown for pushing out the sample. The proper amount of potassium hydroxide was then dissolved in boiling methanol and its concentration was determined by titration with 0.05 *N* oxalic acid. An accurately measured amount of this solution (50 cc.) was taken out and kept in the thermostat until temperature equilibrium was reached and was then poured into the flask with gentle agitation (250–300 r. p. m.). This time was taken as the beginning of the reaction. A 25-cc. sample was taken out at regular intervals and run into a glass-stoppered flask containing 3 cc. of concentrated hydrochloric acid and 50 cc. of water. Twenty cc. of 0.1 *N* bromine water (a solution prepared from potassium bromate and bromide), were then added, the flask was stoppered tightly, and it was allowed to stand for fifteen seconds or thirty minutes before analysis.[4] The mixture was then treated with 5 cc. of 20% potassium iodide solution, and the freed iodine was titrated with 0.05 *N* sodium thiosulfate. The difference between the needed volume of thiosulfate solution and the blank test corresponded to the amount of phenol formed.

Results and Calculations

The bimolecular rate constants shown in Tables I and II were calculated by means of the following equation

$$k = \frac{2.303}{60t(b-a)} \log \frac{a(b-x)}{b(a-x)} \text{ (l./moles} \times \text{sec.)}$$

Here, a is the initial concentration of ether (moles/l.), b that of alkali (moles/l.), x the concentration of phenol after t minutes (mole/l.).[5] In Table I is shown the effect of changes in concentration on the second order rate constant of the methanolysis of 2,4-dinitrodiphenyl ether. It is evident that the rate of formation of phenol is proportional to the product of the concentration of the original ether and methylate ion.

In Table II are shown the rate constants for a number of runs in which various changes were made in the 2,4-dinitrodiphenyl ether molecule. It will be observed that the substitution of an electron attracting group (*e. g.*, NO_2) in the 4′ posi-

(1) Ogata and Okano, THIS JOURNAL, **71**, 3211 (1949).

(2) (a) Raiford and Colbert, *ibid.*, **48**, 2652 (1926); (b) Bost and Nicholson, *ibid.*, **57**, 2368 (1935).

(3) Agitation was necessary, for the methanol solution tended to become heterogeneous when it was allowed to stand for a long time.

(4) From the results obtained with pure materials under these conditions, it was found that standing for thirty minutes is too long for *o*-, *m*-, *p*-cresol, and α- or β-naphthol. Even when the potassium iodide solution was added after fifteen seconds, the estimations of *o*- and *p*-cresol showed that the values were about 103 and 104% of the theoretical values. These estimations were, therefore, carried out rapidly and corrected by dividing the results by 1.04 and 1.03, respectively. See Day and Taggert, *Ind. Eng. Chem.*, **20**, 545 (1928).

(5) It should be noted that phenol and *m*-cresol consume 3 moles of bromine per mole. *p*-Substituted phenols and β-naphthol consume 2 moles, but α-naphthol reacts with 1 mole. Moreover, with *o*- and *p*-cresol, x should be divided by 1.03 and 1.04, respectively; see ref. 4.

TABLE I

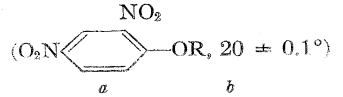
THE EFFECT OF ALKALI CONCENTRATION

2,4-Dinitrodiphenyl ether, 20 ± 0.1°

a	*b*	10^3k
0.01012	0.00454	4.78 ± 0.04
.01011	.00780	4.71 ± .03
.01008	.01030	4.76 ± .03
.00999	.01950	4.72 ± .01

TABLE II

THE EFFECT OF SUBSTITUENTS

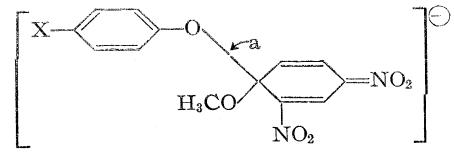


R	*a*	*b*	10^3k
C_6H_5	0.01016	0.01561	4.81 ± 0.03
C_6H_5	.00999	.01647	4.64 ± .01
4′-$C_6H_4NO_2$	.01008	.01561	64.4 ± .5
4′-$C_6H_4NO_2$	.00999	.01647	64.8 ± .3
4′-C_6H_4Cl	.01002	.01561	10.7 ± .1
4′-C_6H_4Cl	.01003	.01647	10.7 ± .1
β-$C_{10}H_7$	.01000	.01496	8.16 ± .03
β-$C_{10}H_7$	.01001	.01639	8.07 ± .04
α-$C_{10}H_7$	.01003	.01496	6.27 ± .03
α-$C_{10}H_7$	.00999	.01639	6.26 ± .03
3′-$C_6H_4CH_3$	.01004	.01496	3.66 ± .04
3′-$C_6H_4CH_3$	.00999	.01639	3.72 ± .03
4′-$C_6H_4CH_3$	.01002	.01561	2.77 ± .05
4′-$C_6H_4CH_3$	.01002	.01647	2.91 ± .04
2′-$C_6H_4CH_3$	.01001	.01561	1.40 ± .03
2′-$C_6H_4CH_3$	.01003	.01647	1.46 ± .03

tion of 2,4-dinitrodiphenyl ether increases the rate of reaction and the introduction of an electron releasing group (*e. g.*, CH_3) in the 2′- or 4′-position decreases the rate of reaction. This behavior resembles the effect of a substituent upon the reactivity of 4-substituted 2,6-dinitroanisoles with *p*-methoxydimethylaniline.[6] It is probaby due to the fact that the electron attracting group not only makes the formation of the activated complex I easier,[7] but also it facilitates fission of the carbon–

(6) Hertel and Lührmann, *Z. Elektrochem.*, **45**, 405 (1939).

(7) Meisenheimer, *Ann.*, **323**, 241 (1902).



(I)

oxygen bond a. By inserting into Hammett's equation, $\log k/k_0 = \rho\cdot\sigma$,[8] the average values of k and k_0 shown in Table II, the values for ρ shown in Table III were calculated using Hammett's σ values. From the average value of ρ (1.46 ± 0.04), the σ value of the α-naphthyl group in α-naphthyl 2,4-dinitrophenyl ether was calculated to be 0.084.

TABLE III

Substituent	$\log (k/k_0)$	ρ
4′-NO_2	1.1354	1.46
4′-Cl	0.3665	1.61
β-C_4H_4	.2347	1.38
3′-CH_3	− .1078	1.56
4′-CH_3	− .2215	1.30
	Av.	1.46 ± 0.04[9]

From this average value of ρ, the σ value of α-naphthyl was calculated to be +0.084.

Summary

The rates of exchange of the substituted phenoxy group of substituted 2,4-dinitrodiphenyl ethers for a methoxy group were measured. It was found that the rate is proportional to the product of the concentration of the original ether and methylate ion. Electron-attracting groups in the 4′-position of the ether increase the rate. Electron-releasing groups in the 2′- or 4′-position decrease it. The effect of the substituent on the rate constant of this reaction satisfied Hammett's equation, giving a σ value of + 1.46 ± 0.04.

KYOTO, JAPAN RECEIVED FEBRUARY 28, 1949

(8) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, pp. 186–188.

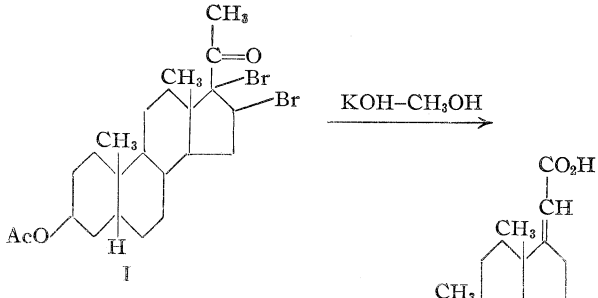
(9) Probable error.

[CONTRIBUTION FROM THE WHITMORE LABORATORIES OF THE PENNSYLVANIA STATE COLLEGE]

Rearrangement of α,β-Dibromoketones[1]

BY R. B. WAGNER

During the course of studies of certain steroidal bromoketones, it was found that 16,17-dibromopregnan-3(β)-ol-20-one acetate (I) under vigorous alkali treatment yields 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid (II) by a rearrangement which had not been previously observed.[2]

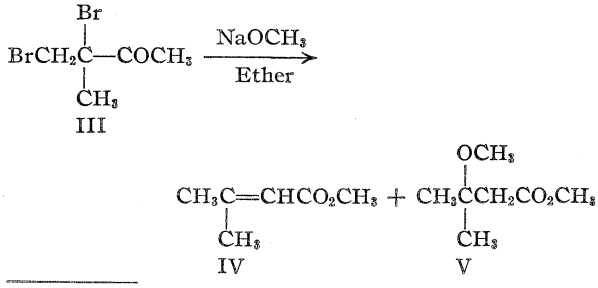


I II

The present paper describes the extension of this rearrangement to aliphatic and simpler alicyclic α,β-dibromoketones, namely, 3,4-dibromo-3-methyl-2-butanone (III), 3,4-dibromo-3-methyl-2-pentanone (VI) and 1-acetyl-1,2-dibromocyclohexane.

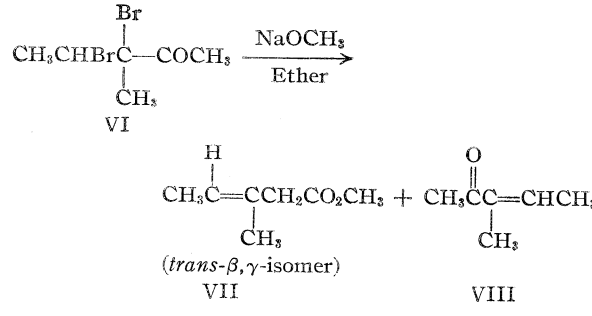
The dibromo compounds were prepared by the reaction of equimolar quantities of bromine and the corresponding α,β-unsaturated ketones. The adjacent positions of the bromine atoms in these compounds are indicated by their almost quantitative removal with hot methanolic sodium iodide to give the original unsaturated ketone.[2]

When 3,4-dibromo-3-methyl-2-butanone (III) was added to an ether suspension of two moles of sodium methoxide at 10–20° and the products were allowed to stand for thirty hours, a mixture of the methyl esters of β,β-dimethylacrylate (IV) (42%) and β-methoxyisovalerate (V) (16%) was obtained; with a reaction time of two and a half hours, a mixture consisting of 64% of IV and 2% of V was obtained.



III IV V

Similarly, using the shorter reaction time, 3,4-dibromo-3-methyl-2-pentanone (VI) gave 3-methyl-3-penten-2-one (VIII) (15%) and the methyl ester of *trans*-3-methyl-3-pentenoic acid (VII) (55%); none of the corresponding isomeric unsaturated ester could be isolated. Under the same conditions, 1-acetyl-1,2-dibromocyclohexane yielded exactly analogous products, namely, the methyl ester of 1-cyclohexenylacetic acid (34%) and methyl 1-cyclohexenyl ketone (19%).



VI

(*trans*-β,γ-isomer) VII VIII

The methyl esters from these rearrangements were characterized by hydrogenation, saponification and oxidation procedures and, in each case, direct comparison with synthetic products and their derivatives were made. With the exception of the β-methoxy ester (V), the products could be obtained by procedures described in the literature.[3,4]

Methyl β-methoxyisovalerate (V) has been synthesized in small yields by the addition of methanol to methyl β,β-dimethylacrylate (IV) in the presence of sodium methoxide. It has been shown that the addition of alcohols to methyl acrylate is a general reaction for the preparation of β-alkoxypropionates.[5] However, the reaction of the disubstituted acrylate is much slower.

None of the corresponding γ-methoxy isomer, methyl γ-methoxyisovalerate, was detected among the rearrangement products from III. For comparison purposes, this compound has been synthesized by the following series of reactions.

The γ-methoxy ester and its acid are completely different from the rearrangement product (V) and its acid.

It is noteworthy that the double bond in the unsaturated esters from the last two mentioned rearrangement reactions is in the β,γ-position,

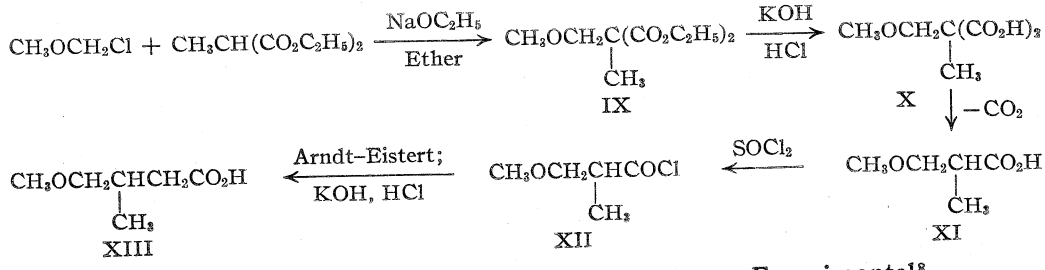
(1) Presented before the Division of Organic Chemistry, American Chemical Society, New York City, September, 1947.

(2) Marker, Wagner and Wittbecker, THIS JOURNAL, **64**, 2093 (1942).

(3) Kon, Linstead and Wright, *J. Chem. Soc.*, 599 (1934).

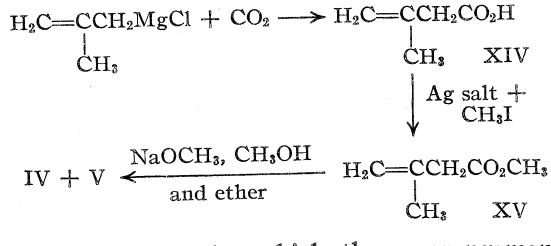
(4) Auwers and Ellinger, *Ann.*, **387**, 200 (1912); these authors report for methyl 1-cyclohexenylacetate, b. p. 93° (15 mm.), $n^{20}D$ 1.4679 and d^{20} 1.002.

(5) Rehberg, Dixon and Fisher, THIS JOURNAL, **68**, 544 (1946).



whereas the first reaction gives an ester having α,β-unsaturation. This anomaly in this series has been investigated further and it has been found that the corresponding β,γ-isomer (XV) of methyl β,β-dimethylacrylate when placed under conditions similar to those used for the bromoketone rearrangement *undergoes a shifting of the double bond to the α,β-position.* In addition, methyl β-methoxyisovalerate (V) is formed during this reaction in the same proportions as noted in the rearrangement reaction. From this experiment, it may be concluded that if the β,γ-unsaturated ester is formed here as in the other cases, it would immediately undergo a secondary reaction to give the α,β-isomer (IV) and the β-methoxy ester (V). Furthermore, since methanol adds to the α,β-isomer (IV) under these conditions of long and short reaction periods to form the β-methoxy ester (V) in 24 and 8% yields, respectively, this source (IV) for the latter (V) is indicated in both the isomerization and the rearrangement reaction. On the other hand, the double bond in the higher β-alkylated-β,γ-unsaturated esters, homologs of XV, does not migrate under these mild conditions; in fact, even under more vigorous alkali treatment, the "equilibrated" mixture favors the β,γ-isomer.[3] However, it should be noted that the double bond in the steroidal unsaturated acid (II) is in the α,β-position, which again appears to be the more stable position.

The β,γ-isomer (XV), methyl 3-methyl-3-butenoate, has been synthesized for these studies by the carbonation of methallyl Grignard reagent followed by esterification of the resulting acid through its silver salt. This ester is readily differentiated from the rearrangement ester (IV).



The mechanism by which the rearrangement occurs is not definitely settled although suggestions have been made.[6,7]

Acknowledgment.—Combustion analyses (C, H, N) were performed by R. N. Walters.

(6) McPhee and Klingsberg, *ibid.*, **66**, 1132 (1944).
(7) Marker, Crooks and Wagner, *ibid.*, **64**, 213 (1942).

Experimental[8]

Unsaturated Ketones.—(a) **3-Methyl-3-buten-2-one** was prepared by the dehydration of 3-methyl-4-butanol-2-one, b. p. 80° (10 mm.), $n^{20}D$ 1.4340, d^{20} 0.9951. The crude ketol prepared by the procedure of Morgan and Griffith[9] was found to be satisfactory for dehydration. The reaction was carried out by adding 1 kg. of the ketol, preheated to 95°, continuously in a slow stream to a hot mixture of 50 g. of fused potassium bisulfate and 4 g. of hydroquinone contained in a flask equipped with the usual Claisen distilling head and condenser. The reaction mixture was heated during the addition causing the distillation of the olefinic ketone and water mixture. When the addition of the ketol was complete and the head temperature had risen to 110°, the reaction was stopped and the product layers were separated. The organic mixture was fractionated through a column with a 45 × 1.8 cm. section packed with 3/32" glass helices, removing additional water in the fore-cut. There was obtained an 80% yield of the unsaturated ketone, b. p. 58° (200 mm.), $n^{20}D$ 1.4232 and d^{20} 0.8540.[10]

(b) **3-Methyl-3-penten-2-one** was prepared in an 87% yield by distilling directly from a reaction mixture consisting of 290 g. of 3-methyl-4-pentanol-2-one, 2 cc. of 38% aqueous hydrobromic acid and 2 g. of hydroquinone. The crude olefinic ketone was fractionated to give material having b. p. 97° (200 mm.), $n^{20}D$ 1.4489 and d^{20} 0.8758.

The pure ketol, b. p. 76° (10 mm.), $n^{20}D$ 1.4350 and d^{20} 0.9704, was prepared in a 67% yield from methyl ethyl ketone and acetaldehyde by the procedure of Kyrides[11] using satisfactorily five times the stated quantities. The reaction mixture was concentrated by a flash evapora-

TABLE I

DIBROMO KETONES

Compound	B. p., °C. (M. p. °C.)	Mm.	d^{20}	Yield, %	Bromine analyses, % (Stepanoff) Calcd.	Found	
2,3-Dibromo-3-methyl-2-butanone (III)	53	1	1.803	97	65.7	65.6	65.7
2,3-Dibromo-3-methyl-2-pentanone (VI)[a]	78–82	5	1.701	90	62.0	61.8	61.7
1-Acetyl-1,2-di-bromocyclohexane[b]	(48)		...	60	56.3	56.8	56.9

[a] This material could be distilled in 10-g. batches without serious decomposition. [b] 1-Acetyl-1,2-dibromocyclohexene (formula not shown) was prepared by brominating the unsaturated ketone dissolved in an equal volume of chloroform. Most of the solvent was removed at a bath temperature of 20° and the remainder at 15 mm. during three days at 30°. The crystalline dibromide was triturated and washed with cold pentane. A sample of this material was heated under reflux for one hour with excess sodium iodide in methanol. The liberated iodine (titrated with standard sodium thiosulfate) corresponded to the theoretical quantity for the complete removal of both bromine atoms. The original olefinic ketone was isolated as its semicarbazone, m. p. and mixed m. p., 217°.

(8) All melting points and boiling points are uncorrected.
(9) Morgan and Griffith, *Chemistry and Industry*, **57**, 885 (1938).
(10) McMahon, *et al.*, THIS JOURNAL, **70**, 2971 (1948), report b. p. 38° (85 mm.), $n^{20}D$ 1.4325 and d^{20} 0.8541.
(11) Kyrides, *ibid.*, **55**, 3431 (1933).

TABLE II

PHYSICAL CONSTANTS AND YIELDS OF PRODUCTS FROM REARRANGEMENT STUDIES

Bromo ketone reacted	Products	B. p. °C.	Mm.	$n^{20}D$	d^{20}	M_D Calcd.	M_D Obs.	Yield, %
III	Methyl β,β-dimethylacrylate (IV)	60	50	1.4378	0.9425	31.10[b]	31.78	64(42)[c]
	Methyl β-methoxyisovalerate (V)	67	20	1.4161	.9786	37.82	37.49	2(16)[c]
VI	3-Methyl-3-penten-2-one (VIII)	63	50	1.4489	.8758	29.45[b]	30.05	15
	Methyl *trans*-3-methyl-2-pentenoate (VII)	74	50	1.4306	.9949	35.71	35.92	55
XVI[a]	1-Acetyl-1-cyclohexene	78	10	1.4904	.9685	36.49[b]	37.10	23
	Methyl 1-cyclohexenylacetate	84	10	1.4668	1.001	42.75	42.73	35

[a] 1-Acetyl-1,2-dibromocyclohexane (formula not shown). [b] Exaltations for the conjugated systems in these compounds would raise the calculated values (*cf.* ref. 4). [c] Yields in parentheses are those obtained when the reaction mixture was allowed to stand thirty hours.

tion technique[12] and distilled through a column with a 53 × 1.8 cm. section packed with 1/8" glass helices.

(c) **1-Acetyl-1-cyclohexene** was prepared in a 50% yield from cyclohexane, acetyl chloride and anhydrous aluminum chloride by the directions of Christ and Fuson[13] and was purified by fractionation through a column with a 53 × 1.8 cm. section packed with 3/32" glass helices; b. p. 88.5° (20 mm.) and $n^{20}D$ 1.4904.[14]

Preparation of the Dibromo Ketones.—The unsaturated ketone, 2–3 moles, contained in a 1-liter three-necked flask which was equipped wth a stirrer, dropping funnel and thermometer and surrounded by an ice–salt-bath, was treated in a dropwise manner with an equimolar quantity of bromine at 0° during six hours. Additional data are summarized in Table I.

Reaction with Sodium Methoxide.—To a suspension of 4 moles of sodium methoxide (Mathieson Alkali Works, 95%) in anhydrous ether was added 2 moles of the dibromo ketone. The reaction mixture was stirred vigorously and was cooled by a salt–ice-bath. The addition was completed in one and one-half hours, keeping the temperature at 20°. An acid–base titration of a 2-ml. aliquot showed the almost complete absence of the basic reagent. After stirring an additional hour, the mixture was poured onto ice, the layers were separated, and the water layer was ether extracted. The total ethereal solution was dried over anhydrous potassium carbonate and the ether was removed through a column. The concentrate was rapidly distilled *in vacuo* through a Claisen apparatus to free it from any high-boiling and bromine-containing material. The crude distillate was then carefully fractionated through a column with a 43 × 1.8 cm. section packed with 3/32" glass helices. Additional data are summarized in Table II.

Identification of Products from the Rearrangement Reactions.[15] (a) **Methyl β,β-Dimethylacrylate (IV).**—Hydrogenation of IV using Adams catalyst gave methyl 3-methylbutanoate, b. p. 116° (732 mm.), $n^{20}D$ 1.3920, d^{20} 0.8807, further characterized by its *p*-toluide, m. p. and mixed m. p., 109–110°. Saponification gave dimethylacrylic acid, m. p. and mixed m. p., 70°, and methanol, b. p. 64° (739 mm.) and $n^{20}D$ 1.3265. Oxidation with magnesium permanganate gave acetone isolated as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 126–127°.

The anilide was crystallized from ether as needles, m. p. and mixed m. p. with an authentic sample, 131–132°.

The *p*-toluide was crystallized from ethanol as needles, m. p. and mixed m. p. with an authentic sample, 106–107°.

Anal. Calcd. for $C_{12}H_{15}ON$: N, 7.40. Found: N, 7.59, 7.58.

(b) **Methyl β-Methoxyisovalerate (V).**—The properties of V are the same as those for the product synthesized by the route described below.

Anal. Calcd. for $C_7H_{14}O_3$: $2CH_3O$, 42.4; sapn. equiv., 146. Found: $2CH_3O$ (Zeisel), 42.4; sapn. equiv., 149.

The *p*-toluide was crystallized from benzene–pentane as needles, m. p. and mixed m. p., 51–52°.

Anal. Calcd. for $C_{13}H_{19}O_3N$: N, 5.90. Found: N, 6.14.

(c) **3-Methyl-3-penten-2-one (VIII).**—The properties of VIII agree with those for the product synthesized as described above. The **semicarbazone** was crystallized from ethanol, m. p. and mixed m. p., 200–201°.[16]

(d) **Methyl *trans*-3-Methyl-3-pentenoate (VII).**—Hydrogenation of VII using Adams catalyst gave methyl 3-methylpentanoate isolated as its anilide which was crystallized from benzene–pentane, m. p. and mixed m. p., 86–87°. Ozonolysis gave acetaldehyde isolated as the 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 167–168°.

Anal. Calcd. for $C_7H_{12}O_2$: sapn. equiv., 128. Found: sapn. equiv., 128.

The amide was crystallized from benzene–pentane as plates, m. p. 130–131°.

The *p*-toluide was crystallized from aqueous ethanol as plates, m. p. and mixed m. p. with the *p*-toluide of the *trans*-isomer, 91–92°.

The anilide was crystallized from benzene–pentane as needles, m. p. and mixed m. p. with the anilide of the *trans*-isomer, 99–100°.

(e) **Methyl 1-Cyclohexenylacetate.**[4]—Saponification gave methanol, b. p. 64° (739 mm.) and $n^{20}D$ 1.3268.

The anilide was crystallized from aqueous ethanol as long needles, m. p. and mixed m. p. with an authentic sample,[17] 118–119°.

Anal. Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96. Found: C, 77.38; H, 7.82.

The *p*-toluide was crystallized from aqueous ethanol as needles, m. p. and mixed m. p. with an authentic sample,[17] 101–102°.

Anal. Calcd. for $C_{15}H_{19}ON$; C, 78.56; H, 8.35. Found: C, 78.59; H, 8.14.

(f) **Methyl 1-Cyclohexenyl Ketone.**—The semicarbazone was crystallized from ethanol, m. p. and mixed m. p., 221°.[14]

3-Methyl-3-butenoic Acid (XIV) and Reactions.—Methallylmagnesium chloride was prepared in an 81% yield by treating 900 g. (10 moles) of methallyl chloride in 10 liters of anhydrous ether with 243 g. (10 moles) of magnesium turnings at 14–16° during ten hours. The reaction was carried out with vigorous stirring in a three-

(12) Whitmore, *et al.*, *Ind. Eng. Chem.*, **38**, 942 (1946).

(13) Christ and Fuson, THIS JOURNAL, **59**, 895 (1937).

(14) Kon, *J. Chem. Soc.*, 1801 (1926), reports b. p. 81° (13 mm.), $n^{20}D$ 1.49042 and d^{20} 0.9685; semicarbazone, m. p. 217°.

(15) All derivatives were prepared by the methods described by Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1940.

(16) Hinkel, *J. Chem. Soc.*, 818 (1931), reports the semicarbazone, m. p. 201°.

(17) The 1-cyclohexenylacetic acid used for the preparation of these derivatives was prepared from cyclohexylideneacetic acid by the procedure of Beesley, Ingold and Thorpe, *J. Chem. Soc.*, 1080 (1915); b. p. 136° (12 mm.).

gallon copper vessel. The Grignard reagent was obtained as a solid suspended in the ether. This was added with vigorous stirring during thirty minutes to 10 kg. of powdered Dry Ice contained in a second copper vessel equipped with a large vent to the hood. The resulting complex was decomposed with ice and concentrated hydrochloric acid mixture (requires 1 liter of concd. hydrochloric acid). After saturating the water layer with sodium chloride, the ether layer was separated and the acid portion was extracted by washing with a solution of 600 g. of sodium carbonate (final *p*H of wash, 8.01). The alkaline extract was layered with 6 liters of ether and acidified by vigorous stirring with 1 liter of concd. hydrochloric acid (final *p*H, 1.5). The ethereal solution was evaporated, and the residue was dried by removing the water as an azeotropic mixture with benzene and then distilled through a Claisen apparatus to give 400 g. of material (40% yield) boiling 68–70° (5 mm.), m. p. 20.2–21.3° and $n^{20}D$ 1.4308.

Anal. Calcd. for $C_5H_8O_2$: neut. equiv., 100. Found: neut. equiv., 100, 101.

Ozonolysis of this material yielded formaldehyde isolated as its dimedone derivative.

(a) Conversion to the Methyl Ester (XV).—To a stirred solution of 213 g. (2.13 moles) of 3-methyl-3-butenoic acid in 4 liters of distilled water was added 85 g. (2.13 moles) of C. P. sodium hydroxide dissolved in 2 liters of distilled water followed by a solution of 392 g. (2.31 moles) of silver nitrate in 1 liter of distilled water. The precipitate was filtered and triturated twice successively with water, absolute ethanol and ether. The silver salt suspended in 2.5 liters of anhydrous ether contained in a 5-liter, three-necked flask, equipped with a stirrer and condenser, was treated with excess methyl iodide (2.3 moles) under reflux for seventy-two hours. After twenty-four hours a yellow precipitate of silver iodide predominated. The reaction mixture was filtered, the ether was evaporated, and the product was fractionated through a column with a 43 × 1.8 cm. section packed with 3/32″ glass helices to give entirely one product, 115 g., b. p. 41° (27 mm.), $n^{20}D$ 1.4168 and d^{20} 0.931; 47% yield. M_D calcd., 31.10; obs., 31.18.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 62.94; H, 9.10.

The *p*-toluide was prepared from the ester and crystallized from aqueous ethanol as needles, m. p. 95°. A mixture with the *p*-toluide of β,β-dimethylacrylic acid, m. p. 107°, melted 68–90°.

Anal. Calcd. for $C_{12}H_{15}ON$: N, 7.40. Found: N, 7.40.

(b) Conversion to β,β-Dimethylacrylic Acid.—A mixture of 10 g. of 3-methyl-3-butenoic acid, 20 ml. of dry ether and 10 g. of 90% sulfuric acid was allowed to stand at room temperature for forty-eight hours. The reaction mixture was diluted with water and extracted with ether, after saturating the water layer with ammonium sulfate. The acid fraction was then transferred to the aqueous sodium salt solution and back to an ethereal solution, which was evaporated to yield 9.7 g. of dimethylacrylic acid, crystallized from water; m. p. and mixed m. p., 68–70°; 97% yield.

(c) Conversion to Methyl β,β-Dimethylacrylate and Methyl β-Methoxyisovalerate.—For reasons discussed above, this reaction was carried out under conditions similar to those used for the rearrangement of the bromo ketones. Since the formation of the unsaturated ester is accompanied by an equimolar quantity of methanol, this was added. Thus a mixture 109 g. (0.96 mole) of methyl 3-methyl-3-butenoate, 32 g. (1.0 mole) of methanol, 10 g. of sodium methoxide and 500 ml. of ether was stirred at room temperature for thirty hours. The reaction mixture was processed as before and the product on fractionation gave 60 g. (0.55 mole) of methyl β,β-dimethylacrylate, b. p. 60° (50 mm.), $n^{20}D$ 1.4381 (53% yield) and 32 g. (0.22 mole) of methyl β-methoxyisovalerate, b. p. 66° (20 mm.), $n^{20}D$ 1.4157 (23% yield).

Under similar conditions using a two and a half-hour reaction time, the yield of the unsaturated ester was 80 and 10% for the β-methoxy ester.

When methyl β,β-dimethylacrylate was treated under the same conditions, the yields were 63% of the unsaturated ester and 24% of the β-methoxy ester for the long reaction period and 81 and 8%, respectively, for the short time.

Methyl β-Methoxyisovalerate (V).—A solution of 3 g. of sodium in 32 g. (1.0 mole) of methanol was added to 83 g. (0.85 mole) of methyl β,β-dimethylacrylate at 28° during ten minutes. The mixture was kept at room temperature for four days, then acidified with 15 cc. of concd. hydrochloric acid and filtered. The filtrate was fractionated to give starting material and 15 g. (0.11 mole) of methyl β-methoxyisovalerate, b. p. 67° (20 mm.), $n^{20}D$ 1.4161 and d^{20} 0.9777; M_D calcd., 37.8; obs., 37.5.

Anal. Calcd. for $C_7H_{12}O_3$: $2CH_3O$, 42.4; C, 57.5; H, 9.65. Found: $2CH_3O$ (Zeisel), 44.0, 44.2; C, 58.1; H, 10.0.

The *p*-toluide was prepared and crystallized from benzene–pentane as needles, m. p. 51°. This gave no depression in melting point with the *p*-toluide of the corresponding rearrangement product.

Synthesis of γ-Methoxyisovaleric Acid (XIII). (a) Ethyl Methoxymethylmethylmalonate (IX).—Finely divided sodium, 115 g. (5 atoms) in 2 liters of anhydrous ether was treated with 855 g. (5.0 moles) of ethyl methylmalonate.[18] The mixture was refluxed and stirred for eight hours at which time all of the sodium had reacted. To the semi-solid sodio-derivative was added 440 g. (5.5 moles) of monochloromethyl ether,[19] b. p. 60–65° (739 mm.), during one hour at reflux temperature. The reaction was vigorous and the mixture became more fluid with the formation of sodium chloride; it was stirred overnight at room temperature.

Titration of a 1-ml. aliquot indicated that only 0.33 mole of base remained. The mixture was acidified with 30 ml. of acetic acid and then treated with water. The ethereal solution was dried rapidly with anhydrous calcium chloride and distilled rapidly through a Claisen apparatus. Material boiling between 94 and 120° (50 mm.), was carefully fractionated to give a 50% yield of product, b. p. 115–117° (16 mm.), $n^{20}D$ 1.4220.

(b) Methoxymethylmethylmalonic Acid (X).—To a solution of 300 g. (7.5 moles) of sodium hydroxide in 200 ml. of water and 1 liter of 95% ethanol was added 530 g. (2.43 moles) of the above ester during one hour at room temperature. The mixture was stirred for two hours and allowed to stand overnight. After dissolving the solid mass in 400 ml. of water, the solution was concentrated to one liter on the steam-bath with air passing through it to remove the alcohol. The concentrate was cooled and acidified with 235 ml. (4.2 moles) of concentrated sulfuric acid dissolved in an equal volume of water and then continuously extracted with ether for four days. The ether extract was evaporated and the residue was crystallized; 393 g. (2.40 moles); yield, 99% of crude acid. An aliquot was recrystallized from ether–pentane, m. p. 104–105°.

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22; neut. equiv., 81.0. Found: C, 44.53; H, 6.49; neut. equiv., 81.4, 82.4.

(c) β-Methoxyisobutyric Acid (XI).—The above crude acid, 383 g. (2.36 moles), was heated under a column with a 53 × 1.8 cm. section packed with 1/4″ glass helices at 150–160° until the evolution of carbon dioxide ceased. The product was fractionated to give 228 g. (1.93 moles) of monocarboxylic acid, b. p. 83° (3 mm.) and $n^{20}D$ 1.4192; 82% yield.

Anal. Calcd. for $C_5H_{10}O_3$: CH_3O, 26.3; neut. equiv., 118. Found: CH_3O (Zeisel), 26.3, 26.6; neut. equiv., 118, 119.

(d) β-Methoxyisobutyryl Chloride (XII).—A mixture of 118 g. (1.00 mole) of XI and 144 g. (1.20 moles) of pure thionyl chloride was warmed at 40° for forty-five minutes and then at 60° for an additional forty-five minutes. The excess thionyl chloride was removed *in vacuo* and the

(18) Cox and McElvain, *Org. Syntheses*, Coll. Vol. II, 279 (1943).
(19) Marvel and Porter, *ibid.*, Coll. Vol. I, 377 (1941).

product was distilled to give material boiling at 48–59° (15 mm.), 122 g. (0.90 mole), representing a 90% yield.

Anal. Calcd. for $C_5H_9O_2Cl$: Cl, 26.0. Found: Cl (Stepanoff), 26.2, 26.2.

(e) **γ-Methoxyisovaleric Acid (XIII).**—The above acid chloride, 114 g. (0.84 mole), was treated in three batches with an ethereal solution of diazomethane and then with a methanol slurry of silver oxide according to the Arndt–Eistert[20] procedure. The resulting product consisted of a mixture of the chloro ketone and the desired methyl ester, 25 g., b. p. 69° (20 mm.); 25% yield.

Although the saponification equivalent agreed closely with the theoretical value, a chlorine analysis showed that the ester was contaminated with the chloro ketone. The latter was removed by converting the above methyl ester, 24 g., to the corresponding acid by refluxing with excess 10% alcoholic potassium hydroxide. The product was isolated in the usual manner and fractionated to give the γ-methoxy acid; 16 g., b. p. 123–125° (20 mm.), $n^{20}D$ 1.4235, d^{20} 1.034; M_D calcd., 33.09; obs., 32.52.

Anal. Calcd. for $C_6H_{12}O_3$: OCH_3, 23.5. Found: OCH_3 (Zeisel), 23.6.

β-Methoxyisovaleric Acid.—For comparison purposes, the ester, 21 g., was hydrolyzed with excess 20% alcoholic potassium hydroxide as above and the product was fractionated to give the β-methoxy acid, b. p. 125° (20 mm.), $n^{20}D$ 1.4333, d^{20} 1.045; M_D calcd., 33.09; obs., 32.81.

Anal. Calcd. for $C_6H_{12}O_3$: neut. equiv., 132. Found: neut. equiv., 132.

***cis*- and *trans*-3-Pentenoic Acid.**—These acids were prepared by general procedures described in the literature[3] and converted to their derivatives, not previously described, for comparisons with the corresponding derivatives of the rearrangement products. Ethyl β-methyl-β-hydroxyvalerate, b. p. 83–88° (13 mm.), prepared by the Reformatsky reaction according to the procedure of Natelson and Gottfried,[21] was converted to the acid by careful alkaline hydrolysis, avoiding the presence of a large excess of base at any time. For this the ester, 280 g. (1.75 moles), in 200 ml. of 95% ethanol was treated at reflux temperature with a solution of 70 g. (1.75 moles) of C. P. sodium hydroxide in 150 ml. of water in a dropwise manner, maintaining a faint coloration with phenolphthalein indicator. The mixture was concentrated by air passing through the hot solution. The cold concentrate was acidified with dilute sulfuric acid and ether extracted to give 200 g. (1.75 moles) of crude acid. This was dehydrated with acetic anhydride according to Wallach[22] to give a mixture of the *cis*- and *trans*-isomers of both the α,β- and β,γ-unsaturated acids. The non-crystalline material,[23] 80 g. (0.70 mole) was partially esterified during twelve hours at room temperature to separate the α,β- and β,γ-isomers as acid and ester, respectively.[2] The former, 53 g. (0.47 mole), was treated with 260 g. (4.65 moles) of potassium hydroxide in 750 ml. of water at 100° for three days; an equilibrium mixture of the *cis*- and *trans*-α,β-acids and the *cis*-β,γ-acid resulted (the *trans*-β,γ-acid is not present to any large extent).[3] The mixture was partially esterified with ethanol to give an acid fraction consisting of the α,β-isomers and a neutral fraction which was the desired ethyl *cis*-3-methyl-3-pentenoate, b. p. 61° (13 mm.), $n^{20}D$ 1.4298 and d^{20} 0.9183; wt., 25 g. (0.16 mole).

Ozonolysis of this material gave acetaldehyde, isolated as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 165–168°.

The *cis*-*p*-toluide was crystallized from aqueous ethanol as needles, m. p. 100.5–101.5°. A mixture with the *p*-toluide from the rearrangement product (IV) or the authentic *trans*-*p*-toluide described below showed a melting point depression of thirty degrees.

Anal. Calcd. for $C_{13}H_{17}ON$: C, 76.80; H, 8.43. Found: C, 76.94; H, 8.47.

The *cis*-anilide was crystallized from aqueous ethanol as needles, m. p. 99–100°. A mixture with the anilide of *trans*-3-methyl-3-pentenoic acid (m. p. 101°) melted 97–98°, a slight depression.

Anal. Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.91. Found: C, 76.30; H, 8.00.

The *cis*-amide was crystallized from benzene–pentane as plates, m. p. 126–127°. A mixture with the amide from the rearrangement product (m. p. 131°) melted 127–130°.

Anal. Calcd. for $C_6H_{11}ON$: N, 12.38. Found: N, 12.13.

The *trans*-acid and its derivatives were obtained by dehydrating a second batch of the hydroxy ester, 256 g. (1.60 moles), with a suspension of 170 g. (1.25 moles) of phosphorus pentoxide in 750 ml. of dry benzene,[24] hydrolyzing the unsaturated esters, and partially esterifying the crude acids, 103 g. (0.90 mole), during five hours at room temperature.[3] The resulting mixture of β,γ-unsaturated esters, 49 g. (0.31 mole), b. p. 62–65° (16 mm.), was treated with a slight excess of 10% ethanolic potassium hydroxide for four days at room temperature. The acid fraction was isolated and crystallized from pentane to give the desired *trans*-acid, m. p. 35°; wt., 10 g.

Anal. Calcd. for $C_6H_{10}O_2$: neut. equiv., 114. Found: neut. equiv., 113, 114.

Ozonolysis of this material gave acetaldehyde, isolated as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 165–168°.

The *trans* *p*-toluide was crystallized from aqueous ethanol as flat needles, m. p. 91.5–92.5°; this did not depress the melting point of the *p*-toluide of the rearrangement product (VII).

Anal. Calcd. for $C_{13}H_{17}ON$: N, 6.91. Found: N, 7.17.

The *trans* anilide was crystallized from aqueous ethanol as needles, m. p. 100–101°; this did not depress the melting point of the *p*-toluide of the rearrangement product (VII).

Anal. Calcd. for $C_{12}H_{15}ON$: N, 7.41. Found: N, 7.38.

Summary

1. Treatment of α-alkyl-α,β-dibromoketones with a suspension of sodium methoxide in ether causes a rearrangement to give the methyl ester of a β-alkyl-β,γ-unsaturated acid. In addition, the original olefinic ketone may be regenerated.

2. The simplest compound in this series, namely, 3,4-dibromo-3-methyl-2-butanone (III), takes an anomalous course in giving methyl β,β-dimethylacrylate (IV) and methyl β-methoxyisovalerate (V). It has been shown that the corresponding β,γ-isomer, methyl 3-methyl-3-butenoate (XV), if formed in the rearrangement reaction, would undergo further reaction to give these products.

3. Methyl *trans*-3-methyl-3-pentenoate and the corresponding *cis*-isomer have been definitely characterized and the identity of the former with an ester from the rearrangement studies has been established.

4. Methyl β-methoxyisovalerate and its γ-methoxy homolog have been synthesized for comparison purposes.

STATE COLLEGE, PENNSYLVANIA

RECEIVED FEBRUARY 21, 1949

(20) Bachman and Struve in "Organic Reactions," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 52.

(21) Natelson and Gottfried, THIS JOURNAL, **61**, 970 (1939).

(22) Wallach, *Ann.*, **365**, 261 (1909).

(23) The crystalline material, 27 g. (0.23 mole), consisted largely of *trans*-3-methyl-2-pentenoic acid.

(24) Treatment of the pure hydroxy ester with gaseous hydrochloric acid gave incomplete dehydration; *cf.* ref. 21.

[CONTRIBUTION FROM THE LABORATORIES OF GEORGE A. BREON & CO., STERLING DRUG CO., INC.]

Analgesics. III. Hydrochlorides of Phenylalkylamines[1]

BY L. H. GOODSON[2] AND R. B. MOFFETT[3]

As reported in the two earlier papers in this series,[4,5] our laboratory is interested in the synthesis of analgesic agents selected from the group of compounds known as the phenylalkylamines. The present paper is a continuation of our earlier work and describes thirty-one additional amines which are listed in Table I.

The synthetic methods used in the preparation of these compounds are not new, but are described briefly in the experimental part. The yields given usually do not indicate the best possible, but, rather, those actually obtained in one preparation.

These compounds have been screened for their analgesic activity by Dr. Harold G. Holck of the University of Nebraska, School of Pharmacy, and publication of results will appear elsewhere. Little or no analgesic activity was exhibited by any of these compounds when compared with morphine or isonipecaine.

Experimental

Amino Ketones and Esters, 1–13 (Table I).—The starting materials, desoxybenzoin, desoxyanisoin, α-cyclohexylacetophenone,[6] α-cyclohexyl-*p*-methoxyacetophenone,[7] 2-naphthyl benzyl ketone[8] and ethyl phenylacetate, were readily available or were prepared by the usual methods. These compounds were brominated by adding the calculated quantity of bromine to a solution of the compound in carbon tetrachloride. The resulting α-bromo compounds were freed of solvent and then used with or without distillation. Each of the crude bromo compounds in absolute ether or benzene was allowed to react with an excess of the appropriate amine, either by allowing the mixture to stand at room temperature for one week or by refluxing for two hours. The product was separated from the excess of reactants by treating the reaction mixture with aqueous sodium hydroxide, washing the organic layer with water, and evaporating to dryness, finally at 80° *in vacuo*. The base was taken up in absolute ether and the hydrochloride was precipitated by passing in hydrogen chloride.

Amino Alcohols, 14–17 (Table I).—These compounds were prepared from the corresponding amino ketones by reduction of the free bases with aluminum isopropoxide in absolute isopropyl alcohol. The slow distillation of the isopropyl alcohol was continued until no trace of acetone was observed in the distillate (eight to fourteen hours). The isopropyl alcohol was then removed under reduced pressure and the residue was shaken with ether and water. The ether layer was dried over potassium carbonate, and dry hydrogen chloride was passed in.

Amino Alcohols, 18–19 (Table I).—These compounds were prepared by the method of Erlenmeyer,[9] in which benzaldehyde is condensed with glycine in the presence of alcoholic alkali to give iso-1,2-diphenylethanolamine. In the present reactions, 2,3-dimethoxybenzaldehyde and 3,4-dimethoxybenzaldehyde were used in place of benzaldehyde. By analogy with the literature we have designated these DL-pairs as *iso* compounds, although we have no evidence concerning the spatial relationships; the so-called normal forms are not yet described.

Amino Alcohol, 20, and Amine, 27 (Table I).—The benzene solution of anisoin or desoxyanisoin was mixed with the amine (ethanolamine or benzylamine), a drop of acetic acid added and the mixture refluxed using a continuous water separator until no more water was liberated. The benzene was removed and the resulting crude ketimine was reduced by dissolving it in absolute ethanol and adding five times the theoretical quantity of sodium required to reduce the double bond. The alcohol was removed and the basic organic material was separated, dried, dissolved in absolute ether, and treated with hydrogen chloride.

Amines, 21–23 (Table I).—These compounds were prepared from 2-acetonaphthone and dibenzyl ketone by use of the Leuckart reaction.[4] The amines used were β-(4-morpholino)-ethylamine and ethanolamine and during the reaction time of three hours the temperature was raised from 170 to 200°. The formyl derivative was hydrolyzed and the products isolated as described earlier.

Amines, 24–26 (Table I).—These compounds were prepared from the corresponding 1,2-di-(*p*-methoxyphenyl)-ethylamines by dissolving them in 48% hydrobromic acid, and boiling them for one-quarter to two hours, then separating the demethylated fraction first by its solubility in alkali and then by recrystallization of the demethylated material after its conversion to its hydrochloride or hydrobromide.

Amine, 28 (Table I). α-Phenyl-2-hydroxy-5-cyclohexylacetophenone and Oxime.—A mixture of 88.1 g. (0.5 mole) of *p*-cyclohexylphenol and 77.3 g. (0.5 mole) of phenylacetyl chloride was warmed on a boiling water-bath until no more hydrogen chloride was evolved (about one and one-half hours). This crude ester was mixed with 84 g. (0.63 mole) of anhydrous aluminum chloride and heated in an oil-bath. At a temperature of 120°, hydrogen chloride was rapidly evolved and at 140° the mixture became very thick. After fifteen minutes at this temperature, it was cooled and decomposed with ice and hydrochloric acid. The product was taken up in ether, washed with water, and after removing the ether, it was distilled first from a Claisen flask and then through a six-inch glass helices-packed column. The fraction, boiling at 120–130° (0.007 mm.), was a light yellow viscous liquid which crystallized on standing. Recrystallization from petroleum ether gave 53.8 g. (37%) of material, m. p. 55–58°.

The oxime was prepared by refluxing for one and one-half hours a solution of 20 g. of the ketone and 20 g. of hydroxylammonium chloride in 50 ml. of ethanol and 50 ml. of pyridine. On evaporation and dilution with water, the oxime crystallized, and a sample was recrystallized from ethanol, m. p. 138.5–140°.

Anal. Calcd. for $C_{20}H_{23}NO_2$: N, 4.53. Found: N, 4.64.

1-(2-Hydroxy-5-cyclohexylphenyl)-2-phenylethylamine (28).—To a solution of 22.4 g. of the crude oxime in 1 l. of absolute ethanol was added 69 g. of sodium. When

(1) Presented before the Division of Organic Chemistry at the Midwest Regional Meeting, Kansas City, Missouri, June 24, 1947.

(2) Present address: Midwest Research Institute, 4049 Pennsylvania Ave., Kansas City, Missouri.

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(4) L. H. Goodson, C. J. W. Wiegand and Janet Splitter, THIS JOURNAL, **68**, 2174 (1946).

(5) R. B. Moffett and W. M. Hoehn, *ibid.*, **69**, 1792 (1947).

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(7) P. Ruggli and A. Businger, *Helv. Chim. Acta*, **24**, 1112–1126 (1941); *C. A.*, **36**, 2547 (1942).

(8) J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 365–377 (1934); P. Ruggli and M. Reinert, *Helv. Chim. Acta*, **9**, 67–79 (1926).

(9) Erlenmeyer, *Ann.*, **307**, 97 (1899); A. Lespagnol, G. Bizard and J. Turlur, *J. Bull. Sci. Pharmacol*, **43**, 555–571 (1936).

TABLE I

No.	R	R′	X	M. p. of HCl deriv., C°.[ff]	Formula	Analyses, % Calcd.	Found	Approx. yield, %
			R—C(=O)—CH(X)—R′					
1	Phenyl	Phenyl	Methylamino	216–220[g]	$C_{15}H_{16}ClNO$	Cl, 13.56	13.62	15
2	Phenyl	Phenyl	Diethylamino	184–188[h]	$C_{18}H_{22}ClNO$	Cl, 11.67	11.64	73
3	Phenyl	Phenyl	1-Piperidyl	239–242[i,j]	$C_{19}H_{22}ClNO$	Cl, 11.23	11.24	85[z]
4	Phenyl	Phenyl	4-Morpholinyl	198–200[g,dd]	$C_{18}H_{20}ClNO_2$	Cl, 11.16	11.05	20
5	*p*-Methoxyphenyl	*p*-Methoxyphenyl	1-Piperidyl	Oil	$C_{21}H_{25}NO_3$[k]	N, 4.14	4.23	59[z]
6	Phenyl	Cyclohexyl	1-Piperidyl	231–234[i,ee]	$C_{19}H_{28}ClNO$	Cl, 11.02	11.09	56
7	Phenyl	Cyclohexyl	4-Morpholinyl	240–241[l]	$C_{18}H_{26}ClNO_2$	Cl, 10.95	10.73	69
8	*p*-Methoxyphenyl	Cyclohexyl	Methylamino	217–219[g]	$C_{16}H_{24}ClNO_2$[a]	Cl, 11.91	12.14	19
9	*p*-Methoxyphenyl	Cyclohexyl	1-Piperidyl	220–222.5[m]	$C_{20}H_{30}ClNO_2$[a]	Cl, 10.07	9.94	20
10	2-Naphthyl	Phenyl	1-Piperidyl	191–193 d.[n]	$C_{23}H_{24}ClNO$[b]	Cl, 9.69	9.59	77
11	2-Naphthyl	Phenyl	4-Morpholinyl	216–219 d.[g]	$C_{22}H_{22}ClNO_2$[b]	Cl, 9.64	9.74	66.5
12	Ethoxy	Phenyl	Allylamino	120.5–122[o,z]	$C_{17}H_{18}ClNO_2$[c]	Cl, 13.92	13.86	77
13	Ethoxy	Phenyl	1-Piperidyl	174–175 d.[p]	$C_{15}H_{22}ClNO_2$	Cl, 12.37	12.46	77
			R—CH(OH)—CH(X)—R′					
14	Phenyl	Phenyl	1-Piperidyl	240–243[g,oo]	$C_{19}H_{24}ClNO$	Cl, 11.16	11.14	22
15	Phenyl	Cyclohexyl	1-Piperidyl	223–226 d.[q]	$C_{19}H_{30}ClNO$	Cl, 10.95	11.02	33
16	Phenyl	Cyclohexyl	4-Morpholinyl	223–224[g]	$C_{18}H_{28}ClNO_2$	Cl, 10.90	10.91	45
17	*p*-Methoxyphenyl	Cyclohexyl	1-Piperidyl	205–215[g]	$C_{20}H_{32}ClNO_2$[a]	Cl, 10.02	9.98	43
18	3,4-Dimethoxyphenyl	3,4-Dimethoxyphenyl	Amino[y]	140–145[q]	$C_{18}H_{24}ClNO_5$[f]	Cl, 9.59	9.86	4
19	2,3-Dimethoxyphenyl	2,3-Dimethoxyphenyl	Amino[y]	120–121[q,r]	$C_{18}H_{24}ClNO_5$[f]	Cl, 9.59	9.56	15
20	*p*-Methoxyphenyl	*p*-Methoxyphenyl	Benzylamino	195–200[g]	$C_{23}H_{26}ClNO_3$	Cl, 8.87	8.83	82
			R—CH_2—CH(X)—R′					
21	Hydrogen	2-Naphthyl	2-(4-Morpholinyl)-ethyl amino	208–210[g,t]	$C_{18}H_{24}N_2O$[d]	N, 9.85	10.02	70[z]
22	Hydrogen	2-Naphthyl	2-Hydroxyethylamino	180–182[q]	$C_{14}H_{19}ClNO$[d]	Cl, 14.10	14.00	84[z]
23	Phenyl	Benzyl	2-Hydroxyethylamino	95–97[o,s]	$C_{17}H_{22}ClNO$[d]	Cl, 12.17	11.97	36[z]
24	*p*-Hydroxyphenyl	*p*-Hydroxyphenyl	Amino	267 d.[u]	$C_{14}H_{16}ClNO_2$[e]	N, 5.27	5.24	25
25	*p*-Hydroxyphenyl	*p*-Hydroxyphenyl	Methylamino	170–172[v]	$C_{15}H_{18}BrNO_2$[s]	Br, 24.64	24.32	50
26	*p*-Hydroxyphenyl	*p*-Hydroxyphenyl	Ethylamino	192–195[aa,v]	$C_{16}H_{20}BrNO_2$[g]	N, 4.14	4.21	25
27	*p*-Methoxyphenyl	*p*-Methoxyphenyl	2-Hydroxyethylamino	126–127[i]	$C_{18}H_{24}ClNO_3$	Cl, 10.49	10.42	18
28	Phenyl	5-Cyclohexyl-2-hydroxy-phenyl	Amino	224–227[g]	$C_{20}H_{26}ClNO$	Cl, 10.68	10.82	40
			Miscellaneous amines					
29	N-Methyl-α-cyclohexylbenzylamine			251–253[i]	$C_{14}H_{22}ClN$	Cl, 14.79	14.73	25[z]
30	1-(*p*-Chlorophenyl)-1-phenyl-2-aminopropanol			238–243[e]	$C_{15}H_{17}Cl_2N$[d,bb]	Cl, 11.90	11.70	10
31	1,2-Di-*p*-methoxyphenylbutylamine			269–271[w]	$C_{18}H_{24}CNO_2$[d]	Cl, 11.02	11.05	32

[a] Prepared by R. F. Shrimpton, formerly of this Laboratory. [b] Prepared by Jack Linsk, formerly of this Laboratory. [c] Prepared by Charlotte Hart, formerly of this Laboratory. [d] Prepared by Janet S. Splitter, formerly of this Laboratory. [e] Prepared by C. J. W. Wiegand, formerly of this Laboratory. [f] Prepared by Eugene Klein, formerly of this Laboratory. [g] Crystallized from absolute ethanol. [h] Crystallized from methyl ethyl ketone. The free base distills at 158–165° at 3 mm. [i] Crystallized from ether–alcohol mixture. [j] The free base is reported to melt at 82° by Rabe, *Ber.*, **45**, 2169 (1912); "Beilstein," **20**, 14; R. E. Lutz, J. A. Freek and R. S. Murphey, THIS JOURNAL, **70**, 2016 (1948), report the hydrochloride to melt at 225 to 227° with decomposition. [k] The free base distils at 235–245° at 1 mm. Analysis on free base. [l] Crystallized from ether–alcohol mixture and washed with methyl ethyl ketone. [m] Crystallized from isopropyl alcohol and ethyl acetate. [n] Crystallized from chloroform and petroleum–hexane mixture. [o] Precipitated from ether with dry hydrogen chloride but not recrystallized. [p] Crystallized from acetone. [q] Crystallized from methanol and ether mixture. [r] After crystallization from isopropyl alcohol the free base melts at 143–145°. [s] The free base distills at 175° at 3 mm. [t] Hygroscopic. Analysis of hydrochloride was unsatisfactory. The free base distils 200–202° at 5 mm. Analysis of free base given. [u] Crystallized from water containing hydrochloric acid. [v] Crystallized from 48% hydrobromic acid and then from acetic acid. [w] Crystallized from water. [z] Free base. [y] *iso*-Form. [z] The free base distills at 92–100° at 1 mm. [aa] Then solidifies and remelts at 230–232°. [bb] Ionic chlorine only. [cc] A. Angeli and L. Alessandri, *Atti accad. Lincei*, **19**, I, 784–93; *C. A.*, **4**, 2634 (1910), report the formation of a compound HOCHPhCHPhNC$_5$H$_{10}$, m. p. 156–157°, but they do not describe a hydrochloride. R. E. Lutz, J. A. Freek and R. S. Murphey, THIS JOURNAL, **70**, 2016 (1948), report both racemates of this compound and report the m. p. of this isomer as 259–260° *in vacuo*. [dd] Emil Eidebenz, German Patent 671,786; *C. A.*, **33**, 6527 (1939). [ee] The free base distills at 130–149° at 0.1 mm. [ff] Melting points determined using a thermometer calibrated for 76-mm. immersion.

the reaction was complete, it was acidified with hydrochloric acid, distilled nearly to dryness *in vacuo*, and shaken with 500 ml. of water. The solid hydrochloride was collected on a filter, washed with ether and water, and dried; yield, 7.3 g., m. p. 224–227°. Recrystallization from ethanol did not raise the melting point.

N-Methyl-α-cyclohexylbenzylamine (29).—The method of preparation was similar to that previously described.[5] Cyclohexylmagnesium bromide was prepared from 14 g. (0.6 mole) of magnesium, 100 g. (0.62 mole) of cyclohexyl bromide and 200 ml. of absolute ether. To this was added 24 g. (0.2 mole) of benzalmethylamine, and the mixture was refluxed for one and one-quarter hours. The base was distilled twice from a Claisen flask, b. p. 89° (0.135 mm.); yield, 10.2 g. (25.2%); n^{25}D 1.5287. It was converted to the hydrochloride by saturating its alcoholic solution with hydrogen chloride and diluting with absolute ether. The crystalline solid was boiled with isopropyl alcohol,

cooled, and filtered from a small amount of insoluble material. Dilution of the filtrate with absolute ether gave the pure hydrochloride, m. p. 251–253°.

1-(4-Chlorophenyl)-2-phenyl-2-aminopropanol (30).—This was prepared by the reaction of a Grignard reagent with an oxime.[10] In this case, 27 g. of 4-chloropropiophenone oxime[11] was heated to 140–145° for one-half hour with an excess of phenylmagnesium bromide. The products were separated and purified as described by Campbell, *et al.*[10]

1,2-Di-*p*-methoxyphenylbutylamine (31).—Ninety grams of α-ethyldesoxyanisoin oxime[12] was dissolved in 3 l. of absolute methanol and treated with 300 g. of sodium. The resulting solution was boiled two hours and poured into 6 l. of 10% hydrochloric acid. The first crop of crystals was yellow, m. p. 60–80°. The second crop weighed 27 g., m. p. 252–258°. Treatment of the filtrate with alkali gave a gummy material, which, on treatment with 5% hydrochloric acid, crystallized to give 15 g., m. p. 200–225°. Crystallization of the second crop of crystals from dilute hydrochloric acid, then alcohol, and finally, distilled water, gave material, m. p. 269–271°.

(10) K. N. Campbell, B. K. Campbell and E. P. Chaput, *J. Org. Chem.*, **8**, 99 (1943).

(11) Collet, *Compt. rend.*, **126**, 1577 (1898); "Beilstein," **7**, 31.

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Summary

1. Thirty-one phenylalkylamines have been prepared and characterized for testing as analgesics.

KANSAS CITY, MISSOURI RECEIVED[13] MAY 28, 1949

(13) Original manuscript received June 17, 1948.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE MUNICIPAL UNIVERSITY OF WICHITA]

Derivatives of 2-Amino-4,8-dimethyl- and 4-Amino-3,8-dimethylquinoline[1]

BY DONALD E. EICHINGER[2] AND C. G. STUCKWISCH

In an attempt to find new types of compounds that exhibit antimalarial activity 2-substituted-4,8-dimethylquinolines and 4-substituted-3,8-dimethylquinolines were investigated.[3]

The key intermediate for the first series of compounds, 2-chloro-4,8-dimethylquinoline (I), was prepared by the reaction of phosphorus oxychloride with 2-hydroxy-4,8-dimethylquinoline. The latter was obtained in essential accordance with the procedure of Roos.[4] 4-Chloro-3,8-dimethylquinoline (II) was prepared as described by Steck, *et al.*[3]

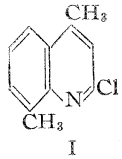
Compounds I and II were condensed with morpholine, piperidine, 1-hydroxymethylpropylamine and 4-diethylamino-1-methylbutylamine. Table I of the experimental section lists the properties of the compounds obtained.

TABLE I

DERIVATIVES OF DIMETHYLQUINOLINES

Compound	Yield, %	Solvent	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
2-Substituted-4,8-dimethylquinolines									
Piperidino	73	Ethanol	47	80.0	79.9	8.33	8.34	11.66	11.67
Morpholino	52	Ethanol	62	74.3	74.5	7.43	7.47	11.56	11.60
1-Hydroxymethyl-propylamino[a]	18	Benzene	163	73.7	73.6	8.20	8.19	11.48	11.65
4-Diethylamino-1-methylbutylamino[a]	31[b]	[b]		75.2	75.4	9.72	9.76	13.42	13.21
4-Substituted-3,8-dimethylquinolines									
Piperidino	65	Methanol	58	80.0	79.8	8.33	8.35	11.66	11.71
Morpholino	63	Methanol	72	74.3	74.2	7.43	7.44	11.56	11.63
1-Hydroxymethylpropylamino[a]	60	Bz–EtOH	129	73.7	73.6	8.20	8.26	11.48	11.56

[a] In these condensations phenol was added to the reaction mixture. The mixture was maintained at reflux temperature for twenty hours. [b] Distilled, 200° (2 mm.).



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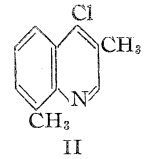


II

(1) Abstracted in part from a Master's Thesis by D. E. Eichinger.

(2) Present address: E. I. Du Pont de Nemours & Co., Philadelphia, Pennsylvania.

(3) Since the inception of this work in September, 1945, 3,8-dimethyl-4-dimethylamino-1-methylbutylaminoquinoline has been described by Steck, Hallock and Holland, THIS JOURNAL, **68**, 132 (1946).

Experimental

2-Chloro-4,8-dimethylquinoline (I).—In a 250-ml. flask, equipped with an air condenser were placed 88 g. (0.51 mole) of 2-hydroxy-4,8-dimethylquinoline and 94 g. (0.61 mole) of freshly distilled phosphorus oxychloride. The mixture was maintained at 80 to 90° for two hours and was then poured into 500 ml. of water and 500 g. of cracked ice. The white precipitate was filtered off, dried and crystallized from 95% ethanol. The yield of white 2-chloro-4,8-dimethylquinoline, melting at 63°, was 93 g. or 96%.

Anal. Calcd. for $C_{11}H_{10}NCl$: N, 7.30; Cl, 18.51; Found: N, 7.46; Cl, 18.21.

4-Chloro-3,8-dimethylquinoline (II).—The sequence of reaction for the preparation of 4-chloro-3,8-dimethyl-

(4) Roos, *Ber.*, **21**, 624 (1888).

quinoline has been described in the literature.[3] Our yields and melting points agreed essentially with those reported.

Derivatives of Dimethylquinolines.—The compounds described in Table I were prepared by refluxing the chloro compound with an excess of the appropriate amine as the solvent. The reflux time was eight to ten hours. The reaction mixture was then poured on ice. The 4-diethylamino-1-methylbutylamino derivative was extracted from the water with ether and was purified by distillation; whereas the solid piperidino, morpholino and 1-hydroxymethylpropylamino derivatives were filtered off and crystallized.

Summary

1. 2-Chloro-4,8-dimethylquinoline has been prepared.

2. Some derivatives of 2-amino-4,8-dimethylaminoquinoline and 4-amino-3,8-dimethylquinoline are described.

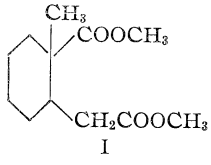
WICHITA, KANSAS RECEIVED APRIL 12, 1949

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Reduction of a Diester to a Hydroxyester by Lithium Aluminum Hydride. Application to the Construction of Rings

BY W. E. BACHMANN AND ANDRE S. DREIDING[1]

No instance of the reduction of one of two ester groups by lithium aluminum hydride has been reported. Nystrom and Brown were unable to reduce one of the two primary carboxy groups of sebacic acid and its half ester at the boiling point of ether and suggested experimentation at lower temperatures.[2] We were interested in reducing selectively the primary ester group of the dimethyl ester of *cis*-2-methyl-2-carboxycyclohexaneacetic acid (I) to the alcohol (II) from which, after a malonic ester synthesis and cyclization, *cis*-9-methyl-1-decalone (III) could be obtained.



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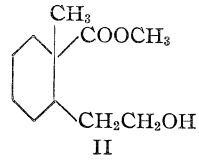

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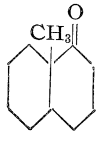
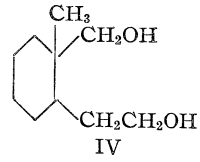


III



IV

Accordingly we examined the reduction of the diester (I) with an amount of lithium aluminum hydride sufficient to reduce only one ester group at low temperatures. Below −15° no visible change occurred. When the reaction mixture was kept near −15° the reagent was used up in reducing the primary carbomethoxy group to yield *cis*-β-2-methyl-2-carbomethoxycyclohexaneëthanol (II). The crude product was converted to the bromoester by the action of phosphorus tribromide. Condensation with sodiomalonic ester followed by hydrolysis and decarboxylation yielded *cis*-γ-2-methyl-2-carboxycyclohexanebutyric acid. Its dimethyl ester underwent the Dieckmann cyclization, hydrolysis, and decarboxylation to give *cis*-9-methyl-1-decalone (III) in a 15% over-all yield from I. These reactions represent a new synthesis of the bicyclic ketone (III) from the diester (I) and the procedure may prove to be generally applicable for the construction of rings since the starting acetic esters are frequently available through the Reformatsky reaction or malonic ester synthesis. Recently we described the preparation of the ketone (III) from the ester (I) through two successive Arndt–Eistert reactions followed by cyclization.[3]

Reduction of the diester (I) with sufficient lithium aluminum hydride to reduce both ester groups yielded *cis*-β-2-methyl-2-hydroxymethylcyclohexaneëthanol (IV). The same product (IV) was obtained when the diester (I) was treated with an excess of sodium in boiling ethanol.

Experimental

Reduction of the Diester (I) to the Hydroxyester (II).—A 0.15-g. piece of lithium aluminum hydride (Metal Hydrides Inc., Beverly, Massachusetts) was softened by allowing it to rest in 15 cc. of boiling anhydrous ether for twenty minutes, while excluding moisture and carbon dioxide. It was broken up with a stirring rod and the resulting supension was refluxed again for twenty minutes. The remaining undissolved particles were crushed and brought into solution almost completely by boiling for another twenty minutes. To the solution, cooled to −60° in a Dry Ice–acetone-bath, a solution of 1.8 g. of the dimethyl ester of *cis*-2-methyl-2-carboxycyclohexaneacetic acid (I, made from the corresponding diacid[4] by esterification with diazomethane) in 10 cc. of ether was added in small portions so that the temperature did not rise above −40°. The colorless solution, which contained only a small amount of undissolved solids, stood at −60° for five hours and was allowed to warm up slowly. At −15° a colorless gelatinous precipitate appeared. The mixture was kept at −15 to −10° for twenty minutes by reinserting the flask in the cold bath from time to time with swirling. After standing at room temperature for three hours, a small amount of 10% sodium hydroxide and then excess hydrochloric acid was added. The ethereal layer was washed with a saturated sodium chloride solution and concentrated, and the crude residue was evaporatively distilled. The colorless camphoraceous oil (0.83 g. or 53%, presumably *cis*-β-2-methyl-2-carbomethoxycyclohexaneethanol, II), which was collected at 70–80° (0.4 mm.), was

(1) Alfred H. Lloyd Postdoctoral Fellow in the Horace H. Rackham School of Graduate Studies 1947/1948.

(2) Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

(3) Bachmann and Dreiding, *J. Org. Chem.*, **13**, 317 (1948).

(4) Chuang, Tien and Huang, *Ber.*, **68**, 866 (1935); Bachmann and Kushner, THIS JOURNAL, **65**, 1963 (1943).

treated in the cold with 0.13 cc. of phosphorus tribromide in 10 cc. of benzene. After standing for four hours at 0° and fifteen hours at room temperature, the mixture was diluted with ether, washed with 10% sodium hydroxide and water, and concentrated. The residue, which had a fruity odor, was evaporatively distilled, and the bromo-ester (0.73 g. or 71%), which was collected at 75–95° (0.3 mm.), was added to a suspension of the sodium salt of diethyl malonate (made from 0.11 g. of sodium, 1.5 cc. of ethanol, and 0.88 g. of diethyl malonate) in 7 cc. of benzene. The mixture was refluxed for fifteen hours, cooled, and treated with dilute hydrochloric acid. The organic layer was separated and concentrated and the residue saponified in 20% aqueous methanolic potassium hydroxide for eight hours. The clear yellow solution was concentrated, washed with ether, and acidified in the cold. The oily malonic acid derivative, isolated by means of ether, was decarboxylated at 180–210° for eight minutes. A solution of the melt in 10% sodium hydroxide was washed with ether and acidified. The precipitated *cis*-γ-2-methyl-2-carboxycyclohexanebutyric acid was taken up in ether, washed with water, and esterified with diazomethane. The ethereal solution was extracted with 5% sodium hydroxide, the solvent evaporated and the residual diester was evaporatively distilled at 90–115° (0.2 mm.); yield, 0.47 g. (66%). The distillate was subjected to a Dieckmann cyclization, hydrolysis, and decarboxylation according to the described method.[3] Evaporative distillation of the product at 60–80° (0.4 mm.) gave *cis*-9-methyl-1-decalone (III) as a colorless camphoraceous liquid; yield, 0.2 g. (66%). The 2,4-dinitrophenylhydrazone, crystallized twice from an ethanol–ethyl acetate mixture, melted at 158–163° alone and when mixed with an authentic sample (m. p. 164–165°).[3] The oxime crystallized from methanol as colorless prisms, m. p. 110–112° alone and when mixed with an authentic sample (m. p. 114–115°).[3]

Reduction of the Diester (I) to the Glycol (IV). (a) By Lithium Aluminum Hydride.—To a solution of 88 mg. of lithium aluminum hydride in 18 cc. of anhydrous ether (prepared as described above) was added in small portions a solution of 0.45 g. of the dimethyl ester of *cis*-2-methyl-2-carboxycyclohexaneacetic acid (I, prepared by esterification of the acid[4]) at room temperature over a period of fifteen minutes; a colorless gelatinous precipitate appeared immediately. After standing at room temperature for twenty minutes, 10% aqueous sodium hydroxide was added, followed by solution of the salts in excess hydrochloric acid. Evaporation of the ethereal layer gave ***cis*-β-2-methyl-2-hydroxymethylcyclohexaneëthanol (IV)**, which crystallized from ether–petroleum ether (b. p. 30–60°) in colorless needles; yield, 0.27 g. (80%), m. p. 112–116°; after another recrystallization, 116–117°.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.71. Found: C, 69.55; H, 11.80.

(b) By Sodium and Alcohol.—To a boiling solution of the diester (I) in 50 cc. of dry ethanol was added 5 g. of sodium in small slices over a period of fifteen minutes. The mixture was kept refluxing for three hours, when all the sodium had reacted. The cooled mixture was treated with ice and water and the product was extracted with ether. The ethereal solution was washed with a saturated sodium chloride solution, dried over magnesium sulfate, and concentrated. Evaporative distillation of the residue at 120–140° (0.4 mm.) gave 3.5 g. (95%) of a colorless glass which crystallized when covered with a small amount of ether, m. p. 114–116°. On recrystallization from 1:1 ether–petroleum ether (b. p. 30–60°) the glycol (IV) melted at 116–117°.

Summary

The selective reduction of the primary carbomethoxy group in the dimethyl ester of *cis*-2-methyl-2-carboxycyclohexaneacetic acid (I) by lithium aluminum hydride and its application to a synthesis of *cis*-9-methyl-1-decalone (III) is described.

ANN ARBOR, MICHIGAN RECEIVED APRIL 29, 1949

[A CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Alkylamine Esters of 7-Aminofluorenone-2-carboxylic Acid

BY H. F. OEHLSCHLAEGER[1] AND IAN R. MACGREGOR

Alkylamine esters of fluorene and fluorenone carboxylic acids have been reported to possess local anesthetic action. For example, the alkylamine esters of fluorene-9-carboxylic acid have been investigated and patented as local anesthetics.[2,3]

Ray and Rieveschl[4,5] prepared the β-diethylaminoethyl ester of fluorene-2-carboxylic acid as well as a series of alkylamine esters of fluorenone-1, -2 and -4 carboxylic acids. Of the series, the esters of fluorenone-2-carboxylic acid proved to be the most active as local anesthetics and as antispasmodics. The water solubility of these esters, however, is low. Subsequent attempts by Ray and MacGregor[6] to produce more soluble anesthetics based on the fluorene nucleus and using a ketone linkage rather than the ester linkage did not appreciably alter the water solubilities.

In this investigation we hoped to increase the effectiveness of the alkylamine esters of fluorenone-2-carboxylic acid by the introduction of an amino group in the 7-position of the fluorenone molecule. Generally the presence of a free amino group in a position para to the ester linkage in compounds of the procaine type has an advantageous effect. There is a noticeable increase in activity with no apparent increase in toxicity in compounds containing the para-amino group over compounds devoid of this group.[7] A series of alkylamine esters of 7-nitrofluorenone-2-carboxylic acid, and 7-aminofluorenone-2-carboxylic acid were prepared.

A modification of a Friedel–Crafts reaction used by Broisman and MacGregor[8] gave 60–65%

(1) Abstracted from a thesis presented to the Graduate School, University of Cincinnati, by H. F. Oehlschlaeger in partial fulfillment of the requirements for the degree of Master of Science, 1948.

(2) Burtner, U. S. Patent 2,262,754 (1941).

(3) Lehmann and Knoefel, *J. Pharmacol.*, **74**, 217, 274 (1942); **76**, 194 (1942).

(4) F. E. Ray and G. Rieveschl, THIS JOURNAL, **65**, 836 (1943).

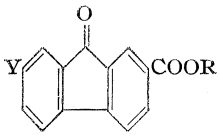
(5) F. E. Ray and G. Rieveschl, U. S. Patent, 2,377,040.

(6) F. E. Ray and I. R. MacGregor, THIS JOURNAL, **69**, 587 (1947).

(7) Gilman and Pickens, *ibid.*, **47**, 245 (1925).

(8) R. Broisman, Master of Science thesis, University of Cincinnati, 1947.

TABLE I



No.	Y	R	M. p., °C.[a]	Formula	Analyses, % Calcd.	Found
1	NO_2	β-Diethylaminoethyl[b,c]	134–136	$C_{20}H_{20}O_5N_2$	N, 7.61	7.67
2	NO_2	β-Diethylaminopropyl hydrochloride[d]	242–244	$C_{21}H_{23}O_5N_2Cl$	N, 6.68	6.91
					Cl, 8.48	8.41
3	NO_2	β-Di-*n*-butylaminoethyl[e,f]	206–207	$C_{24}H_{28}O_5N_2$	N, 6.60	6.31
4	NO_2	γ-Morpholino-β-dimethylaminopropyl[g,h]	166–167	$C_{23}H_{24}O_6N_2$	N, 6.61	6.63
5	NH_2	β-Diethylaminopropyl[i]	215–216	$C_{20}H_{22}O_3N_2$	N, 8.28	8.02
6	NH_2	β-Diethylaminopropyl[j]	91–93	$C_{21}H_{24}O_3N_2$	N, 7.96	8.24
7	NH_2	β-Di-*n*-butylaminoethyl	84–85	$C_{24}H_{30}O_3N_2$	N, 7.11	7.37
8	NH_2	γ-Morpholino-β-dimethylaminopropyl	176–177	$C_{23}H_{26}O_4N_2$	N, 7.11	7.14

[a] All melting points are uncorrected. [b] Hydrochloride m. p. 230–232°. [c] Nitrate m. p. 214–215°; anal. calcd. for N, 9.75; found N, 10.03. [d] Nitrate m. p. 175–176°. [e] Hydrochloride m. p. 209°. [f] Nitrate m. p. 156–157°. [g] Hydrochloride m. p. 232–233°. [h] Nitrate m. p. 165°. [i] Oxime m. p. 242–243°. [j] Oxime m. p. 139–140°.

yields of 7-nitro-2-acetylfluorene from 2-nitrofluorene, acetyl chloride, and aluminum chloride in nitrobenzene solvent. The purified 7-nitro-2-acetylfluorene was readily oxidized in glacial acetic acid by sodium dichromate to 7-nitrofluorenone-2-carboxylic acid, m. p. 324° (uncor.). Some controversy existed over the melting point of the acid since Stockton[9] had reported it as melting at 220°, while Broisman[8] had reported the melting point as 233°. Proof of structure of the 7-nitrofluorenone-2-carboxylic acid was established by reduction of the nitro group to the amine and deamination by diazotization and treatment with hypophosphorous acid to yield the known fluorenone-2-carboxylic acid. The nitrocarboxylic acid formed a reddish-orange phenylhydrazone when refluxed with phenylhydrazine in alcohol solution.

An intermediate compound in the oxidation of 7-nitro-2-acetylfluorene was 7-nitro-2-acetylfluorenone which was easily isolated from the 7-nitrofluorenone-2-carboxylic acid by virtue of the insolubility of the former in aqueous potassium hydroxide.

The carboxylic acid was converted to the corresponding 7-nitrofluorenone-2-carbonyl chloride, by reaction with thionyl chloride. Esterification of 7-nitrofluorenone-2-carbonyl chloride with several amino alcohols was carried out in very good yields using inert solvents such as chlorobenzene or toluene. The resulting 7-nitrofluorenone-2-carboxylates were reduced satsifactorily to the corresponding alkylamine esters of 7-aminofluorenone-2-carboxylic acid by means of ammonium hydroxide and hydrogen sulfide. The reaction was accompanied by some tar formation which accounted for the erratic yields. The esters of the nitro- and aminofluorenonecarboxylic acids that were prepared are listed in Table I.

(9) M. R. Stockton, Doctor of Philosophy thesis, University of Cincinnati, 1943.

Experimental

7-Nitro-2-acetylfluorene.—To a well-stirred suspension of 97 g. (0.46 mole) of crude 2-nitrofluorene[10] were added 500 cc. redistilled nitrobenzene and 113 g. (0.85 mole) of anhydrous aluminum chloride. A deep red color developed as the suspension was warmed to 40°. During a period of one-half hour, 40 cc. (0.56 mole) of acetyl chloride was added dropwise, the temperature being maintained between 40 and 50°. The mixture was stirred and warmed to 50–55° for an additional four hours. The dark green mixture was hydrolyzed by pouring it portionwise into a strongly stirred mixture of 20 cc. of hydrochloric acid, 200 g. of ice and 800 cc. of water. The water layer was poured off and the oily precipitate was extracted twice with 750 cc. of ether to remove the excess nitrobenzene. The residue was collected on a Büchner funnel, pressed dry, and recrystallized from glacial acetic acid. The straw colored needles melted at 228°; the yield was 62.8%.

Anal. Calcd. for $C_{15}H_{11}O_3N$: N, 5.53. Found: N, 5.50.

7-Nitrofluorenone-2-carboxylic Acid.—To a solution of 30 g. (0.12 mole) of 7-nitro-2-acetylfluorene in 2000 cc. of glacial acetic acid was added, in small quantities, 150 g. (0.50 mole) of powdered sodium dichromate. After refluxing the mixture for two hours, 100 cc. of acetic anhydride was added slowly after which refluxing was continued for four hours longer. The reaction mixture was poured into 2.5 gallons of hot water, into which was passed live steam to coagulate the oxidation products. The suspension was filtered, washed with very dilute acid and pressed dry. The entire solution was warmed with 1000 cc. of 0.5% potassium hydroxide and filtered while hot. The filtrate was acidified with an excess of 1:1 hydrochloric acid, and the heavy yellow flocculent precipitate of the carboxylic acid was isolated by filtration, washed with water and recrystallized from glacial acetic acid. The alkali insoluble material was reoxidized with 75 g. of sodium dichromate in 1200 cc. of glacial acetic acid, yielding an additional amount of the acid after treatment in the same manner as the first oxidation reaction solution. The total crude product obtained from the oxidation was 20 g. (62.5% theoretical). Two recrystallizations from glacial acetic acid yielded a yellow crystalline product which melted at 322–324°.

Anal. Calcd. for $C_{14}H_7O_5N$: N, 5.20. Found: N, 5.14.

A solution of 1.0 g. of 7-nitrofluorenone-2-carboxylic

(10) Kuhn, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. XIII, 1943, p. 74.

acid in 100 cc. of ethyl alcohol was refluxed for fifteen minutes with 2.0 cc. (2.19 g., 0.02 mole) of phenylhydrazine. The mixture was cooled in an ice-bath and water was added dropwise to the solution until 100 cc. had deen added. The resulting precipitate was isolated by filtration and recrystallized from ethyl alcohol. The recrystallized phenylhydrazone melted at 264–265°.

7-Aminofluorenone-2-carboxylic Acid.—To a suspension of 10 g. (0.04 mole) of 7-nitrofluorenone-2-carboxylic acid in 600 cc. of ethyl alcohol was added 80 cc. of concentrated ammonium hydroxide. The suspension was heated to its boiling point and hydrogen sulfide gas was passed into it for one hour during which time the solid material dissolved and the solution took on a dark red color. The solution was boiled an additional half hour to remove excess hydrogen sulfide and ammonia. After cooling the solution it was filtered and the filtrate poured into 800 cc. of water. Acidification of the aqueous solution with 1:5 hydrochloric acid gave a dark red solid. The crude product was dissolved in 400 cc. of hot 2% potassium hydroxide and 0.5 g. of Darco. After filtration the hot filtrate was acidified by dropwise addition of 20 cc. of hydrochloric acid (1:5), the product separating as a precipitate. The resulting dark red powder did not melt below 360°. The yield was 7.5 g. (85%).

Anal. Calcd. for $C_{14}H_9O_3N$: C, 70.29; H, 3.77; N, 5.85. Found: C, 69.89; H, 4.00; N, 5.73.

7-Nitro-2-acetylfluorenone.—The alkali insoluble material from the oxidation described above was recrystallized twice from glacial acetic acid and once from xylene. The product formed as fine lemon-yellow needles, melting sharply at 234°.

Anal. Calcd. for $C_{15}H_9O_4N$: N, 5.24. Found: N, 5.08.

7-Nitrofluorenone-2-carbonyl Chloride.—Fifteen grams (0.056 mole) of crude 7-nitrofluorenone-2-carboxylic acid was refluxed with 400 g. of redistilled thionyl chloride for twelve hours, provision being made to trap the escaping sulfur dioxide and hydrochloric acid. The excess thionyl chloride was removed by distillation and the residue recrystallized from toluene or chlorobenzene. The yield of acid chloride was 15.0 g. (99 + % theoretical). The bright yellow crystalline compound melted at 246–248°.

Anal. Calcd. for $C_{14}H_6O_3NCl$: N, 4.87; Cl, 12.34. Found: N, 5.16; Cl, 12.42.

β-Diethylaminoethyl-7-nitrofluorenone-2-carboxylate Hydrochloride.—This preparation is typical of the method used for the preparation of the esters used in this work. To a solution of 6.5 g. (0.023 mole) of 7-nitrofluorenone-2-carbonyl chloride in 350 cc. of dry chlorobenzene in reflux was added dropwise over a period of one half hour a solution of 3.2 cc. (2.8 g., 0.025 mole) of β-diethylaminoethanol in 25 cc. of chlorobenzene. The hydrochloride of the alkylamine ester separated as a yellow crystalline solid which was collected and washed twice with 30-cc. portions of ether. The yield of the crude product was 8.5 g. (92.4 %). A portion, recrystallized from methyl alcohol, melted with decomposition at 230–232°.

The free base, prepared by dropwise addition of sufficient ammonium hydroxide to neutralize the hydrochloride, separated as bright yellow crystals which, recrystallized from a methyl alcohol–water mixture, melted at 134–136°.

Anal. Calcd. for $C_{20}H_{20}O_5N_2$: N, 7.61. Found: N, 7.67.

The nitric acid salt was prepared as a finely crystalline, water insoluble, yellow material by adding 5 cc. of dilute nitric acid (6 *N*) to a solution of 0.1 g. of the ester hydrochloride in 250 cc. of hot water. The product melted sharply at 214–215°.

Anal. Calcd. for $C_{20}H_{21}O_8N_3$: N, 9.75. Found: N, 10.03.

β-Diethylaminoethyl-7-aminofluorenone-2-carboxylate.—Six grams (0.015 mole) of β-diethylaminoethyl-7-nitrofluorenone-2-carboxylate was dissolved in 400 cc. of hot ethyl alcohol and 8 cc. of ammonium hydroxide. Hydrogen sulfide was bubbled into the hot solution over a period of one half hour, the solution changing to a dark red color. A solution of 50 cc. of 12 *N* hydrochloric acid in 400 cc. of water was added to the warm reaction mixture. The hot acid solution was filtered twice to remove free sulfur and then made alkaline with 6 *N* ammonium hydroxide and allowed to stand overnight. The bright red, finely divided precipitate which separated was recrystallized from an alcohol–water solution yielded 2.5 g. (50% theoretical) of the amine as red needles which melted at 215–216°.

Anal. Calcd. for $C_{20}H_{22}O_3N_2$: N, 8.28. Found: N, 8.02.

Summary

1. A series of alkylamino esters of 7-nitrofluorenone-2-carboxylic acid and 7-aminofluorenone-2-carboxylic acid have been prepared for evaluation as topical anesthetics or for possible antispasmodic action.

2. The preparation of pure 7-nitrofluorenone-2-carboxylic acid and the proof of its structure has resolved the question of its correct melting point.

CINCINNATI 21, OHIO RECEIVED MARCH 17, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Lower Iodides of Boron

BY WALTER C. SCHUMB, E. LEE GAMBLE AND MARIO D. BANUS

Although numerous points of resemblance may be observed in the chemistry of boron and silicon compounds, up to the present time a striking exception in the behavior of boron has been the lack of halides other than the well-known series of trihalides, BX_3. Except for the compound B_2Cl_4, first reported by Stock,[1] who succeeded in isolating a drop of the unstable liquid, no binary halides with B–B bonds appear to have been prepared. From the known instability of Stock's B_2Cl_4, it seemed reasonable to believe that synthetic methods operating at elevated temperatures would probably fail to yield such compounds as B_2Br_4 or B_2I_4 unless some means of "freezing-out" the desired products could be resorted to, whereby their decomposition might be held in check.

Preliminary experiments in which it was planned to prepare a lower iodide of boron, such as B_2I_4, by reduction of boron triiodide under conditions favoring the prevention of decomposition of the desired product, included the use of the "hot–cold" tube devised by St. Claire Deville[2]

(1) Stock, Brandt and Fischer, *Ber.*, **58B**, 653 (1925).

(2) St. Claire Deville, "Leçons sur la Dissociation, Leçons de Chemie," Soc. Chim. de Paris, 1864–1865.

and successfully employed by various other experimenters.[3,4] When a mixture of the vapors of boron triiodide and hydrogen was passed through such an apparatus, indications of the formation of a sub-iodide on the cold element of the tube were obtained, but in exceedingly small yields, together with a copious deposit of elementary boron on the hot glass surfaces.

Again the reduction of boron triiodide by means of metallic silver in a reaction analogous to that for the preparation of Si_2I_6[5,6] led to the result that, contrary to the earlier reports of Moissan,[7] reaction is appreciable at as low a temperature as 185°, iodine being liberated which is converted by the silver present into silver iodide, and a black, non-volatile solid being formed which was not separated in a pure form but which, from its similarity in properties to preparations by other methods, described below, we believe contained the monoiodide, $(BI)_n$.

Furthermore, it had been noted in the preparation of boron triiodide that the pure white color of the freshly prepared compound changed to a dark color when the substance was melted and that when heated above the melting point in a sealed evacuated tube boron triiodide decomposed, liberating iodine and forming a dark-colored solid, the color deepening as the temperature was increased. That an equilibrium process was not involved was shown by the fact that the depth of color did not lessen when the temperature was lowered to just above the melting point and held for a long time. The dark solid formed from 4 g. of triiodide heated at 250° for twenty-four hours in the sealed tube, when separated from unchanged triiodide by volatilization of the latter, gave reactions consistent with a lower iodide of boron and closely resembled the product described below which was obtained by the action of the electrodeless discharge on the vapors of boron triiodide.

In view of the results obtained from the exploratory experiments it was concluded that in order to prepare tetraiododiborine, a method of reduction would be required that did not raise the temperature of the products above room temperature. In the method used, a radio-frequency electrodeless discharge supplied the "cold" energy for the reduction.

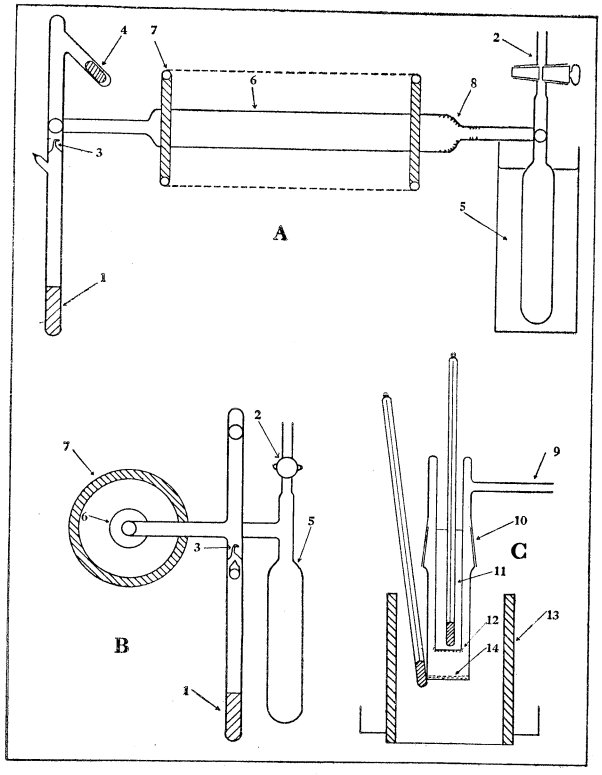


Fig. 1.—A and B: 1, Boron triiodide in sealed ampule; 2, outlet to pumping system; 3, break-off tip; 4, glass-covered steel magnetic breaker; 5, trap, cooled by liquid nitrogen; 6, 20 × 250 mm. glass tube; 7, 3″ copper solenoid, R. F. antenna; 8, crystals of yellow tetraiododiborine formed during reduction; C: 9, 9-mm. tubing to Hyvac-backed, mercury diffusion pump; 10, 29/42 ground joint; 11, ethanol cooled by Dry Ice to −20 to −30°; 12, pure tetraiododiborine as pale yellow sublimate; 13, Variac-controlled heating element; 14, crude tetraiododiborine from glow reduction.

Experimental

The electrodeless radio-frequency discharge apparatus used was that described by Schumb and Bickford[8] for use in the study of the dissociation of carbon dioxide at low temperatures. A 2000 v. d. c. power supply drove a 250-watt 204-A transmitting tube at frequencies from 4600 to 5200 k. c. with a tank current output of from 7–8 amp. R. F. The glass system (Fig. 1, A and B) made it possible to fill the boron triiodide ampule in the dry box with 4–8 g. of freshly sublimed boron triiodide followed by evacuation to <0.5 mm. and sealing, then to assemble the glass apparatus through the central 3″ solenoid. When the glass system was flame-dried and evacuated carefully by a Hyvac pump, the stopcock was closed, sealing the system. The break-off tip to the boron triiodide ampule was broken by the magnetic breaker allowing the iodide to sublime through the glow tube to the liquid nitrogen cooled trap. By keeping the boron triiodide supply at between 35 to 40°, a pressure of 1 to 3 mm. could be maintained in the glow tube, this vapor pressure giving an intense greenish-yellow glow when the R. F. transmitter was turned on. Under certain conditions, the glow would extend some distance beyond the ends of the glow tube in both directions. Free iodine along with the un-

(3) See R. C. Young, *J. Chem. Education*, **20**, 8, 378 (1943).
(4) Schumb and Morehouse, THIS JOURNAL, **69**, 2696 (1947).
(5) Friedel and Ladenburg, *Bull. soc. chim.*, **12**, 92 (1869).
(6) Schwarz and Pflugmacher, *Ber.*, **75B**, 1062 (1942).
(7) Moissan, *Compt. rend.*, **112**, 717 (1891), observed no reaction up to 500°.
(8) Schumb and Bickford, THIS JOURNAL, **58**, 1038 (1936).

reacted boron triiodide condensed in the liquid nitrogen, and the boron triiodide could be recovered later for reuse.

It required from four to six hours to sublime the boron triiodide through the discharge apparatus. Shortly after the glow started, fine yellow crystals could be seen at the exit constriction of the glow tube, gradually building up to a mass of yellow, crystalline material. Near its inlet, the glow tube gradually became coated with a black deposit which spread finally along the full length of the glow tube and back toward the boron triiodide supply, becoming so dense that it obscured the glow in the tube. When all the boron triiodide had passed through, the glow tube was sealed beyond the bends at both ends and placed in the dry box where it was opened carefully and the yellow crystals and black wall deposit scraped into weighed vials. The former, when sublimed at <0.1 micron and 60 to 70° in the molecular still (C, Fig. 1) gave a pale yellow sublimate and a trace of black residue. This yellow material had to be analyzed promptly since it decomposed even at room temperature. It could be kept undecomposed for a longer period in sealed evacuated ampules if refrigerated and kept out of the light. Analysis showed this compound to be B_2I_4. From the weight of solid products obtained in the reduction, it was calculated that 40% of the boron triiodide was reduced and recovered as lower iodides. One third of the reduced portion went to B_2I_4 according to the equation: $2BI_3 \rightarrow B_2I_4 + I_2$. The rest of the reduced boron triiodide was converted to the black deposit, a boron iodide or mixture of variable composition, B_xI_y, where $x > y$, according to the equation: $xBI_3 \rightarrow B_xI_y + (3x - y)/2I_2$.

Properties of the Lower Iodides.—Tetraiododiborine (B_2I_4) is a pale yellow, crystalline substance which at room temperature showed slow decomposition which increased rapidly with rising temperature and with exposure to sunlight. This decomposition occurred according to the equation: $xB_2I_4 \rightarrow yBI_3 + (BI)_{2x-y} + (x - y)I_2$. However, at room temperature only a trace of iodine was formed so that the decomposition became essentially a disproportionation. Larger quantities of iodine were formed at higher temperatures or under the action of sunlight. The decomposition of tetraiododiborine therefore proved to be an excellent method for preparing the monoiodide of boron, $(BI)_x$, a black, non-volatile, polymerized material. Tetraiododiborine dissolved in water with rapid, vigorous hydrolysis, forming an acid solution with strong reducing properties from which silver nitrate precipitated silver iodide, followed, on adding more of the reagent, by silver metal. On hydrolysis in 10% sodium hydroxide nearly the theoretical quantity of hydrogen was evolved according to the equation: $B_2I_4 + 8OH^- \rightarrow 2HBO_3^= + H_2 + 2H_2O + 4I^-$. Tetraiododiborine showed no melting point when heated in a sealed evacuated melting point tube, but started to decompose at about 80°, being completely decomposed by 250° with I_2 and BI_3 subliming to the top of the tube, leaving behind a black residue. It was not possible to detect any solubility of the iodide in carbon disulfide, carbon tetrachloride or cyclohexane, since these solvents slowly decompose the iodide with the liberation of iodine.

The black, polymerized monoiodide of boron was far more stable than the tetraiododiborine. It could be kept apparently indefinitely at room temperature if it were in a sealed, dry vial or ampule. Like tetraiododiborine, the $(BI)_x$ was apparently insoluble in carbon disulfide and carbon tetrachloride, with the solvents decomposing the iodide and giving a concentrated solution of iodine. The monoiodide was hydrolyzed by water to give a similar clear acid solution with strong reducing properties, but in this case the silver metal precipitated at the same time as did the silver iodide, giving a red-brown curd unlike the two-layer precipitate from the hydrolysis solution of the B_2I_4. In addition it was a much harder task to oxidize all the boron back to the trivalent state in the case of the monoiodide. On heating $(BI)_x$ in a sealed, evacuated, melting point tube it gave no melting point but did decompose above 125°, giving off iodine and leaving a black residue. On rapid heating in a micro flame a second sample appeared to be decomposed into boron and iodine. $(BI)_x$ had a vapor pressure of <0.1 micron at 110°.

The boron iodide of variable composition, B_xI_y, was very similar to $(BI)_x$ and was originally thought to be the latter compound. However, with larger samples and further study, indications of difference were found, especially with regard to their hydrolysis. B_xI_y when hydrolyzed gave the expected acid solution with strong reducing properties, but in addition it always gave varying amounts of a pale yellow, highly unreactive hydrolysis product which contained boron, iodine, oxygen and probably hydrogen. When the total analysis of boron and iodine from the solution and residue was made, the atomic ratio of boron to iodine varied between 1 and 3. The material may have been a mixture of $(BI)_x$ and another iodide but since the latter was apparently just as non-volatile and insoluble as the monoiodide no separation could be made. B_xI_y was found to be very stable to heat, giving only a trace of decomposition up to 260°; but with rapid higher heating in a free flame it decomposed to the elements. It was much more stable than the other iodides described toward the solvents carbon tetrachloride, cyclohexane and benzene, being only slowly decomposed over a period of several days. It did not show any tendency to dissolve, however.

Analysis of the Lower Iodides.—The iodides were analyzed by hydrolyzing weighed samples in 50-ml., glass-stoppered Erlenmeyer flasks, diluting to volume in volumetric flasks and taking two aliquots each for the boron

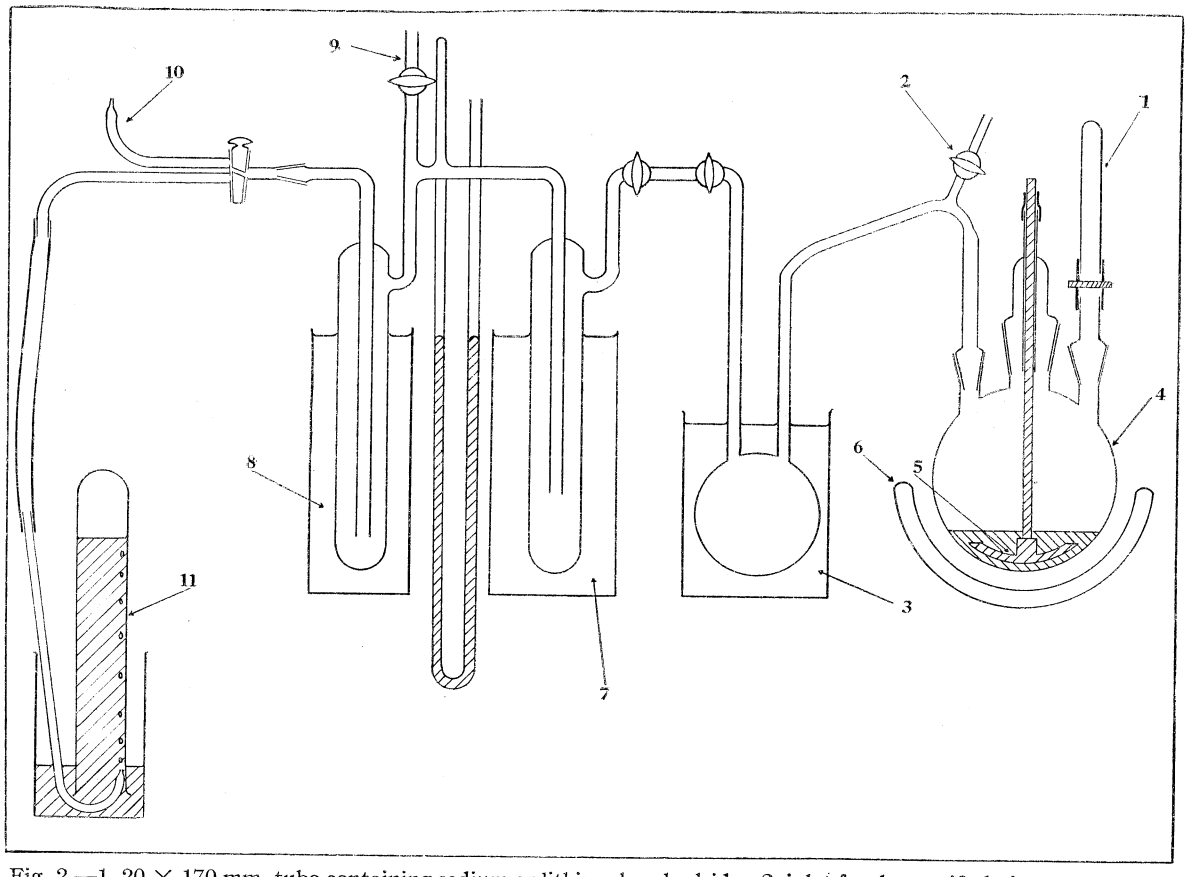


Fig. 2.—1, 20 × 170 mm. tube containing sodium or lithium borohydride; 2, inlet for dry purified nitrogen; 3, trap 1, 500-ml. flask cooled by ice; 4, 500-ml. 3-necked reaction flask containing the molten I_2; 5, nickel-shafted, Monel stirrer; 6, Variac-controlled Glas-col heating mantle; 7, trap 2, cooled by Dry Ice and ethanol; 8, trap 3, cooled by liquid nitrogen; 9, outlet to pumping system; 10, sweeping vent; 11, hydrogen measuring cylinder, 48 × 385 mm.

and iodine analyses. The aliquots were treated with 50% hydrogen peroxide and then made just basic to oxidize the boron. When the oxidation was complete, the excess hydrogen peroxide was destroyed by the use of platinum foil. For boron analysis the sample was made just acid to methyl red with sulfuric acid, then titrated to the methyl red end-point with standard base in a Koch microburet. Mannitol and phenolphthalein were added and the titration continued to the phenolphthalein end-point, giving the volume necessary for the boric acid. For iodine the sample was made acid with sulfuric acid excess, 0.2 *N* silver nitrate added, digested for one-hour hour and then filtered into weighed, fritted glass crucibles.

Analysis of B_2I_4			Calcd.
Sample taken, g.	0.2808	0.2493	
Boron found, %	4.2	4.03	4.09
Iodine found, %	94.5	94.5	95.9
Atomic ratio of B:I	1:2.009	1:2.008	

Analysis of $(BI)_n$			Calcd.
Sample taken, g.	0.1052	0.1075	
Boron found, %	7.7	7.8	7.9
Iodine found, %	90.9	92.7	92.1
Atomic ratio of B:I	1:1.008	1:1.013	

Preparation of Boron Triiodide.—The method developed for the preparation of boron triiodide used in the preparation of the lower iodides consisted of the reaction of sodium or lithium borohydride[9] with iodine, the reaction being carried out in a three-necked, round-bottom flask provided with an efficient mechanical stirrer and heated by means of an electric mantle. The temperature used in the case of sodium borohydride was about 200°; with lithium borohydride, 120–125°. Yields of 45–50% with the former compound and 64–66% on the basis of the boron involved with the latter were obtained. In a typical run from 5.1 g. of lithium borohydride (not recrystallized), 61 g. of BI_3 was obtained. The sodium borohydride was recrystallized before use from dried isopropylamine: the solution was centrifuged and decanted, the sodium borohydride freed from the amine by evaporation, followed by drying at 125° for thirty-six hours before it was finely powdered in an agate mortar. The reactions occurring between the borohydrides and iodine are somewhat complicated, but the principal over-all reaction deduced from the quantities of the respective products obtained may be represented as follows: $3NaBH_4 + 8I_2 \rightarrow 3NaI + 3BI_3 + 4H_2 + 4HI$; this main reaction being followed by side reactions involving reduction of boron to lower valences and to the element.

The preparation of boron triiodide was carried out in the apparatus shown in Fig. 2. Intermittent stirring was essential to high yields in the case of the preparation from sodium borohydride. On the other hand, temperature control to within the range mentioned was required for maximum yields with lithium borohydride so that a ther-

(9) We are indebted to the Ethyl Gas Corporation, Detroit, Mich., to Metal Hydrides, Inc., of Beverly, Mass., for the sodium borohydride, and to Linde Air Products Co., Tonawanda, N. Y., for the lithium borohydride used in this work.

mocouple well and thermocouple replaced the stirrer in this case. At the end of the run, all the boron triiodide and the excess iodine were sublimed into trap no. 1, now cooled by Dry Ice and then this trap was sealed at the inlet and cut out of the system between the pair of stopcocks at the outlet of trap no. 1.

Purification of boron triiodide as obtained from the borohydrides was effected first by dissolving it and some of the excess iodine in purest carbon disulfide, reduction of the iodine by mercury and zinc dust, filtering to get a clear solution, then vacuum evaporation of the carbon disulfide to get the crude BI_3. This was then further purified by slowly subliming it over a small quantity of mercury at a pressure of about a millimeter. The resulting crystalline product was of varying shades of pink due to admixed mercuric iodide. Resublimation at low pressure in a type of molecular still (C, Fig. 1) gave colorless, glistening crystals, melting at 49.9 ± 0.5°, the melt assuming a pale pink color. The melting point previously reported for BI_3 is 43°.[6] Analysis of this purified product agreed well with the theoretical requirements of BI_3. Found: B, 2.78; I, 96.95. Calcd.: B, 2.77; I, 97.23.

Summary

1. Tetraiododiborine, B_2I_4, and a lower iodide of boron, B_xI_y, where $x > y$, have been prepared by the action of an electrodeless discharge at room temperature upon the vapors of boron triiodide at 1 to 3 mm. pressure. The decomposition is irreversible and is accompanied by a brilliant yellowish-green glow. Free iodine is formed and is trapped out by liquid nitrogen. Forty per cent. of the boron triiodide is reduced in one pass through the glow; one-third of the reduced boron triiodide is recoverable as tetraiododiborine.

2. B_2I_4 is a well-crystallized, pale yellow solid, which is slowly decomposed at room temperature, forming BI_3 and a black non-volatile residue of a polymerized monoiodide, $(BI)_x$. Decomposition is hastened by higher temperature and by the action of sunlight.

3. The lower iodides of boron are hydrolyzed by water yielding strongly reducing solutions which react with silver nitrate precipitating metallic silver and silver iodide.

4. A new and satisfactory method for the preparation of boron triiodide has been developed, in which solid sodium or lithium borohydride reacts with iodine at 200 or 120°, respectively. Yields as high as 66% on the basis of the boron involved were obtained using lithium borohydride.

5. The reduction of boron triiodide to lower iodides has been shown to occur in other ways, such as by the action of silver wool at 185° or by means of hydrogen in a "hot–cold" tube apparatus. These methods, however, are less satisfactory for preparative purposes than those employing the electrodeless discharge.

Cambridge, Massachusetts Received July 6, 1949

[Contribution from the Chemistry Department of DePauw University]

Trichloroaminoalcohols. I. 1,1,1-Trichloro-3-aminopropanol-2 and Derivatives

By Maryann Compton,[1] Harvey Higgins,[2] Lorne MacBeth,[3] Jane Osborn[4] and Howard Burkett

In 1942 Malkiel and Mason[5] described the synthesis of a compound (I), m. p. 167.4–167.7° (cor.), by the catalytic hydrogenation of 1,1,1-trichloro-3-nitropropanol-2 (II). They reported I to be 1,1,1-trichloro-3-aminopropanol-2 (III). The synthesis of III, m. p. 123°, was first reported[6] in 1935. In addition to III, Chattaway and Witherington also described and reported analyses for its hydrochloride, sulfate and oxalate salts and the mono- and di-acetyl derivatives.

Upon repeating the work of Malkiel and Mason, we obtained a product, m. p. 159–159.5° (uncor.), which was apparently the same as I. It was noted in our work that about 3.8–3.9 moles of hydrogen was consumed per mole of the nitro compound and that the product was much more soluble in water than was expected. Moreover, this product gives instantly a copious precipitate with aqueous silver nitrate. It was suspected that one of the chlorine atoms had been removed by hydrogenolysis, forming 1,1-dichloro-3-aminopropanol-2 hydrochloride (IV), which would give nearly the same nitrogen analysis as III. We have prepared the free amine and the N-benzoyl and O,N-dibenzoyl derivatives from this product, all of which give the correct analysis for the dichloro compound. As further confirmation of its structure, IV has also been synthesized as represented by the following equations.

$$Cl_2CHCH(OC_2H_5)_2 \longrightarrow Cl_2CHCHO$$

$$Cl_2CHCHO \xrightarrow{CH_3NO_2} Cl_2CHCHOHCH_2NO_2$$

$$Cl_2CHCHOHCH_2NO_2 \longleftarrow Cl_2CHCOHCH_2NH_2.HCl$$

The mixed melting point of this latter product with that from the catalytic hydrogenation of II is not depressed. From this evidence, it is thought that the compound reported by Malkiel and Mason was IV and not III.

Chattaway and Witherington prepared III by the reduction of II with tin and hydrochloric acid but they did not report the yield. A similar re-

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(5) Malkiel and Mason, This Journal, **64**, 2515 (1942).

(6) Chattaway and Witherington, *J. Chem. Soc.*, **137**, 1623 (1935).

duction by us gave a poor yield. We have synthesized III in good yield, using stannous chloride and hydrochloric acid, and prepared several of its derivatives.

Malkiel and Mason describe the preparation of a benzoyl derivative, m. p. 167.4°, from their crude reduction mixture. It is confusing to note that this melting point is different from that of the mono- or di-benzoyl derivatives of either the dichloro- or trichloro-compound prepared in our work. The product obtained by us upon benzoylating the crude hydrogenation mixture, in the same manner[7] as they, was N-benzoyl-1,1-dichloro-3-aminopropanol.

Experimentation on the synthesis of II[5,8,9,10] by the base-catalyzed condensation of chloral hydrate and nitromethane has culminated in a procedure which gives a high-quality product in 92–98% yield. Attempts to make the benzoyl and *p*-nitrobenzoyl derivatives of II failed.

The N-acyl and O,N-diacyl derivatives of III are easily prepared. However, numerous attempts to synthesize O-acyl 1,1,1-trichloro-3-aminopropanol-2 hydrochloride by acylation of the hydrochloride[11–14] or by the rearrangement of the N-acyl 1,1,1-trichloro-3-aminopropanol-2[12,14] have been unsuccessful.

Pharmacology.—Several of these compounds were tested by Eli Lilly and Company for local anesthetic, pressor, analgesic and chemotherapeutic action and were found to have none.

Experimental

All melting points are uncorrected. Analyses were done by one of us (L. M.).

1,1,1-Trichloro-3-nitropropanol-2.—In a 250-ml. erlenmeyer flask were placed 165.5 g. (1 mole) of chloral hydrate and 73.2 g. (1.2 moles) of nitromethane. After the chloral hydrate had dissolved by warming to 50°, 1.9 g. of anhyd. potassium carbonate was added in portions with vigorous stirring so that the temperature remained at 70–80°, cooling in ice as necessary. The stirring was continued until the mixture had cooled to room temperature. Then, the product was washed three times with 50-ml. portions of water. The combined water washes were extracted with ether and the ether added to the main portion of the product. After the solvent had been removed under reduced pressure with warming on the steam-bath, the residue was distilled through a 15-cm. Vigreux column. The colorless fraction, boiling at 105.5–106.5° at 3.5 mm., amounted to 204.3 g. (98%). Upon standing, it gradually solidified, m. p. 44–46°.

1,1-Dichloro-3-aminopropanol-2 Hydrochloride (from 1,1,1-Trichloro-3-nitropropanol-2).—A mixture of 10.4 g. (0.05 mole) of 1,1,1-trichloro-3-nitropropanol-2, 75 ml. of ethanol and about 6 g. of Raney nickel was hydrogenated in the Adams machine, using an initial pressure of 50 p.s.i. In thirty-five minutes, a pressure drop corresponding to 0.190 mole of hydrogen was observed. The catalyst was filtered off and the filtrate evaporated to a small volume. The solid, obtained upon the addition of ethyl acetate and cooling, was recrystallized from ethanol and washed with ether, yielding 3.1 g. (34.7%) of white product, m. p. 159–159.5°.

Anal. Calcd. for $C_3H_7ONCl_2 \cdot HCl$: N, 7.75. Found: N, 7.49.

In another experiment, in which 3.9 moles of hydrogen was consumed per mole of compound, an aliquot of the reduced mixture was treated with an excess of silver nitrate solution. The amount of precipitated silver chloride indicated 1.19 equivalents of chloride ion per mole of compound reduced.

1,1-Dichloro-3-aminopropanol-2.—A small sample of the hydrochloride described in the previous section was recrystallized from butanol-1. This material, m. p. 162–163°, was dissolved in abs. alcohol and an excess of dry ammonia was added. Addition of anhyd. ether caused the precipitation of ammonium chloride, which was removed by filtration. The filtrate was evaporated to dryness at room temperature under reduced pressure. The residue was extracted with anhyd. ether and this solution evaporated to a small volume. After cooling in the refrigerator, the white crystalline product, m. p. 57–58°, was filtered off. It was somewhat hygroscopic and began to turn yellow in a few days.

Anal. Calcd. for $C_3H_7ONCl_2$: N, 9.69. Found: N, 9.49.

A sample of this amine was dissolved in anhyd. ether and dry hydrogen chloride was added. The resulting precipitate melted at 162–163° and gave no depression of the mixed melting point with the original hydrochloride, proving that there were no deep-seated changes in the compound.

1,1-Dichloro-3-aminopropanol-2 Hydrochloride (from Dichloroacetaldehyde).—To a mixture of 12.7 g. (0.112 mole) of dichloroacetaldehyde[15] (obtained from dichloroacetal[16]), 2.03 g. (0.112 mole) of water and 8.25 g. (0.135 mole) of nitromethane was added 0.22 g. of anhydrous potassium carbonate in portions. After an initial exothermic reaction, the temperature was kept at 80° for a few minutes. The cool reaction mixture was washed twice with small portions of water. The aqueous portions were extracted with ether and the combined organic materials were dried for a few seconds over anhyd. sodium carbonate and distilled. The portion (6.13 g.) boiling at 103–107° at 5 mm. was added to a solution of 47.6 g. of stannous chloride (hydrated) in 33 ml. of concd. hydrochloric acid. The reaction mixture was heated to 90°, at which temperature it darkened considerably. It was evaporated to dryness at 60° under reduced pressure and the residue was dissolved in water. The tin was removed by adding ammonium hydroxide and hydrogen sulfide and filtering. The solid residue, obtained upon evaporating the filtrate to dryness, was extracted thoroughly with boiling butanol-1. After evaporation to one-fourth volume and cooling, a crude product was obtained. One crystallization from butanol-1 yielded 0.24 g. of pure white product, m. p. 161–162°. The melting point of this product with that from the hydrogenation of 1,1,1-trichloro-3-nitropropanol-2 was 161–162°.

N-Benzoyl-1,1-dichloro-3-aminopropanol-2.—The reaction mixture from a hydrogenation identical to that described previously was evaporated to dryness under reduced pressure. The residue was mixed with a little water and 10 ml. of benzoyl chloride; then, with continuous stirring and cooling as necessary, 75 ml. of 10% sodium hydroxide was added in 20-ml. portions. After cooling and filtering, the solid was thoroughly extracted with warm ethyl acetate. The crude product, precipitated by adding petroleum ether, was crystallized twice from ethyl acetate-

(7) Private communication.

(8) Henry, *Bull. Acad. Roy. Belg.*, **32**, 17 (1896).

(9) Chattaway and Witherington, *J. Chem. Soc.*, **137**, 1178 (1935).

(10) Studies on the condensation of aldehydes with nitro compounds have been carried out by Vanderbilt and Hass, *Ind. Eng. Chem.*, **32**, 34 (1940); Lindal, *ibid.*, **33**, 65 (1941); Sprang and Degering, THIS JOURNAL, **64**, 1063 (1942); Nightingale, *ibid.*, **66**, 352 (1944).

(11) Cope and Hancock, THIS JOURNAL, **66**, 1448, 1453 (1944).

(12) Cope and Hancock, *ibid.*, **66**, 1738 (1944).

(13) Hancock, Hardy, Heyl, Wright and Cope, *ibid.*, **66**, 1747 (1944).

(14) Day, *J. Org. Chem.*, **5**, 515 (1940).

(15) Wohl and Roth, *Ber.*, **40**, 217 (1907).

(16) Magnani and McElvain, THIS JOURNAL, **60**, 2210 (1938).

petroleum ether, yielding 2.3 g. of white product, m. p. 131.3–132.5°.

Anal. Calcd. for $C_{10}H_{11}O_2NCl_2$: N, 5.67. Found: N, 5.87.

O,N-Dibenzoyl-1,1-dichloro-3-aminopropanol-2.—To 0.694 g. (0.0038 mole) of 1,1-dichloro-3-aminopropanol-2 hydrochloride suspended in 8 ml. of dry benzene was added, with cooling and stirring, 1.40 g. (0.0138 mole) of triethylamine; then, 1.94 g. (0.0138 mole) of benzoyl chloride, keeping the temperature below 30°. After the addition of the benzoyl chloride, the mixture was warmed to 40–45° for one hour. Filtration of the warm reaction mixture and addition of petroleum ether to the filtrate gave an oil, which upon two crystallizations from ethanol–water afforded 0.211 g. of white solid, m. p. 87–88°. The filtrates yielded 0.6 g. more of slightly less pure product.

Anal. Calcd. for $C_{17}H_{15}O_3NCl_2$: N, 3.95. Found: N, 3.75.

Treatment of the N-benzoyl-1,1-dichloro-3-aminopropanol-2, obtained from the crude hydrogenation mixture, in a similar manner gave the same product, m. p. 87–88° (mixed m. p. 87–88°).

1,1,1-Trichloro-3-aminopropanol-2.—In an erlenmeyer flask 580 g. (2.57 moles) of stannous chloride (hydrated) was dissolved in 400 ml. of concd. hydrochloric acid. With good stirring, 82.3 g. (0.394 mole) of 1,1,1-trichloro-3-nitropropanol-2 was added in one portion. The temperature rose spontaneously to 106°. When the temperature began to drop, the mixture was heated to boiling (114°) for a few minutes; then allowed to cool slowly. After finally cooling for three hours in an ice-bath, the tin-containing salt was filtered off and air-dried. A solution of this in 800 ml. of water was saturated with hydrogen sulfide and filtered. The filtrate was evaporated to dryness. To a solution of the resultant white solid in 85 ml. of water was added concd. ammonium hydroxide until no more precipitate formed. After cooling in an ice-bath and filtering, there was obtained 48.7 g. (69.4%) of product, m. p. 115.3–116.5°. Sublimation at 2 mm. pressure gave a pure product, m. p. 118–119°.

Anal. Calcd. for $C_3H_6ONCl_3$: N, 7.85. Found: N, 7.66.

In another preparation the tin-containing salt was thoroughly dried and analyzed.

Anal. Calcd. for $C_3H_6ONCl_3 \cdot H_2SnCl_4$: N, 3.28. Found: N, 3.40.

N-Benzoyl-1,1,1-trichloro-3-aminopropanol-2.—To a suspension of 5 g. (0.028 mole) of 1,1,1-trichloro-3-aminopropanol-2 in 50 ml. of benzene was added 3.75 g. (0.037 mole) of triethylamine; then, dropwise with stirring, 4.14 g. (0.029 mole) of benzoyl chloride. When the odor of benzoyl chloride was gone, the cooled reaction mixture was filtered. Thorough washing with water, followed by crystallizing from ethanol–water, yielded 6.65 g. (84%) of product, m. p. 144–144.5°.

Anal. Calcd. for $C_{10}H_{10}O_2NCl_3$: N, 4.96. Found: N, 4.96.

N-*p*-Nitrobenzoyl-1,1,1-trichloro-3-aminopropanol-2.—To a solution of 4.5 g. (0.025 mole) of 1,1,1-trichloro-3-aminopropanol-2 in 15 ml. of pyridine was added 4.6 g. (0.025 mole) of *p*-nitrobenzoyl chloride in small portions with stirring and cooling. After standing overnight, the mixture was warmed gently for thirty minutes, cooled and poured into water. The tan solid was filtered and was crystallized three times from ethanol–water and once from methanol, furnishing 1.6 g. (19.5%) of white solid, m. p. 134–136°.

Anal. Calcd. for $C_{10}H_9O_4N_2Cl_3$: N, 8.54. Found: N, 8.37.

O,N-Di-*p*-nitrobenzoyl-1,1,1-trichloro-3-aminopropanol-2.—To a solution of 4.0 g. (0.0224 mole) of 1,1,1-trichloro-3-aminopropanol-2 in 40 ml. of dry benzene and 4.95 g. (0.049 mole) of triethylamine was added 8.7 g. (0.047 mole) of *p*-nitrobenzoyl chloride in small portions with stirring so that the temperature did not rise above 30°. After standing for two days at room temperature, the mixture was refluxed for thirty minutes, cooled and filtered. The solid was washed thoroughly with water and crystallized twice from acetone–water, affording 6.8 g. (63.9%) of white product, m. p. 207.5–208.5°,

Anal. Calcd. for $C_{17}H_{12}O_6N_3Cl_3$: N, 8.81. Found: N, 8.70.

N-Phenylacetyl-1,1,1-trichloro-3-aminopropanol-2.—Handling 3.7 g. (0.0208 mole) of 1,1,1-trichloro-3-aminopropanol-2, 7.0 ml. (0.05 mole) of triethylamine and 5.6 ml. (0.042 mole) of phenylacetyl chloride by the same procedure as the preceding experiment yielded a product which sintered at 120° and melted at 129°.

Anal. Calcd. for $C_{11}H_{12}O_2NCl_3$: N, 4.74. Found: N, 4.86.

O,N-Di-diphenylacetyl-1,1,1-trichloro-3-aminopropanol-2.—This compound was made in the same manner as the preceding one from 1.78 g. (0.01 mole) of 1,1,1-trichloro-3-aminopropanol-2, 3 ml. of triethylamine and 4.9 g. (0.021 mole) of diphenylacetyl chloride. After one crystallization from ethanol, there was obtained 4.3 g. (77%) of white product, m. p. 142–143°.

Anal. Calcd. for $C_{31}H_{26}O_3NCl_3$: N, 2.47. Found: N, 2.32.

N-Benzenesulfonyl-1,1,1-trichloro-3-aminopropanol-2.—To a suspension of 3.56 g. (0.02 mole) of 1,1,1-trichloro-3-aminopropanol-2 in 15 ml. of water was added 7.77 g. (0.044 mole) of benzenesulfonyl chloride and 24 ml. of 10% aqueous sodium hydroxide in small portions alternately with stirring so that the temperature did not rise above 30° and the mixture was at no time strongly basic. When the odor of the benzenesulfonyl chloride was almost gone, the product was filtered, washed with water and crystallized from ethanol–water, yielding 3.7 g. (58%) with m. p. 162–163°.

Anal. Calcd. for $C_9H_{10}O_3NSCl_3$: N, 4.41. Found: N, 4.52.

Summary

Evidence for the identity of 1,1-dichloro-3-aminopropanol-2 hydrochloride was presented.

The synthesis of 1,1,1-trichloro-3-aminopropanol-2 and several of its derivatives were described.

GREENCASTLE, INDIANA RECEIVED DECEMBER 21, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUQUESNE UNIVERSITY]

A Synthesis of S-Benzyl-*dl*-cysteine

BY OSCAR GAWRON AND ANDREW J. GLAID, III

Wood and du Vigneaud[1] previously have synthesized S-benzyl-*dl*-cysteine from benzylthiolmethyl chloride and sodiophthalimidomalonic ester and subsequently[2] have converted it into *dl*-cystine.

In view of the use of S-benzyl-*dl*-cysteine as an intermediate in the preparation of *dl*-cystine and continued interest[3] in the synthesis of *dl*-cystine, we have synthesized S-benzyl-*dl*-cysteine from benzylmercaptoacetaldehyde by a modified Strecker synthesis.

Benzylmercaptoacetaldehyde has previously been found by Herbst[4] among the products of a reaction between S-benzyl-*l*-cysteine and pyruvic acid and was characterized by several derivatives. Fromm and Landmann[5] mention it as one of the decomposition products obtained when 1,2-dibenzylmercaptoethylene is treated with sulfuric and acetic acids. For our purpose, we have synthesized benzylmercaptoacetaldehyde by treating the sodium salt of benzylmercaptan with the dimethyl acetal of bromoacetaldehyde and hydrolyzing the obtained dimethyl acetal of benzylmercaptoacetaldehyde.

Treatment of benzylmercaptoacetaldehyde with sodium bisulfite and sodium cyanide yielded β-benzylmercapto-α-hydroxypropionitrile and this on treatment with gaseous ammonia at 100° was converted to β-benzylmercapto-α-aminopropionitrile. Hydrolysis of the latter with hydrochloric acid, followed by neutralization, yielded S-benzyl-*dl*-cysteine.

Application of the Bücherer hydantoin synthesis to benzylmercaptoacetaldehyde yielded 5-benzylmercaptomethylhydantoin. Preliminary attempts at hydrolysis of this hydantoin resulted in decomposition without yielding S-benzyl-*dl* cysteine and so no further attempts were made at obtaining S-benzyl-*dl*-cysteine by this method.

Experimental

Benzylmercaptoacetaldehyde Dimethyl Acetal.—Under reflux, 23 g. (1 gram-atom) of sodium was added slowly to 500 ml. of absolute ethanol. After solution of the sodium, 124 g. (1 mole) of benzyl mercaptan[6] was slowly added with stirring. The reaction mixture was then cooled and to it, with stirring, 169 g. (1 mole) of the dimethyl acetal of bromoacetaldehyde[7] was added over a period of ten minutes. The reaction mixture was then heated gently, the reaction proceeding vigorously at the start, and then refluxed for three hours. After cooling and filtering free of sodium bromide, 250–300 ml. of alcohol was removed by distillation. The concentrated solution was treated with 500 ml. of water and thoroughly extracted with ether. The combined ether extracts were washed once with water and dried over anhydrous sodium sulfate. After evaporation of the ether, the product was distilled at 140–141° (6 mm.); yield, 148 g. (70%) of a colorless liquid; d^{22}_4 1.0757; $n^{22}D$ 1.5303.

Anal. Calcd. for $C_{11}H_{16}O_2S$: C, 62.28; H, 7.55. Found: C, 62.55; H, 7.72.

Benzylmercaptoacetaldehyde.—One hundred ten grams (0.52 mole) of the dimethylacetal of benzylmercaptoacetaldehyde was heated with 350 ml. of 1 *N* sulfuric acid for one and one-half hours under reflux and with stirring. The reaction mixture was then cooled and extracted with ether. The ether extract was washed once with water and dried over anhydrous sodium sulfate. After evaporation of the ether, the product was distilled at 125.5–127° (6 mm.); yield, 65 g. (75%) of a colorless liquid; d^{22}_4 1.1105; $n^{22}D$ 1.5699.

Anal. Calcd. for $C_9H_{10}OS$: S, 19.28. Found: S, 19.01.

The aldehyde forms a crystalline bisulfite derivative and a crystalline yellow 2,4-dinitrophenylhydrazone, melting at 155–156°.[8] The semicarbazone, prepared in the usual fashion, consists of small white needles, melting at 105–107°.[9]

Anal. Calcd. for $C_{10}H_{13}N_3OS$: C, 53.81; H, 5.82; N, 18.82; S, 14.35. Found: C, 53.88; H, 5.47; N, 18.98; S, 14.26.

β-Benzylmercapto-α-hydroxypropionitrile.—Thirty-five grams (0.21 mole) of the aldehyde was added slowly and with shaking to a solution of 23 g. (0.22 mole) of sodium bisulfite in 75 ml. of water. After shaking for ten minutes, a pasty mass of the bisulfite derivative was obtained. To this was added, portionwise and with shaking, a solution of 11 g. (0.23 mole) of sodium cyanide in 30 ml. of water. Shaking was continued for thirty minutes after addition of the final portion of cyanide solution. The oily cyanohydrin was extracted four times with 75-ml. portions of benzene. The combined benzene extracts were washed once with a small amount of bisulfite solution, dried over anhydrous sodium sulfate and then vacuum concentrated. The crude cyanohydrin was a colorless oil which slowly turned yellow; yield 35.5 g. (86% of theory). No attempt was made at further purification, the crude cyanohydrin being used as such.

β-Benzylmercapto-α-aminopropionitrile.—Essentially the method of Pierson, *et al.*,[10] was used to prepare the aminonitrile. Thirty-five and one-half grams of crude β-benzylmercapto-α-hydroxypropionitrile was placed in a small flask arranged in a distillation setup. The flask was heated to 100° and anhydrous ammonia was bubbled through for one-half hour, the water distilling as formed. After cooling, the reaction mixture was dissolved in 100 ml. of benzene and extracted with 50-ml. portions of 10% hydrochloric acid. The combined extracts were made alkaline with concentrated ammonia and extracted three times with 75-ml. portions of benzene. The benzene extracts were combined and washed once with water, then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude aminonitrile (23.0 g., 65%) was a yellowish oil. No attempt was made at further purification.

S-Benzyl-*dl*-cysteine.—Twenty-three grams of the crude aminonitrile was heated, under reflux, at 100° with 100 ml. of concentrated hydrochloric acid for four hours and then the reaction mixture was vacuum concentrated

(1) Wood and du Vigneaud, *J. Biol. Chem.*, **130**, 109 (1939).
(2) Wood and du Vigneaud, *ibid.*, **131**, 267 (1939).
(3) Farlow, *ibid.*, **176**, 71 (1948).
(4) Herbst, THIS JOURNAL, **58**, 2239 (1936).
(5) Fromm and Landmann, *Ber.*, **56B**, 2290 (1923).
(6) Marker, *Ann.*, **136**, 75 (1865).
(7) Bedoukian, THIS JOURNAL, **66**, 651 (1944).
(8) Herbst[4] reports 156–157° as the melting point of this derivative.
(9) All melting points are uncorrected.
(10) Pierson, Giella and Tishler, THIS JOURNAL, **70**, 1450 (1948).

to 50 ml. To this was added 75 ml. of water and concentrated ammonia to alkalinity, followed by acetic acid to *p*H 4.5. The S-benzyl-*dl*-cysteine was filtered off and partially purified by suspending in 70 ml. of water followed by the addition of sufficient 10% sodium hydroxide to cause solution. The brown solution was filtered free of gummy material and the product was precipitated with acetic acid. Repetition of this treatment followed by a crystallization from water yielded 17 g. (67.5% of theory) of S-benzyl-*dl*-cysteine, melting at 209–211°. Another recrystallization gave material melting at 213–214°, no depression of the melting point with synthetic S-benzyl-*l*-cysteine, melting 213–214°, prepared according to du Vigneaud, *et al.*[11]

Anal. Calcd. for $C_{10}H_{13}NO_2S$: N, 6.64; S, 15.18; neut. equiv., 211. Found: N, 6.64; S, 15.26; neut. equiv.,[12] 213.

5-Benzylmercaptomethylhydantoin.—The procedure used was similar to that of Pierson, *et al.*,[10] for the preparation of 5-(β-methylmercaptoethyl)-hydantoin.

Twenty grams (0.12 mole) of benzylmercaptoacetaldehyde, 57 g. (0.59 mole) of ammonium carbonate, 12.7 g. (0.26 mole) of sodium cyanide and 340 ml. of 50% ethyl alcohol were heated under reflux, and with stirring, at 40–45° for four hours. The reaction mixture was cooled and filtered and the filter cake was washed with a small amount of 95% alcohol. The filtrate and washings were combined and concentrated *in vacuo* to one-half volume. The concentrated solution was heated under reflux to 100° and then 25 ml. of concentrated hydrochloric acid was added. The reaction mixture was allowed to remain at this temperature for ten minutes. It was then cooled and the hydantoin filtered off and recrystallized from hot water to yield 20 g. (70% of theory) of 5-benzylmercaptomethylhydantoin, white needles, m. p. 118–119°.

For purposes of comparison by mixed melting points, the *levo* 5-benzylmercaptomethylhydantoin, melting at 129–130°, was prepared from S-benzyl-*l*-cysteine and was racemized with dilute aqueous sodium hydroxide solution. The *dl*-form prepared in this fashion melted at 118–119° and showed no depression of the melting point on admixture with the hydantoin prepared from benzylmercaptoacetaldehyde.

Preliminary attempts at hydrolysis of 5-benzylmercaptomethylhydantoin with alkali or ammonium sulfide or acid resulted in decomposition without yielding S-benzyl-*dl*-cysteine.

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.90; H, 5.12; N, 11.88; S, 13.58. Found: C, 56.10; H, 4.94; N, 11.87; S, 13.32.

(11) du Vigneaud, Audrieth and Loring, *ibid.*, **52**, 4500 (1930).

(12) The determination was carried out by a modified formol titration. The compound was dissolved in excess standard sodium hydroxide in the presence of formaldehyde and the excess sodium hydroxide was titrated with standard acid.

Summary

Benzylmercaptoacetaldehyde has been synthesized and used as a starting material for the preparation of S-benzyl-*dl*-cysteine by a modified Strecker reaction.

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NOTES

Carbonyl-cyanyls of Nickel(0)

BY ANTON B. BURG AND JUNE CHASE DAYTON[1]

The compound $K_4Ni(CN)_4$, discovered by Eastes and Burgess,[2] has been interpreted as an analog of nickel carbonyl, in that the cyanide ion is isoelectronic with carbon monoxide, and could replace it in complex compounds.[3] Such cyanide complexes, having the central atom in oxidation state zero, have been designated as "cyanyls" by Ormont.[4] In a search for chemical reality in this analogy, we have carried on reactions in which cyanide ion displaces carbon monoxide from nickel carbonyl, and others in which carbon monoxide displaces cyanide ion from $K_4Ni(CN)_4$. Under the conditions of the experiments, neither reaction could be brought to completion, and the products appeared to be mixtures of the intermediate compounds $KNiCN(CO)_3$, $K_2Ni(CN)_2(CO)_2$, and possibly $K_3Ni(CN)_3CO$.

(1) Abstracted from a thesis presented by June Chase Dayton to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the degree of Master of Science.

(2) J. W. Eastes and W. M. Burgess, THIS JOURNAL, **64**, 1189 (1942).

(3) J. J. Burbage and W. C. Fernelius, *ibid.*, **65**, 1484 (1943).

(4) Ormont, *Acta Physicochim. U. R. S. S.*, **19**, 571 (1944)

Reaction of $Ni(CO)_4$ with KCN.—The first experiments showed that a yellow to orange solid (containing no dark material) is formed with the evolution of carbon monoxide when nickel carbonyl is allowed to react with solid potassium cyanide at ordinary temperatures. The solid product proved to be soluble in methyl cyanide, which then was adopted as the reaction medium. The solubility of potassium cyanide (0.03%) aided the reaction but was too low to interfere with the isolation of the product.

The apparatus employed for the reaction is shown in Fig. 1. Potassium cyanide was placed at A and dried by evacuation of the apparatus. Then methyl cyanide and nickel carbonyl were distilled in from the high-vacuum system with A at −196°, and warmed to room temperature. After three days, the carbon monoxide was removed through a trap at −196°, collected by a Töpler pump and measured. With the methyl cyanide solution at −196°, the lower part of the apparatus was sealed off *in vacuo* at D. Now the solution was melted and decanted into the weighed tubes designated as 1, 2 and 3. Next the solvent and any excess nickel carbonyl were distilled off through a vacuum tube-opener[5] operating at F, with the sample tubes 1, 2 and 3 in ice–salt to avoid decomposition of the solid product. Finally at half-hour intervals, the sample tubes were sealed off at E (leaving a tip suitable for the tube-opener) and the contents subjected to analysis. The sample-weight (usually about 0.3 g.) was determined as the gain in weight of the sealed tube and joint-socket.

The first step of the analysis was decomposition *in vacuo* at 200°, with collection and measurement of carbon

(5) A. Stock, *Ber.*, **51**, 985 (1918).

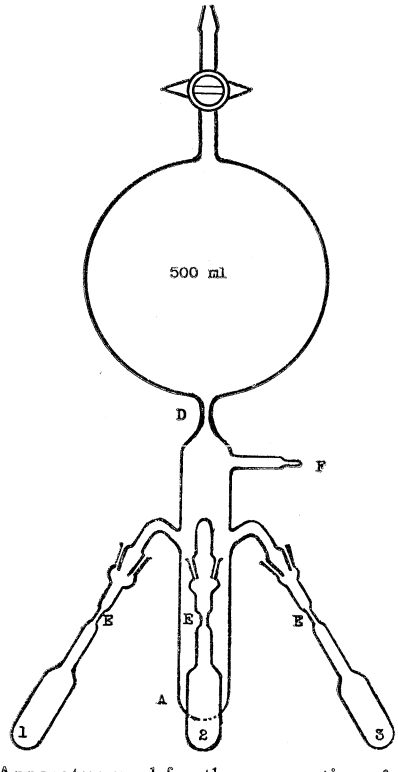

Fig. 1.—Apparatus used for the preparation of carbonyl-cyanyl compounds.

monoxide. Nickel carbonyl (perhaps due to disproportionation of a cyanyl-carbonyl) was condensed in a trap and decomposed on a hot glass surface, with collection and measurement of carbon monoxide. Finally all solids were dissolved in concentrated hydrochloric acid and analyzed for nickel by dimethylglyoxime and potassium by the cobaltinitrite method,[6] using aliquots of the solution.

One result was 43.4% KCN, 25.9% Ni, and 31.3% CO, corresponding perfectly to the formula $(KCN)_3Ni_2(CO)_5$. This could mean equal molar proportions of $K_2Ni(CN)_2(CO)_2$ and $KNiCN(CO)_3$. The average of all the results was: 39.8% KCN, 26.3% Ni, and 35.6% CO, corresponding to $(KCN)_4Ni_3(CO)_8$, or two moles of $KNiCN(CO)_3$ to one of $K_2Ni(CN)_2(CO)_2$. These simple formulas probably are fortuitous since the mixtures seem to vary continuously as indicated by measurements of carbon monoxide evolved in numerous experiments in which the composition of the solute was not determined.

It is also to be noted that in some experiments an insoluble yellow solid was obtained. This was not collected for analysis.

Reaction of $K_4Ni(CN)_4$ with CO.—The displacement of cyanide ion from $K_4Ni(CN)_4$ by the action of carbon monoxide was qualitatively demonstrated as follows. A sample of the salt $K_4Ni(CN)_4$ was prepared by the reaction of $K_2Ni(CN)_4$ with potassium in liquid ammonia.[2] After evaporation of all the ammonia *in vacuo*, methyl cyanide was distilled into the reaction tube, partially dissolving the copper-colored solid. Carbon monoxide now was introduced to a total pressure of 726 mm. During a week, at constant temperature (25°), the pressure fell to 654 mm. and a white precipitate (presumably KCN) appeared. A yellow solid apparently distinct from $K_4Ni(CN)_4$ also was noticed. More carbon monoxide was added and the pressure fell to the same point, 656 mm. Although the question of an established equilibrium was quite uncertain in this and preceding experiments, the fact that carbon monoxide could be either absorbed or evolved depending upon the conditions left no doubt of the reversibility of a series of displacements.

Discussion.—In view of the higher base strength of cyanide ion, it would seem surprising that carbon monoxide is capable of displacing it. The apparent similarity in the strength of bonding to nickel can be understood in terms of the double bonded situation in nickel carbonyl and the argument that the cyanide is chiefly single bonded.

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LOS ANGELES 7, CALIFORNIA RECEIVED MARCH 26, 1949

(6) L. V. Wilcox, *Ind. Eng. Chem., Anal. Ed.*, **9**, 137 (1937).

Preparation of Arylethynylcarbinols[1]

BY E. T. CLAPPERTON AND W. S. MACGREGOR

Vanillin, veratraldehyde, 4-ethoxy-3-methoxybenzaldehyde and piperonal were converted to the corresponding arylethynylcarbinols by reaction with sodium acetylide in liquid ammonia.[2,3,4] The yields, Table I, ranged from 77 to 93% only when anhydrous conditions were carefully maintained. Hurd and McPhee[5] found that 0.0032 mole of water in a one-fifth mole reaction of acetone with sodium acetylide reduced the yield of dimethylethynylcarbinol from 86 to 49%. In the reaction of benzaldehyde 0.02 mole of water reduced the yield of phenylethynylcarbinol in a one-half mole reaction to 17.5%. The water in this case caused incomplete reaction and induced side reactions yielding nitrogen-free polymers, benzoic acid and benzyl alcohol.

When sodium acetylide and a nine-fold excess of benzaldehyde reacted in the presence of excess acetylene, 139% of phenylethynylcarbinol (based on sodium) was isolated. The high yield would be expected if the anion of phenylethynylcarbinol and acetylene were in equilibrium with the free carbinol and the acetylide anion as suggested by Campbell, Campbell and Eby.[2]

Acknowledgments.—The authors wish to express their appreciation of a grant from Research Corporation in support of this work.

Experimental

General Procedure.—The procedure used was adapted from those previously described.[2-5] The reactions were run in a 2-liter 3-neck flask fitted with a Hershberg stirrer having a hollow shaft for introducing gases. All outlets were protected from atmospheric moisture by Drierite tubes. Commercial acetylene, passed through water, a calcium chloride tube and a Dry Ice trap, was bubbled through a stirred mixture of one-half mole of sodium and 500 ml. of refrigeration-grade ammonia. After the blue

(1) From the thesis of E. T. Clapperton presented in May, 1948, in partial fulfillment of the requirements for the Master of Science Degree at the University of Portland. Presented before the Cellulose Division of the American Chemical Society at the 114th meeting.

(2) Campbell, Campbell and Eby, THIS JOURNAL, **60**, 2882 (1938).

(3) Hennion and Murray, *ibid.*, **64**, 1220 (1942).

(4) Jones and McCrombie, *J. Chem. Soc.*, 733 (1942).

(5) Hurd and McPhee, THIS JOURNAL, **69**, 239 (1947).

TABLE I

SUBSTITUTED PHENYLETHYNYLCARBINOLS[a]

Substituents	Yield, %	M. p., °C.	Empirical formula	OCH₃, % Calcd.	OCH₃, % Found	Mol. wt. Calcd.	Mol. wt. Found	Acetate M. p., °C.	Acetate Empirical formula	Acetate OCH₃, % Calcd.	Acetate OCH₃, % Found	Acetate Acetyl, % Calcd.	Acetate Acetyl, % Found
4-OH-3-CH₃O[f]	77	83–84	$C_{10}H_{10}O_3$	17.4	17.3	178	169	93.5–94	$C_{14}H_{14}O_5$	11.8	11.7	32.8	32.3
3,4-Dimethoxy[g]	78	99	$C_{11}H_{12}O_3$	32.3	32.3	192	206	42–42.5	$C_{13}H_{14}O_4$	26.5	26.6	18.4	17.9
4-C_2H_5O-3-CH_3O[h]	91	81–82.5	$C_{12}H_{14}O_3$	30.1[e]	30.3[e]	206	201	64.5–65[c]	$C_{14}H_{16}O_4$	25.0[e]	25.3[e]	17.3	16.6
3,4-CH_2O_2[b,i]	93	34.5–35	$C_{10}H_8O_3$	...	...	...	...	55.5–56.5[d]	$C_{12}H_{10}O_4$	...	...	19.7	19.8

[a] Phenylethynylcarbinol, obtained in 79% yield, melted at 29–30°, $n^{20}D$ 1.5511. The reported values are: m. p., 22°,[4] $n^{20}D$ 1.5508,[2] 1.5505,[3] $n^{21}D$ 1.5482.[4] The benzoyl derivative m. p. was 82–84° and the mercury derivative m. p. was 162–163° (reported m. p., 167–168°[4]). [b] $n^{20.5}D$ 1.5696. [c] $n^{20}D$ 1.5292. [d] $n^{20.5}D$ 1.5375. [e] Total alkoxyl calculated as methoxyl. [f] Yielded a mercury derivative as an unstable salt unsuitable for characterization. [g] Mercury deriv. obtained in 91% yield, m. p. 147.5–150°. *Anal.* Calcd. for $C_{22}H_{22}O_6Hg$: methoxyl, 21.3. Found: methoxyl, 21.5. [h] Mercury deriv. obtained in 96% yield, m. p. 140–142°. *Anal.* Calcd. for $C_{24}H_{26}O_6Hg$: alkoxyl (as methoxyl), 20.3. Found: alkoxyl, 20.1. [i] Mercury deriv. obtained in 76% yield, m. p. 170–171°. *Anal.* Calcd. for $C_{20}H_{14}O_6Hg$: Hg, 36.4. Found: Hg, 35.6.

color was dispelled a solution of 0.5 mole[6] of the aldehyde in anhydrous ether was added dropwise and the mixture stirred six hours. The flow of acetylene was continued throughout the reaction period. Ammonium chloride (0.5 mole) was then added and the ammonia evaporated overnight under nitrogen. The carbinol was separated from the salt with ether and recovered from the washed and dried ether solution in a suitable manner. In the reaction with benzaldehyde the carbinol was recovered by fractional distillation. The crude carbinols from veratraldehyde and 4-ethoxy-3-methoxybenzaldehyde, which were crystalline and only slightly soluble in ether, were separated by filtration and purified by recrystallizing from ethanol. The dried ether solutions from the reactions with piperonal and vanillin were added to petroleum ether to precipitate the carbinols as oils which crystallized. The carbinol from piperonal was purified by distillation and that from vanillin by several recrystallizations from toluene.

The acetyl derivatives were prepared using excess acetic anhydride in pyridine at room temperature and the mercury derivatives were obtained by the procedure of Johnson and McEwen.[7]

(6) In the case of vanillin one-fourth mole was used because one equivalent of sodium acetylide was lost through reaction with the phenolic hydroxyl.

(7) Johnson and McEwen, THIS JOURNAL, **48**, 469 (1926).

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Steric Inhibition of Resonance in Pentachlorostyrene

BY TURNER ALFREY, JR., AND W. H. EBELKE

Ross[1] has recently reported that the ultraviolet absorption spectrum of 2,6-dichlorobenzoic acid shows characteristics which may be attributed to steric inhibition of resonance.

We have studied the copolymerization behavior of pentachlorostyrene, with styrene and with methyl methacrylate. Our results indicate a similar steric effect in pentachlorostyrene. Apparently the two ortho chlorine atoms and the vinyl group are sufficiently large so that the latter is forced out of the plane of the benzene ring, reducing the extent of conjugation and therefore the reactivity of this styrene derivative with free radicals. (Lewis and Mayo[2] have postulated a similar steric inhibition of resonance in esters of maleic acid, to explain the low copolymerization reactivities of maleates as compared with the corresponding fumarates.)

The low reactivity of pentachlorostyrene is apparent from the reactivity ratios and particularly from the low Q value reported below. The Q–e values indicate that the substitution of chlorine atoms in the ring has made the vinyl double bond more positive, as expected, but has *reduced* the average reactivity to about 20% of that of styrene. Since in other ring chlorinated styrenes either a slight increase, or no change, in reactivity is observed, the suggestion of steric inhibition of resonance in pentachlorostyrene seems reasonable. We would expect a similar reduction in copolymerization reactivity in the case of 2,6-dichlorostyrene. Marvel and co-workers[3] have reported copolymerization of 2,6-dichlorostyrene with butadiene at a single monomer ratio; their results are in harmony with this expectation, although the point cannot be definitely established from this single measurement.

Experimental

Pentachlorostyrene, provided by Dr. S. Ross and the Sprague Electric Company, was purified by recrystallization (m. p. 110.5–112°) and was copolymerized to low conversion at 70° with styrene and methyl methacrylate, using benzoyl peroxide as catalyst. Copolymers were precipitated with methanol, and monomers were removed by extraction with ether and repeated precipitation from benzene. Copolymer composition was determined by chlorine analysis, using a Parr Bomb method. Reactivity ratios were evaluated graphically with the aid of the well-known copolymerization equation

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]}{[M_2]} \cdot \frac{r_1[M_1] + [M_2]}{r_2[M_2] + [M_1]}$$

Q and e values for pentachlorostyrene were also estimated graphically, using as reference standards the values initially assigned to styrene and methyl methacrylate by Alfrey and Price[4] in their semi-empirical scheme for resolving the copolymeriza-

(1) Ross, THIS JOURNAL, **70**, 4039 (1948).

(2) Lewis and Mayo, *ibid.*, **70**, 1533 (1948).

(3) Marvel, Inskeep, Deanin, Juve, Schroeder and Goff, *Ind. Eng. Chem.*, **39**, 1486 (1947).

(4) Alfrey and Price, *J. Polymer Sci.*, **2**, 101 (1947).

tion behavior of a monomer into a "reactivity" term Q, correlated with the degree of conjugation, and a "polarity" factor e. Experimental data are summarized in Tables I, II and III.

TABLE I

STYRENE (M_1)–PENTACHLOROSTYRENE (M_2) SYSTEM

Monomer composition Mole fraction M_2	Polymer composition % Cl	Polymer composition Mole fraction M_2
0.070	8.4	0.054
.159	15.2	.105
.274	24.8	.192
.428	31.1	.261
.654	42.2	.420
.842	48.6	.541
1.000	64.0	.999
$r_1 = 1.31 \pm 0.2$	$r_2 = 0.10 \pm 0.02$	

TABLE II

METHYL METHACRYLATE (M_1)–PENTACHLOROSTYRENE (M_2) SYSTEM

Monomer composition Mole fraction M_2	Polymer composition % Cl	Polymer composition Mole fraction M_2
0.2	8.6	0.051
.4	21.7	.156
.6	33.9	.289
.8	49.7	.553
.9	56.0	.715
1.0	63.9	.994
$r_1 = 4.0 \pm 0.4$	$r_2 = 0.35 \pm 0.05$	

TABLE III

Monomer	Q	e
Styrene	1.0	−1.0
Methyl methacrylate	0.64	0.0
Pentachlorostyrene	0.2	+0.25

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Heterocyclic Basic Compounds. XII. 7-Bromo- and 7-Iodo-quinolines[1]

BY A. E. CONROY,[2] HARRY S. MOSHER[3] AND FRANK C. WHITMORE[4]

Various workers[5–8] have synthesized N-substituted 4-amino-7-halogen quinolines, certain of which possess considerable antimalarial activity. Outstanding among these is 4-(7-chloro-4-quinolylamino)-2-diethylaminomethylphenol,[9] SN 10,751.[10] The present note describes the synthesis of the 7-bromo- (SN 13,167) and the 7-iodo- (SN 13,168) analogs, which were obtained by coupling, according to Burckhalter, *et al.*,[9] 4-amino-2-diethylaminomethylphenol and the appropriate 4-chloro-7-haloquinoline. The 4-chloro-7-haloquinolines were prepared by the method of Price and Roberts[7] starting with the *m*-haloaniline and ethoxymethylenemalonic ester. The intermediate 4-hydroxy-7-haloquinolines and 4-chloro-7-haloquinolines have also been prepared by Surrey and Hammer[6] by another method. The melting points reported by these authors do not agree in certain cases with those found in this work.

Experimental[11]

3-Carbethoxy-4-hydroxy-7-bromoquinoline.—The intermediate ethyl α-carbethoxy-β-*m*-bromoanilinoacrylate was obtained in 40% yield (45 g.) by allowing a mixture of 50 g. of *m*-bromoaniline[12] and 63 g. of ethoxymethylenemalonic ester[13] to stand overnight. The resulting solid mass was twice recrystallized from a 1:1 solution of ether and ligroin; white needles, m. p. 70–71°. This material, 40 g., was cyclized by refluxing in diphenyl ether according to Price and Roberts.[7] After recrystallization from diphenyl ether, followed by thorough washing with diethyl ether, there was obtained a 44% yield (15 g.) of 3-carbethoxy-4-hydroxy-7-bromoquinoline as a white powder, m. p. 307–309°.

Anal. Calcd. for $C_{12}H_{10}O_3NBr$: C, 48.65; H, 3.38. Found: C, 48.74; H, 3.54.

3-Carbethoxy-4-hydroxy-7-iodoquinoline.—The intermediate ethyl α-carbethoxy-β-*m*-iodoanilinoacrylate was obtained in 43% yield (78 g.) by allowing a mixture of 90 g. of *m*-iodoaniline[12] and 89 g. of ethoxymethylenemalonic ester to stand overnight. The resulting solid mass was recrystallized once from acetone and once from a 1:1 solution of ether and ligroin; white needles, m. p. 92–93°. The product, 70 g., was cyclized and purified as in the above case. There was obtained a 45% yield (28 g.) of 3-carbethoxy-4-hydroxy-7-iodoquinoline as a white powder, m. p. 302–304°.

Anal. Calcd. for $C_{12}H_{10}O_3NI$: C, 42.00; H, 2.92. Found: C, 42.44; H, 3.17.

4-Hydroxy-7-bromoquinoline.—The intermediate 4-hydroxy-7-bromoquinoline-3-carboxylic acid was obtained in 70% yield (8 g.) by the hydrolysis of 13 g. of the 3-carbethoxy-4-hydroxy-7-bromoquinoline with 5% sodium hydroxide solution according to the method of Price and Roberts[7]; light yellow powder, m. p. 266° dec. The decarboxylation of 7 g. of this material was carried out by heating at 300° until the evolution of carbon dioxide ceased. The resulting crystalline cake was recrystallized from 95% ethanol giving 4 g. (68%) of 4-hydroxy-7-bromoquinoline as light tan crystals, m. p. 289–291° (lit.[6] 279–281°).

Anal. Calcd. for C_9H_6ONBr: C, 48.20; H, 2.68. Found: C, 48.01; H, 2.76.

4-Hydroxy-7-iodoquinoline.—The intermediate 4-hydroxy-7-iodoquinoline-3-carboxylic acid was obtained in 66% yield (15 g.) by the hydrolysis of 25 g. of the 3-carbethoxy-4-hydroxy-7-iodoquinoline with 5% sodium hydroxide solution; light grey powder, m. p. 263° dec. The

(1) Taken in part from a thesis submitted by Edward A. Conroy to The Pennsylvania State College in partial fulfillment of the requirements for the Ph.D. degree.

(2) Present address: American Cyanamid Company, Calco Division, Bound Brook, New Jersey.

(3) Present address: Department of Chemistry, Stanford University, Stanford, California.

(4) Deceased.

(5) Andersag, Breitner and Jung, U. S. Patent 2,333,970, *C. A.*, **35**, 3771 (1941); German Patent 683,692, *Chem. Zentr.*, **110**, II, 2446 (1939).

(6) Surrey and Hammer, THIS JOURNAL, **68**, 115 (1946).

(7) Price and Roberts, *ibid.*, **68**, 1206 (1946).

(8) Burckhalter, *et al.*, U. S. Patent 2,419,199, *C. A.*, **41**, 4815 (1947).

(9) Burckhalter, *et al.*, presented before the Medicinal Section of the American Chemical Society, April 9, 1946.

(10) The Survey Number, designated SN, serves to identify a drug in the Monograph "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, editor, Edwards Brothers, Ann Arbor, Mich., 1946.

(11) All melting points are uncorrected. Analyses by Arlington Laboratories, Fairfax, Virginia.

(12) Winans, THIS JOURNAL, **61**, 3564 (1939).

(13) Fuson, Parham and Reed, *J. Org. Chem.*, **11**, 194 (1946).

decarboxylation of 13 g. of this material was carried out by heating at 330° until the evolution of carbon dioxide ceased. The resulting crude 4-hydroxy-7-iodoquinoline was recrystallized from 50% ethanol; 6 g. (54%) of light yellow powder, m. p. 306–308° (lit.[6] 346–348°).

Anal. Calcd. for C_9H_6ONI: C, 39.85; H, 2.22. Found: C, 40.31; H, 2.55.

4-Chloro-7-bromoquinoline.—Three grams of the 4-hydroxy-7-bromoquinoline was converted to 4-chloro-7-bromoquinoline by treatment with phosphorus oxychloride essentially as described by Surrey and Hammer.[6] After recrystallization from 95% ethanol there was obtained a 61% yield (2.0 g.) of the 4-chloro-7-bromoquinoline as white crystals, m. p. 105–106° (lit.[6] 100.5–101.5°).

Anal. Calcd. for C_9H_5NClBr: C, 44.50; H, 2.06. Found: C, 44.76; H, 2.35.

4-Chloro-7-iodoquinoline.—This was obtained in an analogous manner from 4 g. of 4-hydroxy-7-iodoquinoline. Recrystallization from 75% ethanol gave a 35% yield (1.5 g.) of light yellow crystals, m. p. 101–102° (lit.[5] 101°; lit.[6] 95.5–97°).

4-(7-Bromo-4-quinolylamino)-2-diethylaminomethylphenol.—The hydrolysis of 35.4 g. of 2-diethylaminomethyl-4-acetylaminophenol[14] was accomplished by refluxing for two hours with 300 ml. of 6 *N* hydrochloric acid. The *p*H of the solution was adjusted to approximately 3 with 105 ml. of a 40% sodium hydroxide solution. To 250 ml. of this solution was added 22 g. of 4-chloro-7-bromoquinoline and the reaction mixture was refluxed for three and one-half hours according to the method of Burckhalter and co-workers.[8,15] The viscous oil which separated was removed, dissolved in methanol, and reprecipitated by dilution with dilute ammonia solution. The product, after twice recrystallizing from a 1:1 solution of 95% ethanol and acetone, was obtained in 55% yield (20 g.) as a light yellow powder, m. p. 206–208° dec.

Anal. Calcd. for $C_{20}H_{22}ON_3Br$: C, 60.00; H, 5.50. Found: C, 59.96; H, 5.73.

4-(7-Iodo-4-quinolylamino)-2-diethylaminomethylphenol.—This was prepared and purified in a similar manner from 16 g. of 4-chloro-7-iodoquinoline; 49% yield (12 g.), light yellow powder, m. p. 196–198° dec.

Anal. Calcd. for $C_{20}H_{22}ON_3I$: C, 53.70; H, 4.92. Found: C, 54.18; H, 5.16.

Acknowledgment.—The authors are indebted to Parke, Davis and Company, Detroit, Michigan, for financial assistance.

(14) Supplied by Parke, Davis and Company.

(15) Burckhalter, *et al.*, THIS JOURNAL, **70**, 1363 (1948).

DEPARTMENT OF CHEMISTRY
SCHOOL OF CHEMISTRY AND PHYSICS
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNSYLVANIA RECEIVED MAY 5, 1949

N-(Hydroxylethylmethylaminoethyl)-phenothiazine SC 1923: a New Antihistaminic

BY JOHN W. CUSIC

Many derivatives of phenothiazine have recently been made and studied for their anti-histaminic properties.

The 8-chlorotheophyllin salt of N-(dimethylaminoethyl)-phenothiazine was made by the author and tried clinically by Gay and Carliner.[1] Halpern[2] has reported extensively on several phenothiazines and recently N-pyrrolidylethylphenothiazine has been reported by Hunter, *et al.*[3]

(1) Gay, *etc.*, *Bull. Johns Hopkins Hosp.*, **83**, 356 (1948).

(2) Halpern, *Compt. rend. soc. biol.*, **140**, 361, 363 (1946).

(3) Hunter, *et al.*, THIS JOURNAL, **70**, 3100 (1948).

N-(Hydroxylethylmethylaminoethyl)-phenothiazine (SC 1923) has been prepared by the reaction of N-methylethanolamine with N-(β-chloroethylphenothiazine).[4] Its hydrochloride melted at 185–186°. *Anal.* Calcd. for $C_{17}H_{21}N_2SOCl$; S, 9.52. Found: S, 9.62. The methobromide melted at 154–155°. *Anal.* Calcd. for $C_{18}H_{23}N_2SOBr$; Br, 20.21; S, 8.11. Found: Br, 20.24; S, 8.02.

When tested by Dr. Homer Freese of our Pharmacology Department according to the histamine spray technic of Loew[5] SC 1923 had an ED_{50} = 0.43 ± 0.15 mg./kg. as compared to an ED_{50} of 0.66 ± 0.13 mg./kg. for β-dimethylaminoethylbenzhydryl ether.

Its effect on the mammalian capillary bed has been studied by Haley.[6]

(4) Gilman, THIS JOURNAL, **66**, 888 (1944).

(5) Loew, *etc.*, *J. Pharm. and Exper. Therap.*, **83**, 120 (1945).

(6) Haley and Harris, *ibid.*, **95**, 293 (1949).

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Non-exchange of Sulfur between Carbon Disulfide and Hydrogen Sulfide in Benzene Solution

BY DAVID L. DOUGLAS, ROBERT A. COOLEY AND DON M. YOST

The recent communication of Edwards, *et al.*,[1] in which they mention a study of the exchange of $S^{=35}$ in aqueous solution with carbon disulfide as a separate phase, prompts us to report some work done in this laboratory in 1941. We undertook the investigation of the exchange of S^{35} between H_2S^{35} and carbon disulfide in benzene solution. Our experiments, detailed in Table I, showed that no exchange greater than the experimental error (1%) occurs between carbon disulfide and hydrogen sulfide in benzene solution after ninety-five hours at 120°.

TABLE I

THE NON-EXCHANGE BETWEEN CARBON DISULFIDE AND HYDROGEN SULFIDE IN BENZENE SOLUTION[2]

Temp., °C.	Time of exchange, hr.	Concns. of reactants, moles/liter × 10^3 H_2S	CS_2	Observed activity, counts/min. H_2S	CS_2	% exchange, max.
97	1	4.2	108	411 ± 3	0 ± 1	0.3
120	95	4.2	108	178 ± 1	0 ± 2	.8
120	95	4.2	108	181 ± 1	0 ± 1	.3

Experimental.—The source of the active sulfur and the counting technique are described in a previous paper.[3] A CS_2–C_6H_6 solution was made up by weighing out reagent grade carbon disulfide and mixing it with reagent benzene in a volumetric flask. The H_2S^{35}–C_6H_6 solution was prepared and analyzed by standard methods.

In a typical experiment 1 ml. of each of the two solutions were pipetted into a glass bulb of 5–10 ml. capacity. This was immediately immersed in liquid air and sealed off. The bulb was then placed in boiling water or a thermostated oven for a measured period of time. On completion of the run the hydrogen sulfide was trapped in 1 *N* sodium hydroxide and precipitated as silver sulfide. The carbon disulfide in the benzene was separated as potassium xanthate and precipitated as copper xanthate. The

(1) R. R. Edwards, F. Nesbitt and A. K. Solomon, THIS JOURNAL, **70**, 1670 (1948).

(2) Ph.D. Thesis, R. A. Cooley, 1941, Cal. Tech.

(3) R. A. Cooley and D. M. Yost, THIS JOURNAL, **62**, 2474 (1940).

method is described by E. S. Johnson[4] and Harding and Doran.[5] The activities of the precipitates were measured, no account being taken of differences in self absorption or back scattering. Multiplying the total measured activity for a run by the ratio of the equivalents of sulfur in the carbon disulfide to the total equivalents gave the expected activity. The ratio of the activity observed in the copper xanthate to that expected gave the "% exchange."

(4) E. S. Johnson, THIS JOURNAL, **28**, 1209 (1906).
(5) Harding and Doran, *ibid.*, **29**, 1476 (1907).

CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA 4, CALIF. RECEIVED APRIL 30, 1949

The Exchange between Br_2^* and $HgBr_2$ in Carbon Disulfide Solution

BY DAVID L. DOUGLAS, ROBERT A. COOLEY AND DON M. YOST

The exchange of bromine atoms between bromine and various inorganic bromides has been previously reported.[1-3] In view of the lack of published quantitative data and because of the general usefulness of the reaction in preparing samples of pure radioactive bromine, we are reporting some work done in this Laboratory in 1941. A study was made of the exchange of Br^{82} atoms between Br_2^* and $HgBr_2$ in carbon disulfide solution. The results of six experiments showed that the exchange is complete within at least two and one-half minutes at somewhat less than 0°. Table I contains the details of the experiments and results.

TABLE I

EXCHANGE OF BROMINE BETWEEN MERCURIC BROMIDE AND BROMINE IN CARBON DISULFIDE AT 0°[4]

Reaction time, sec.	Concentrations in moles/liter × 10^3 Br_2	$HgBr_2$	Measured activity (cor.) Br_2	$HgBr_2$	Fraction of Br_2 actually measured	Exchange, %
245	6.82	1.67	1136 ± 10	274 ± 2	1.00	99 ± 2
266	6.82	1.67	992 ± 8	362 ± 3	0.854	121 ± 2
324	1.34	1.67	82 ± 1	252 ± 6	.406	100 ± 3
290	1.34	1.67	130 ± 1	250 ± 5	.650	100 ± 3
245	6.26	1.67	3066 ± 18	1160 ± 7	.666	96 ± 1
157	6.26	1.67	2863 ± 16	1318 ± 9	.593	102 ± 1

Experimental.—Radioactive bromine was prepared in the usual manner by irradiating *n*-butyl bromide with neutrons from a Rn–Be source. A solution of the active bromine in reagent carbon disulfide was prepared and analyzed by standard methods. The mercuric bromide solution was prepared by weighing out the pure solid into a known volume of carbon disulfide.

The actual exchange reaction and separation were carried out as follows: 5 ml. of the solutions of Br_2^* and $HgBr_2$, cooled to 0°, were pipetted into a 250-ml. distilling flask which was surrounded by an ice-bath. As soon as the solutions were mixed thoroughly the bromine and carbon disulfide were distilled off in a vacuum and collected in a trap at −78°. The time elapsed from the moment of mixing to the completion of the distillation is recorded in column 1 of Table I. Clearly the temperature dropped below 0° during this time; however, no attempt was made to measure this drop.

The bromine was reduced and precipitated as silver bromide. The mercuric bromide residue in the flask was dissolved in nitric acid and the bromine precipitated as silver bromide. The activities of the precipitates were measured by counting techniques. Determination of the fraction of the bromine which was actually trapped was accomplished by analyzing the silver bromide precipitate.

The activities were corrected for time of measurement and background—the short lived activity being allowed to decrease to a negligible value before use. The "% exchange" was calculated thus

$$\%\ \text{exchange} = \frac{\text{Activity from } HgBr_2}{\text{Fraction of } Br_2 \text{ measured}} \times \frac{100}{\text{Mole fraction } Br_2 \text{ in } HgBr_2\text{–}Br_2 \times \text{Sum of activities}}$$

(1) J. N. Wilson and R. G. Dickinson, THIS JOURNAL, **61**, 3519 (1939).
(2) Kolthoff and O'Brien, *J. Chem. Phys.*, **7**, 401 (1939).
(3) R. Muxart, *Compt. rend.*, **224**, 1107 (1947).
(4) R. A. Cooley, Ph.D. Thesis, Cal. Tech., 1941.

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p-Chloro-α-(trichloromethyl)-benzyl Alcohol and a Chlorination Apparatus

BY EDWARD M. FRY

At the time the insecticidal value of 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)-ethane became evident very little was known of its toxicology and as part of a program aimed at evaluating these properties a synthesis designed to utilize isotopic carbon at the point of attachment of the two chlorophenyl rings was undertaken. However, rapid and widespread use of DDT soon revealed its low toxicity with respect to humans and the project was discontinued, the synthesis being halted at *p*-chloro-α-(trichloromethyl)-benzyl alcohol. Carbon dioxide containing isotopic carbon was not used in this investigation and as none of the intermediate compounds are new, nor were any new or improved synthetic procedures used, the work is of interest only with respect to the method used with brief mention of experimental conditions. The scheme is as follows

$$ClC_6H_4MgBr \xrightarrow{CO_2} ClC_6H_4COOH \xrightarrow[90\%]{\substack{(1)\ SOCl_2 \\ (2)\ CH_2N_2 \\ (3)\ HCl}} ClC_6H_4COCH_2Cl \xrightarrow[125^\circ]{Cl_2} ClC_6H_4COCCl_3 \xrightarrow{Al(i\text{-}PrO)_3}$$

88% 93%

$ClC_6H_4CHOHCCl_3$

95% (70% from $BaCO_3$)

Carbon dioxide generated from barium carbonate reacted in a threefold excess of 1 *N* Grignard reagent to give the acid. The acid chloride in benzene solution reacted with cold ethereal diazomethane, then in the cold with dry hydrogen chloride to give *p*,α-dichloroacetophenone. The ketone in an equal volume of trichloroacetic acid on treatment with chlorine for two days at 120–125° gave *p*,α,α,α-tetrachloroacetophenone which, on reduction with a small excess of 3 *N* aluminum isopropoxide in isopropyl alcohol, gave the alcohol.

Chlorobenzoic acid has been prepared in the above manner,[1] and also from the corresponding lithium compound.[2] p,α-Dichloroacetophenone has been made by the action of chlorine on p-chloroacetophenone,[3] and by the action of chloroacetyl chloride on chlorobenzene.[4] p,α,α,α-Tetrachloroacetophenone has been made by the action of chlorine on p,α,α-trichloroacetophenone,[3] and p-chloro-α-(trichloromethyl)-benzyl alcohol by the condensation of chloroform with p-chlorobenzaldehyde.[5] This alcohol was also found to be a constituent of technical DDT.[6]

The apparatus described below was constructed so that the effect of solvent, temperature and light on chlorine reactions could be followed manometrically. Circulation of the gas is required for the removal of hydrogen chloride, and the corrosive action of moist chlorine makes a glass apparatus necessary. Circulation is achieved by means of an aspirator actuated by a stream of carbon tetrachloride–water which also serves to remove hydrogen chloride. The diagram shows the aspirator unit on the left, the reaction flask with a small condenser in the center, and the chlorine reservoir on the right. Movement of chlorine is in a clockwise direction and its absorption is followed by means of a manometer shown at the center hole of the reservoir stopper. The device proved a valuable index to the rate of chlorination under varying conditions and gave an estimate of the amount reacted. Sources of error are diluents such as air and gaseous decomposition products.

Construction and Operation.—Although a single five-gallon bottle is shown as the reservoir, more than one connected in series may be more convenient. The rubber stopper was substantially unaffected after several months in contact with chlorine. Chlorine is appreciably soluble in the carbon tetrachloride–water mixture used in the aspirator unit, and when the aspirator is shut off its pressure must be high enough so that its subsequent absorption by the cooling carbon tetrachloride–water does not result in manometer water being sucked into the reservoir. The manometer is long enough to measure a pressure of about 80 cm. of water. Chlorine should be added only when the aspirator flask is hot. Otherwise expulsion of chlorine from the hot carbon tetrachloride–water might cause such an increase in pressure as to blow the water from the manometer and release chlorine into the room. A drop in atmospheric pressure or a rise in room temperature can have the same effect if the apparatus is operated too closely to the pressure limit of the manometer. Changes of this nature during a run are observed and corrected for by means of a blank manometer (not shown). If dry chlorine is desired, calcium chloride is used to fill the enlarged portion of tubing extending to the bottom of the bottle.

To fill the apparatus, flask A, equipped with an electric heating jacket and containing carbon tetrachloride and water, is heated until its contents begin to boil. Chlorine is then slowly admitted through stopcock E, stopcock D being turned so as to deflect the chlorine into the reservoir and allow the displaced air to escape into the hood. The displacement of air is followed visually and when completed stopcock D is turned to the illustrated position and the pressure in the system brought to the desired level. Stopcocks B and C are for the purpose of isolating the reaction flask so that it can be removed with negligible chlorine loss.

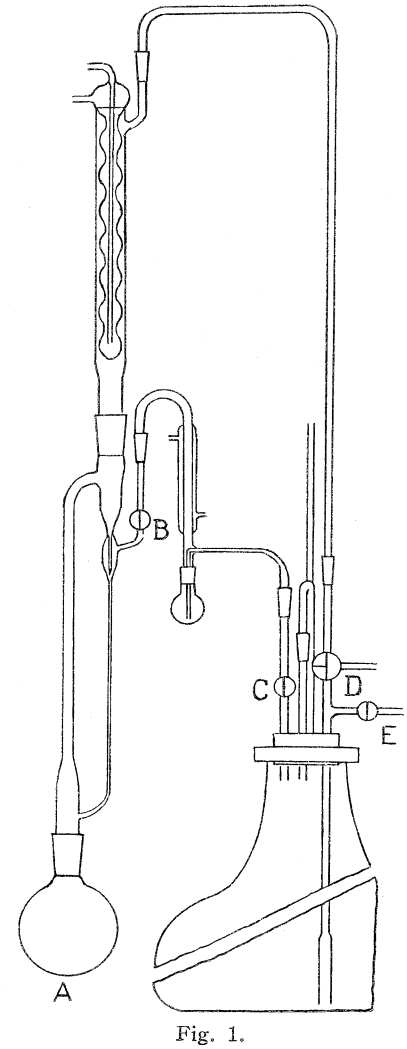

Fig. 1.

The various parts of the apparatus are connected with 24/40, 10/30, and 14/20 joints, lubricated with Dow-Corning silicone grease, and in the two smaller sizes held together with rubber bands secured between hooks (not shown). It is felt that ball-type joints would be more satisfactory than the 10/30 joints in that the apparatus could be allowed to stand unused for longer periods of time without danger of freezing at these relatively fragile junctures. The lubricant is slowly hardened by chlorine. The only construction feature requiring care is that of the aspirator unit. The tube should be symmetrically placed in the throat taper and about 1 mm. in diameter at the tip. Four mm. O. D. tubing was used for both the inner aspirator tube and for the discharge column which was found to operate best at a length of 20 cm., the range for satisfactory operation being between 15 and 25 cm. A rate of from 60–80 bubbles a minute against a head of 5 cm. of water was realized and the efficiency of the aspirator appears to be greatest with a moderate rate of reflux.

LABORATORY OF PHYSICAL BIOLOGY
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RECEIVED APRIL 27, 1949

(1) Bodroux, *Compt. rend.*, **137**, 711 (1903).
(2) Gilman, Langham and Moore, THIS JOURNAL, **62**, 2327 (1940).
(3) Gautier, *Ann. chim. phys.*, [6] **14**, 337–404 (1888).
(4) Collet, *Compt. rend.*, **125**, 718 (1897).
(5) Howard, THIS JOURNAL, **57**, 2317 (1935).
(6) Haller, *et al.*, *ibid.*, 1591 (1945).

The Reaction between Carboxylic Acid Chlorides and Salts of *p*-Toluenesulfinic Acid

BY H. T. HOOKWAY

During the course of an investigation of a series of α-methylene sulfones[1] it was found desirable to attempt the synthesis of α-ketosulfones, and an examination was made of the reaction between carboxylic acid chlorides and salts of *p*-toluenesulfinic acid.

By analogy with the reaction between *p*-toluenesulfonyl chloride and sodium *p*-toluenesulfinate to give an α-disulfone,[2] the reaction between benzoyl chloride and sodium *p*-toluenesulfinate was expected to follow the course shown below

$$C_6H_5COCl + C_7H_7SO_2Na = C_6H_5COSO_2C_7H_7 + NaCl$$

Ethereal solutions of benzoyl and acetyl chlorides respectively were heated under pressure with sodium *p*-toluenesulfinate dihydrate and in both cases the products isolated were the corresponding carboxylic acids and di-*p*-tolyl disulfoxide (shown to be a thiolsulfonate, $C_7H_7SO_2SC_7H_7$[3,4]; no trace of a ketosulfone could be detected.

Since it does not appear possible to dehydrate sodium *p*-toluenesulfinate dihydrate without decomposition, this salt was used in the two experiments described above: presumably the acid chloride was first hydrolyzed to carboxylic acid and hydrochloric acid; the latter then liberated free *p*-toluenesulfinic acid which forms di-*p*-tolyl disulfoxide on heating alone or, more readily in the presence of aqueous acids[5,6]

$$C_7H_7SO_2H + C_7H_7SO_3H + C_7H_7SO_2SC_7H_7$$

p-Nitrobenzoyl chloride was then heated with sodium *p*-toluenesulfinate: it was anticipated that this chloride, containing a strongly electron attractive nitro-group, would be more resistant to hydrolysis under the conditions obtaining in these experiments than either acetyl or benzoyl chlorides. Again, no ketosulfone was obtained, but a small amount of disulfoxide was isolated.

An attempt was made to avoid the use of a hydrated salt by preparing silver *p*-toluenesulfinate. This salt is stated to be anhydrous when obtained by precipitation by addition of silver nitrate to an aqueous solution of the sodium sulfinate.[7] The analysis of the silver salt used in these experiments indicated that it still contained a small amount of water. When the silver salt and benzoyl chloride were heated together in ether, di-*p*-tolyl disulfoxide was obtained.

It is interesting to note Kohler and MacDonald claimed that by heating an ethereal solution of benzoyl chloride with sodium *p*-toluenesulfinate an α-ketosulfone was obtained as an ether soluble oil which readily gave a solid hydrate on trituration with water[2]

$$C_6H_5COCl + C_7H_7SO_2Na = C_6H_5COSO_2C_7H_7 \xrightarrow{H_2O} C_7H_7C(OH)_2SO_2C_7H_7$$

A similar reaction was also stated to take place when other acid chlorides were used, but the properties of the reaction products were not described. It must also be noted that Kohler and MacDonald did not state whether they had prepared and used anhydrous sodium *p*-toluenesulfinate or a hydrated material in their experiments. These authors stated that their products gave crystalline derivatives with typical ketone reagents, such as hydroxylamine and phenylhydrazine. Reaction of di-*p*-tolyl disulfoxide with 2,4-dinitrophenylhydrazine in methanolic sulfuric acid, under conditions such that a ketone gives the corresponding dinitrophenylhydrazone, gave only unchanged disulfoxide. When di-*p*-tolyl disulfoxide was warmed with hydroxylamine in an acetic acid–sodium acetate buffer, however, amongst other products, di-*p*-tolyl disulfide was obtained. A similar breakdown of the disulfoxide was observed with phenylhydrazine in buffered solution: these observations will be the subject of a further communication.

Acknowledgment.—The author wishes to express his indebtedness to Dr. J. Kenyon, F.R.S., for his interest in this work.

Experimental

Reaction between Sodium *p*-Toluenesulfinate and Benzoyl Chloride.—Sodium *p*-toluenesulfinate dihydrate (4.0 g., 0.019 mole) was suspended in ether (10 cc.) in a stout walled glass tube and benzoyl chloride (3.0 g., 0.021 mole) was added. The tube was then sealed and heated at 100° for thirty-six hours. After cooling, the contents of the tube were extracted with sodium carbonate solution (25 cc. of 3 *N*); the residual ethereal solution after drying and evaporation to small bulk gave di-*p*-tolyl disulfoxide; yield, 1.0 g., m. p. 78.5–79° (after three recrystallizations from 96% ethanol). Found: C, 60.6; H, 4.7; S, 22.6. Calcd. for $C_{14}H_{14}O_2S_2$: C, 60.5; H, 5.04; S, 23.0. Mixed m. p. with authentic specimen of di-*p*-tolyldisulfoxide[8] 78.5°. The alkaline extract on acidification gave 2.5 g. of benzoic acid, m. p. 122° (theoretical yield from hydrolysis of benzoyl chloride, 2.6 g.).

Reaction between Sodium *p*-Toluenesulfinate and Acetyl Chloride.—Sodium *p*-toluenesulfinate dihydrate (2.0 g., 0.009 mole) was suspended in ether (10 cc.) in a stout walled glass tube and acetyl chloride (0.84 g., 0.011 mole) was added. The tube was then sealed and heated at 100° for thirty-six hours. The reaction mixture was worked up as described in the previous experiment; yield of di-*p*-tolyl disulfoxide, 0.97 g., m. p. 78.5–79°; mixed m. p. with authentic specimen, 78°.

Reaction between Sodium *p*-Toluenesulfinate and *p*-Nitrobenzoyl Chloride.—Sodium *p*-toluenesulfinate dihydrate (8.0 g., 0.037 mole) was suspended in ether (100 cc.) in a stout-walled glass bottle and *p*-nitrobenzoyl chloride (6.92 g., 0.037 mole) was added. The reaction mixture was heated at 100° for twelve hours and gave 1.57 g. of di-*p*-tolyl disulfoxide, m. p. 78°, on working up.

(1) To be published shortly.
(2) Kohler and MacDonald, *Am. Chem. J.*, **22**, 219 (1899).
(3) Gilman, *et al.*, THIS JOURNAL, **47**, 851 (1925).
(4) Miller and Smiles, *J. Chem. Soc.*, **127**, 224 (1925).
(5) Otto, *Ber.*, **15**, 121 (1882).
(6) Smiles and Gibson, *J. Chem. Soc.*, **125**, 180 (1924).
(7) Otto, *Ann.*, **142**, 97 (1867).
(8) Prepared by the method of Smiles and Gibson, ref. 6.

Reaction between Silver *p*-Toluenesulfinate and Benzoyl Chloride.—Silver *p*-toluenesulfinate was prepared from the sodium salt and silver nitrate by precipitation from aqueous solution. The precipitated silver salt was washed with water and acetone and air dried. Found: Ag, 39.9. Calcd. for $C_7H_7O_2SAg$: Ag, 41. The silver salt (2.00 g., 0.0076 mole) was suspended in ether (20 cc. of sodium dried) in a stout-walled glass tube and benzoyl chloride (1.07 g., 0.0076 mole) was added. The tube was then sealed and heated at 100° for twelve hours. The reaction mixture yielded 0.2 g. of di-*p*-tolyl disulfoxide, m. p. 78°. All m. p.'s are uncorrected. Kohler and MacDonald quote 80° as m. p. for the keto-hydrate $C_{14}H_{14}O_4S$.

DEPARTMENT OF CHEMISTRY
BATTERSEA POLYTECHNIC
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RECEIVED NOVEMBER 29, 1948

The Influence of Substituents on the Ultraviolet Absorption Spectrum of Styrene

BY Y. HIRSCHBERG

In view of the recent paper by Murray and Gallaway,[1] the following measurements on the spectra of some substituted (ortho-, alpha- and beta-positions) styrenes may be recorded (alcohol as solvent).

Hydrocarbon	Max., Å.	Log ε	Max., Å.	Log ε	Max., Å.	Log ε	Max., Å.	Log ε
Styrene	2910	2.77	2820	2.88	2730	2.88	2440	4.23
β-Methylstyrene[a,b]	2930	2.84	2840	2.99			2460	4.25
α-Methylstyrene[a]							2435	3.96
α,β-Dimethylstyrene							2440	3.94
o-Methylstyrene[c]	2980	2.03					2460	3.36
o,α-Dimethylstyrene[d,e]	No maximum between 2100–3000 Å.							

[a] Ramart-Lucas and Amagat, *Bull. soc. chim.*, [4] **51**, 108 (1932); [5] **1**, 719 (1934). [b] Hillmer and Schorning, *Z. physik. Chem.*, **A167**, 407 (1934). [c] Ramart-Lucas and Hoch, *Bull. soc. chim.*, [5] **2**, 327 (1935). [d] Ref. (1). [e] Ramart-Lucas and Hoch, *Bull. soc. chim.*, [5] **5**, 848 (1938). [f] Campbell and co-workers, THIS JOURNAL, **69**, 880 (1947).

Introduction of a methyl group into the β-position of styrene has very little influence on the resonating system, whilst α-substitution, and to a minor degree *o*-substitution,[2] destroys the resonance. This is particularly clear for the *o*,α-dimethylstyrene for which no absorption maximum at all has been observed. It is reasonable to assume that the phenyl group is crowded out of the plane of the exocyclic double bond, and the monoplanarity required is thus destroyed.[2]

Materials

α-Methylstyrene was prepared according to Staudinger and Breusch,[3] the β-isomer from ethylphenylcarbinol with acetic anhydride, according to Spaeth and Koller.[4] For the synthesis of α,β-dimethylstyrene,[5] acetophenone was converted by reaction with ethylmagnesium bromide into phenylmethylethylcarbinol and the crude product dehydrated with boiling acetic anhydride: b. p. 107–109° (21 mm.); yield 75.5%. *o*-Methylstyrene was obtained by reaction of *o*-tolylmagnesium bromide with acetaldehyde and adding the carbinol obtained (b. p. 120–130° (29 mm.)) dropwise to molten potassium hydrogen sulfate, containing 1% of hydroquinone, at a bath temperature of 200° and in a vacuum of 100 mm.[6] The product which distilled off immediately, was fractionated, b. p. 75–78° (21 mm.).[7] Analogous reaction of *o*-tolylmagnesium bromide with *acetone* gave *o*-tolyldimethylcarbinol, b. p. 120–122° (25 mm.) and dehydration of the latter with boiling acetic anhydride, *o*,α-dimethylstyrene, b. p. 83–85° (25 mm.) in 70% yield.[8]

(1) Murray and Gallaway, THIS JOURNAL, **70**, 3867 (1948).

(2) Compare, Buck, Kennedy, Morton and Tanner, *Nature*, **162**, 103 (1948), and the dipole measurements of Everard and Sutton, *ibid.*, **162**, 104 (1948).

(3) Staudinger and Breusch, *Ber.*, **62**, 449 (1929).

(4) Spaeth and Koller, *ibid.*, **58**, 1268 (1925).

(5) Klages, *ibid.*, **35**, 2641 (1902).

(6) Brooks, THIS JOURNAL, **66**, 1295 (1944).

(7) Eisenlohr and Schulz, *Ber.*, **57**, 1816 (1924); b. p. 170–174° at atmospheric pressure.

(8) Eisenlohr and Schulz, *loc. cit.*, b. p. 183–185° at atmospheric pressure.

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The Behavior of 1-Naphthyl Tetraacetyl-β-D-glucoside toward Diazotized *p*-Nitroaniline

BY CHARLES D. HURD AND WILLIAM A. BONNER

This note describes attempts to couple 1-naphthyl tetraacetyl-β-D-glucopyranoside (I) with diazo compounds. The ease of coupling should compare with that of 1-methoxynaphthalene.

Meyer and Lenhardt[1] record difficulty in coupling diazotized *p*-nitroaniline with anisole but claim that 4-(*p*-nitrophenylazo)-1-methoxynaphthalene, m. p. 169°, is formed on coupling with 1-methoxynaphthalene.

Attempts to couple (I) with aqueous solutions of diazotized *p*-nitroaniline led to difficulties caused by the insolubility of the acetylated glucoside. When a solution of *p*-nitrobenzenediazonium sulfate was prepared in glacial acetic acid after the manner of Hodgson and Walker[2] and mixed with a solution of the acetylated glucoside in acetic acid, a slight color developed. In the course of several days, however, this mixture assumed the intense purple coloration characteristic of control experiments with 1-methoxynaphthalene. The only product found was 4-(*p*-nitrophenylazo)-1-naphthol in 22% yield, showing cleavage as well as coupling. About half of the starting glucoside was recovered. It has frequently been observed[3] that phenolic ethers couple with partial or complete dealkylation.

In view of this result we studied 1-methoxynaphthalene under approximately identical con-

(1) Meyer and Lenhardt, *Ann.*, **398**, 78 (1913).

(2) Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

(3) K. H. Saunders, "The Aromatic Diazo Compounds," Edward Arnold and Co., London, 1936, p. 112.

ditions. Here too, coupling took place with substantial cleavage of the ether. We were also unable to duplicate the results of Meyer and Lenhardt[1] using their 50% aqueous acetic acid solution. Coupling again was accompanied by demethylation, an observation which is in line with that of Jambuserwala and Mason[4] who found that 2-methoxy-3-naphthoic acid coupled with diazotized *p*-nitroaniline with complete removal of methoxyl.

Since the above coupling was conducted under strongly acid conditions, it seemed advisable to duplicate the process under conditions whereby the acidity of the sulfuric acid was neutralized by sodium acetate. When the acetic acid solution of *p*-nitrobenzenediazonium sulfate and (I) stood in contact with sodium acetate for several days, a red product was obtained on dilution with water. This was separated by adsorption methods into an amber glass, a red solid, and 1,3-bis-*p*-nitrophenyltriazene. The first two substances were not characterized. While the evidence here neither indicated nor precluded complete cleavage, it is pertinent to note that 1-methoxynaphthalene coupled with cleavage under these same buffered conditions.

Experimental

Coupling of 1-Naphthyl Tetraacetyl-β-D-glucopyranoside with Diazotized *p*-Nitroaniline.—Finely powdered sodium nitrite (1.7 g.) was added to 12 ml. of cold sulfuric acid. The mixture, warmed to about 70°, was stirred until completely dissolved, then was cooled to 20°. *p*-Nitroaniline (3 g.) was dissolved in hot acetic acid (36 ml.), and the mixture was cooled rapidly to room temperature. This solution was added slowly with stirring to the first solution.

One gram of 1-naphthyl tetraacetyl-β-D-glucopyranoside was dissolved in 20 g. of acetic acid. Into this mixture (at 20°) was added 15 ml. of the above diazonium solution. A pink coloration appeared. After standing for forty hours, the solution became intensely purple. On pouring into water (300 ml.), an orange solid resulted which rapidly became gummy. Extraction with ether

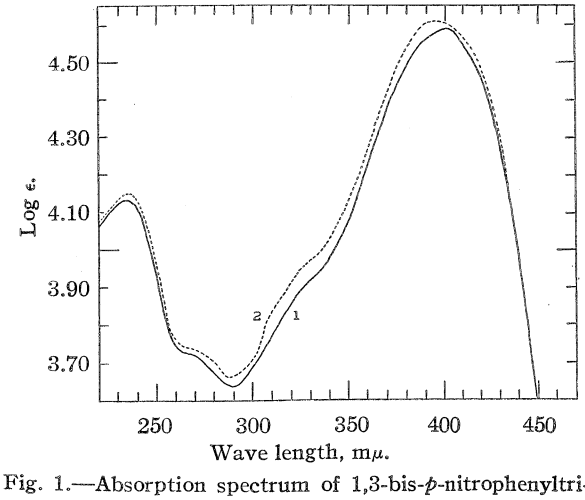

Fig. 1.—Absorption spectrum of 1,3-bis-*p*-nitrophenyltriazene: 1, known sample; 2, suspected sample.

(4) Jambuserwala and Mason, *J. Soc. Dyers Colourists*, **46**, 339 (1930).

(300 ml.) dissolved the gum but left a small amount of red solid which was filtered. The ether extract was washed with water and evaporated. The residue was redissolved in ether, and again a small amount of red solid remained undissolved. It was separated and combined with that above. The ether extract was dried over anhydrous sodium sulfate, filtered, and evaporated. There resulted 0.78 g. of reddish solid. This was recrystallized from 2-propanol to yield about 0.5 g. of the starting glucoside in slightly impure condition; m. p. 172–175°, mixed m. p. 175–177°.

The ether-insoluble red solids weighed 0.13 g. They were triturated with ether, air-dried, and found to melt at 275–278°. A mixed melting point of this material with 4-(*p*-nitrophenylazo)-1-naphthol (m. p. 284–285° (cor.)) gave the value 278–280°.

Attempts to couple 1-naphthyl tetraacetyl-β-D-glucoside with diazotized aniline or *p*-aminobenzoic acid under conditions comparable to those above led only to the isolation of starting material.

Several attempts were made to conduct the above coupling under well-buffered conditions. In a typical experiment 1-naphthyl tetraacetyl-β-D-glucoside (1.0 g.) in acetic acid (20 ml.) was treated with one-third (15 ml.) of the acetic acid solution of *p*-nitrobenzenediazonium sulfate prepared as described above. Anhydrous sodium acetate (12.3 g.) was added, the mixture shaken to an emulsion and permitted to stand for four days. The original yellow color became deep red, once the mixture was poured into water. The crude red solid was collected on a filter, suspended in water, collected again, and dried over phosphoric anhydride; yield, 1.80 g. Half a gram of this was dissolved in ethyl acetate (10 ml.) and ether (30 ml.). The red solution was filtered, and the filtrate was introduced into a column of alumina wet with ether. The absorbed band was developed with ether, but only a very thin orange band separated; this was not investigated. The effluent was evaporated to yield 0.19 g. of a reddish, amber glass, $[\alpha]^{25}D$ −48.5° (*c*, 1.90; chloroform). Attempts were made to crystallize this from 2-propanol, but only gummy crystals resulted. The main adsorbed band was extracted from the adsorbent in a Soxhlet thimble with ethyl acetate. Removal of the solvent left 0.22 g. of red solid. This was digested with methanol and filtered, leaving a gray-brown solid, m. p. 225–230° (dec.).

About 0.8 g. of the crude yield was digested twice with a total of 55 ml. of hot methanol, leaving 0.15 g. of orange solid, m. p. 228–229° (dec.). This was recrystallized from a mixture of acetone and water to give a yellow-gray solid, m. p. 229.5–230°(dec.). This was proven by melting point, mixed melting point, absorption spectrum (Fig. 1) and analysis to be 1,3-bis-*p*-nitrophenyltriazene.

Anal. Calcd. for $C_{12}H_9N_5O_4$: C, 50.2; H, 3.16; N, 24.4. Found: C, 49.62; H, 3.25; N, 24.56.

Coupling of 1-Methoxynaphthalene with Diazotized *p*-Nitroaniline.—1-Methoxynaphthalene (1 ml.) was dissolved in acetic acid (5 ml.) and sodium acetate (*ca.* 0.5 g.) was added. About 5 ml. of the non-aqueous diazo solution described above was added giving an immediate intense purple coloration. The homogeneous mixture was poured into water (100 ml.). A red product precipitated, which was collected on a filter and washed. A portion of the product was separated by means of its relative insolubility in hot ethanol. It was impure 4-(*p*-nitrophenylazo)-1-naphthol, m. p. 272–280°. The alcohol solution deposited solid on standing, m. p. around 120–125°. This was possibly a mixture of the previous high-melting solid plus the more soluble 4-(*p*-nitrophenylazo)-1-methoxynaphthalene of m. p. 169°.

The directions of Meyer and Lenhardt[5] for preparing *p*-nitrophenylazo-1-methoxynaphthalene are not specific, but it is stated that the coupling is carried out in 50% acetic acid. We attempted to duplicate these conditions by dissolving 1-methoxynaphthalene (1 ml.) in acetic acid (4 ml.) containing water (1 ml.) and adding this solution to a portion of the above diazo solution (3 ml.) diluted with water (13 ml.). A red solid formed instantly.

This proved quite insoluble in ethanol and was treated as above. The recrystallized portion melted at 277–282°, and the alcohol-insoluble portion had an indistinct m. p. above 280°.

In an attempt to encourage coupling without cleavage by buffering, 1-methoxynaphthalene (2 ml.) was treated with a mixture of 15 ml. of the non-aqueous diazo solution, 15 ml. of acetic acid, and 12.3 g. of anhydrous sodium acetate. After addition of more acetic acid (15 ml.), the red-black mixture was shaken thoroughly and poured into water. The red solid was filtered, rinsed, and washed by suspension in methanol and refiltration. The insoluble portion, when dry, melted at 275–280°.

1,3-bis-*p*-Nitrophenyltriazene.—The procedure used in this preparation was a modification of that of Meldola and Streatfield.[5] *p*-Nitroaniline (2.76 g., 0.02 mole) was dissolved with heating in concd. hydrochloric acid (50 ml.). The solution was cooled and a solution of sodium nitrite (0.69 g., 0.01 mole) in water (5 ml.) was slowly added dropwise with stirring. Water (20 ml.) was added to the mixture, which then stood for nineteen hours. The clear yellow solution was thrown into excess water, and on standing fine yellow needles formed. These were filtered and dried *in vacuo;* yield, 0.70 g., m. p. 224–228° (dec.). The mother liquors deposited a second crop, weight 0.05 g., m. p. 228–230° (dec.).

In order to establish without doubt the identity of this material and the product from the previous buffered coupling reaction involving the 1-naphthyl tetraacetyl-β-D-glucoside, absorption spectra of both samples were measured and found identical (Fig. 1). Solutions 10^{-3} molar in each sample were made for the measurements. In taking the readings, it soon became apparent that Beer's law was failing to apply. Thus at 440 mμ the 10^{-3} molar solution of each sample had a density reading on the Beckman Model DU Spectrophotometer of 1.84. A 10^{-4} molar solution at the same wave length had a density of 0.860 instead of 0.184. Similarly, at 410 mμ the density of the 10^{-4} molar solution was 1.800, while that of a 10^{-5} molar solution was 0.360. As the wave length region between 445 and 400 mμ was crossed, the density readings for 10^{-3} molar and 10^{-4} molar solutions approached constant values within the range of the spectrophotometer scale, and it was necessary to use 10^{-5} molar solutions in order to cover the lower visible and ultraviolet spectrum. These effects were observed on two different spectrophotometers. They are probably attributable to the ionization of dinitrodiazoaminobenzene in alcoholic solution, and are currently under more extensive study.

(5) Meldola and Streatfield, *J. Chem. Soc.*, **49**, 627 (1886).

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The Dissociation of Lead Chloride in Ethylene Glycol–Water Mixtures

BY J. C. JAMES

Norman and Garrett[1] have recently reported measurements of the conductance of lead chloride solutions at 25° in ethylene glycol–water mixtures, and conclude that activity and conductance data for such solutions show deviations from the Debye–Hückel and Onsager theories which cannot be accounted for by the assumption of incomplete dissociation. Discrepancies between theoretical and experimental values were attributed to differences between the macro and micro dielectric constants of the solutions, and "effective micro-dielectric constants" were calculated by comparison of experimental slopes with those predicted by the Debye–Hückel and Onsager theories.

These conclusions are surprising, as in aqueous solution previous workers[2–4] have assumed that the intermediate ion $PbCl^+$ was present, and have derived dissociation constants of the order of 0.02–0.03 from activity and conductance data; also, Fromherz and Kun-Hou Lih[5] have shown that the ultraviolet absorption spectra indicated presence of this ion. Similarly, conductance data for the salts zinc malonate, zinc sulfate and lanthanum ferricyanide in glycol–water mixtures have been accounted for satisfactorily by assuming dissociation to be incomplete.[6]

Norman and Garrett[1] have rejected this treatment on the grounds that as curves for the plots of both Λ *vs.* $\sqrt{m}$ and γ *vs.* $\sqrt{m}$ were straight in the lower concentration regions, a constant degree of dissociation would result in any solvent. Such behavior, however, does not necessarily imply complete dissociation, as the effect of actual variation in α may be cancelled out almost completely by the effect of higher terms neglected in the limiting Debye–Hückel and Onsager equations. Thus it has been shown by Davies[7] that dissociation is not complete in calcium mandelate solutions, although the Λ *vs.* $\sqrt{m}$ plot is linear up to $m = 0.02$, far beyond the limits of Onsager's equation. It is shown in this Note that the data of Norman and Garrett can be given an alternative explanation on the assumption that the intermediate ion $PbCl^+$ is formed in solution by the process $Pb^{++} + Cl^- \rightleftarrows PbCl^+$, further association to give the neutral salt being negligible.

Activity Data.—Dissociation constants for lead chloride in water at 25° have been calculated from the activity data of Carmody[8] using the method described by Davies,[9] and are given in Table I, γ being the stoichiometric activity coefficient, and f the true mean ionic activity coefficient. Dissociation constants in glycol–water mixtures have been calculated by the same method from the activity data of Garrett, Bryant and Kiefer,[10] up to concentrations of 0.006 N and are summarized in Table III. Mean ionic activity coefficients have been obtained from the empirical equation

$$-\log f = S\left[\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.20\,\mu\right]$$

where S is the limiting Debye–Hückel slope;

(1) J. W. Norman and A. B. Garrett, THIS JOURNAL, **69**, 110 (1947).

(2) E. C. Righellato and C. W. Davies, *Trans. Faraday Soc.*, **26**, 592 (1930).

(3) G. Scatchard and R. F. Teft, THIS JOURNAL, **52**, 2272 (1930).

(4) H. S. Harned and M. E. Fitzgerald, *ibid.*, **58**, 2624 (1936).

(5) H. Fromherz and Kun-Hou Lih, *Z. physik. Chem.*, **A153**, 321 (1931).

(6) J. C. James, unpublished work.

(7) C. W. Davies, *J. Chem. Soc.*, 271 (1938).

(8) W. R. Carmody, THIS JOURNAL, **51**, 2905 (1929).

(9) C. W. Davies, *J. Chem. Soc.*, 349 (1939).

(10) A. B. Garrett, R. Bryant and G. F. Kiefer, THIS JOURNAL, **65**, 1905 (1943).

this equation fits the data of Knight, Masi and Roesel[11] for the activity of hydrogen chloride in glycol–water mixtures to $\mu = 0.02$ with a maximum deviation of 2%, and is sufficiently accurate for the purpose. Molal quantities have been converted to molar quantities, assuming the densities of the solutions to be equal to those of the pure solvent mixtures.

TABLE I

$m \times 10^4$ (molality)	γ	f	K
3.3333	0.912	0.966	(0.016)
10.000	.847	.926	.019
20.000	.791	.888	.022
26.666	.764	.869	.023
33.333	.740	.850	.024
100.00	.604	.729	.025
200.00	.505	.619	.025
266.66	.464	.568	.024
308.67	.443	.542	.023

Conductance Data.—Dissociation constants have been calculated in water from the data of Norman and Garrett,[1] by the method of Righellato and Davies,[2] evaluating mobility terms from the empirical equations

$$[\Lambda (Pb^{++}) + \Lambda (Cl')] = \Lambda_0 - bf_{2-1}(\mu)$$

and

$$[\Lambda (PbCl^{+}) + \Lambda (Cl')] = \Lambda' - b'f_{1-1}(\mu)$$

where b, b' are the respective Onsager slopes. For $f_{1-1}(\mu)$ values have been given by Robinson and Davies,[12] and for $f_{2-1}(\mu)$ values were calculated from the data of Shedlovsky and Brown[13] for calcium and magnesium chlorides, which have been assumed to be completely ionized. The mobility of the intermediate ion $PbCl^+$ at zero concentration has been estimated as 45 at 25°, from the value used by Righellato and Davies[2] at 18°. Values for the ionization constant K were derived from the equation

$$\log K = \log \frac{\alpha(1+\alpha)}{(1-\alpha)} m - 2\left[\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.20\,\mu\right]$$

and are given in Table II.

TABLE II

$m \times 10^4$ (molarity)	α	K
4.5284	0.971	0.025
4.8136	.970	.026
5.9780	.964	.026
6.9169	.963	.028
11.930	.935	.026
24.020	.884	.025
27.646	.886	.028
49.688	.819	.026
53.523	.815	.028

In glycol–water mixtures, the values summarized in Table III have been calculated up to concentrations of 0.002 N, using the limiting forms of the Onsager and Debye–Hückel equations, and assuming that the transport numbers of the ions do not change with the change in solvent. Limiting conductance values have been re-extrapolated by the method of Onsager,[14] as the values given by Norman and Garrett were obtained by Kohlrausch's square-root method, which is known to give Λ_0 values that are too high for incompletely dissociated electrolytes.[15]

TABLE III

% Glycol (ω/ω)	Mean K (conductance data)	Mean K (activity data)
0	0.026	0.023
20	.023	.030
40	.025	.025
60	.012	.015
80	.0083	.0095
100	.0026	∞

Dissociation constants calculated for lead chloride in glycol–water mixtures from conductance and activity data are in good agreement except in 100% glycol, for which the anomalously high activity coefficients appear to indicate complete dissociation. (Similar discrepancies have been noted by Garrett and Vellenga[16] with thallium chloride at high glycol concentrations.)

The results are of interest as lead chloride is one of the few inorganic salts which have been studied in a binary solvent mixture over the entire range of composition. Moelwyn-Hughes[17] has applied the Wynne-Jones equation[18]

$$\left[\frac{\mathrm{d} \ln K}{\mathrm{d}\,(1/D)}\right]_{T,P,} = \frac{z_A z_B \epsilon^2}{rkT}$$

to dissociation constants calculated from conductance data for silver nitrate in various solvents, plotting ΔG as a function of $1/D$ and obtaining a straight line, from the slope of which a value for r the sum of the ionic radii, was found. Application of this procedure to the data for lead chloride gave a linear plot leading to the value $r = 5.6$ Å. For $K = 0.025$ in water, the Bjerrum equation,[19] however, gives a value of 1.85 Å. for r. The observed decrease in K with decrease in D is considerably less than is to be anticipated from this treatment, which predicts $K = 2.5 \times 10^{-5}$ in 100% glycol, assuming r to remain unchanged. From the abnormally low dissociation constant in water and from the ultraviolet absorption spectra of lead chloride solutions, it appears possible that the ionic interaction goes further than can be explained by Coulomb's law, and that in consequence the

(11) S. B. Knight, J. F. Masi and D. Roesel, THIS JOURNAL, **661**, 68 (1946).

(12) R. A. Robinson and C. W. Davies, *J. Chem. Soc.*, 574 (1937).

(13) T. Shedlovsky and A. S. Brown, THIS JOURNAL, **56**, 1069 (1943).

(14) L. Onsager, *Physik. Z.*, **28**, 277 (1927).

(15) C. W. Davies, *J. Chem. Soc.*, 645 (1933).

(16) A. B. Garrett and S. J. Vellenga, THIS JOURNAL, **225**, 67 (1945).

(17) E. A. Moelwyn-Hughes, "Kinetics of Reactions in Solution," 2nd Edition, Oxford University Press, 1947, p. 198.

(18) W. K. F. Wynne-Jones, *Proc. Roy. Soc.* (*London*), **A140**, 440 (1933).

(19) N. Bjerrum, *K. danske vidensk. Selskab, Math.-fys. Medd.*, **7**, 9 (1926).

equations of Wynne-Jones and Bjerrum are not applicable to this case.

Since this paper was submitted, R. M. Garrels and F. T. Gucker have published a valuable study of aqueous lead chloride solutions [*Chem. Rev.*, **44**, 117 (1949)]. These authors give considerable additional evidence for incomplete dissociation in such solutions, and derive values for K of about 0.03 from e.m.f. and conductance data.

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The Liberation of Diazotizable Amine from Pteroylglutamic Acid[1]

BY B. KOFT AND M. G. SEVAG

During a study of the possible role of pteroylglutamic acid (PGA)[2] and *p*-aminobenzoic acid (*p*-ABA) on the inhibition by sulfonamides of the growth of *Lactobacillus arabinosus* strain 17-5 and other bacteria, certain inconsistancies have been observed by us. These inconsistencies suggested the possibility that pteroylglutamic acid was undergoing decomposition in the sterile medium. Certainly, if this were so, it would have considerable bearing on the interpretations of the results of physiological experiments with pteroylglutamic acid.

TABLE I

RATE OF THE DECOMPOSITION OF PTEROYLGLUTAMIC ACID (PGA)

Pteroylglutamic acid solutions[a]	μg *p*-ABA/1000 μg of PGA[c] 0 hr.	20 hr.	40 hr.	64 hr.	120 hr.	168 hr.
1 Distilled water brought to *p*H 7.0	1.62	3.00	3.91	6.36	9.09	11.82
2 *M*/30 phosphate buffer *p*H 7.3	1.72	2.73	4.27	6.36	9.54	12.36
3 *M*/30 Na_2HPO_4, *p*H 9.18	1.36	2.55	4.27	11.36	13.63	81.82
4 *M*/30 KH_2PO_4 *p*H 4.5[b]	1.36	2.18	2.72	3.36	4.32	5.45
5 Growth medium (*p*H 7.0) (used for *L. arabinosus*[3])	2.50	3.82	6.18	14.54	18.86	45.44
6 Medium as in (5) without PGA	0	0	0	0	0	0
7 1 μg *p*-ABA/ml. of *M*/30 phosphate buffer of *p*H 7.3	1	1	1	1	1	1

[a] All solutions were autoclaved for ten minutes at 10 lb. pressure. Systems 1 to 5 contained 500 μg of PGA/ml. The solutions were then kept in a constant temperature incubator at 30°. [b] Pteroylglutamic acid dissolves on autoclaving and a precipitate forms on cooling; determinations for *p*-ABA were made on uniform suspensions. [c] *p*-ABA content of the various systems were determined according to Bratton and Marshall[4] using Klett–Summerson photoelectric colorimeter with filter No. 54, 1 μg of *p*-ABA/10 ml. reaction system gives a colorimetric reading of 22.

(1) This investigation was supported, in part, by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

(2) The authors are indebted to Dr. C. W. Waller, Lederle Laboratories, Pearl River, New York, for a freshly recrystallized sample of PGA. It contained 1 μg of *p*-ABA/1000 μg of PGA.

(3) T. D. Luckey, G. M. Briggs, Jr., and C. A. Elvehjem, *J. Biol. Chem.*, **152**, 157 (1944).

(4) A. C. Bratton and E. K. Marshall, Jr., *ibid.*, **128**, 537 (1939).

The data presented in Table I pertain to this observation.

It can be seen from the table that PGA decomposes at a regular rate on incubation at 30°. A very great rate of decomposition occurs in the sterile medium which has been generally used for the growth of *Lactobacillus arabinosus* 17-5. In this medium, 6.18 to 14.54 μg. of diazotizable amine calculated as *p*-ABA per 1000 μg. of PGA are liberated during an incubation period of from forty to sixty-four hours. The diazotizable component liberated in this medium is significantly greater than the amounts liberated in either aqueous or neutral phosphate buffer solutions of PGA. These results indicate that certain substances in the sterile medium accelerate the decomposition of PGA. The nature of these substances is under investigation.

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Lithium Borohydride as a Reducing Agent

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Lithium borohydride shares with lithium aluminum hydride the property of solubility in ether and other organic solvents. In ether solution it is a more powerful reducing agent than sodium borohydride (in water or alcohol solution) but is milder than lithium aluminum hydride. This combination of properties, together with the prospect of early commercial availability, suggests useful applications for lithium borohydride particularly in the execution of selective reductions.

Solid lithium borohydride has been known to flash on exposure to humid air, some samples being more prone than others, and for this reason transfers of the solid should be conducted in a dry atmosphere. However, solutions of lithium borohydride are relatively insensitive to moisture and in the experiments to be described no special precautions were taken to exclude moisture. Otherwise the procedures followed in lithium borohydride reductions were generally similar to those employed in reductions by lithium aluminum hydride. Tetrahydrofuran proved advantageous as a solvent, since more concentrated solutions of the hydride could be used, *viz.*, 3.5 M as compared with 0.5 M in diethyl ether.

The aldehydes and ketones (*cf.* Table I) were reduced rapidly at room temperature in exothermic reactions whereas the esters reacted slowly and the mixtures were heated to reflux for periods up to six hours. In the selective reduction of the ketone groups of the keto-esters, and of *m*-nitroacetophenone, ice-bath cooling was employed to enhance selectivity. The attempted selective reduction of ethyl acetoacetate gave rise to a borate complex from which the reduction product could not be

isolated. Similar difficulties have been encountered in the reduction of keto-acids by sodium borohydride.[1]

TABLE I

REDUCTIONS BY LITHIUM BOROHYDRIDE

Compound	Product	Yield, %
n-Heptaldehyde	*n*-Heptanol	83
Benzaldehyde	Benzyl alcohol	91
Crotonaldehyde	Crotyl alcohol	70
Methyl ethyl ketone	*s*-Butanol	77
Benzophenone	Benzhydrol	81
n-Butyl palmitate	*n*-Hexadecanol	95
Ethyl benzoate	Benzyl alcohol	62
Ethyl sebacate	Decamethylene glycol	60
β-Benzoylpropionic acid	γ-Phenylbutyrolactone	78
Ethyl levulinate	γ-Valerolactone	44
m-Nitroacetophenone	α-(*m*-Nitrophenyl)-ethanol[a]	93

[a] This product was obtained in an unstable crystalline modification, m. p. 25°, reverting on melting to the stable form, m. p. 61.5°; reported [Lund, *Ber.*, **70**, 1520 (1937)] m. p. 62.5°.

The action of lithium borohydride on carboxylic acids is complex. Benzoic acid caused decomposition of the hydride with the evolution of some diborane, but the benzoic acid was recovered unchanged. Butyric acid, after one half hour, was reduced to butyl alcohol to the extent of 8% and 75% of the acid was recovered. Crotonic acid, refluxed two hours, was recovered to the extent of 45%, the only isolable products being butyl alcohol (4%) and butyric acid (10%).

Nitrobenzene, after refluxing for eighteen hours with excess lithium borohydride in an ether–tetrahydrofuran mixture, furnished 22% aniline, 30% of an intractable dark red oil, and 30% unchanged nitrobenzene.

As the examples given in Table I show, neither the nitro group (*m*-nitroacetophenone) nor the free carboxyl group (β-benzoylpropionic acid) seriously interferes in the reduction of carbonyl groups.

(1) Chaikin and Brown, THIS JOURNAL, **71**, 122 (1949).

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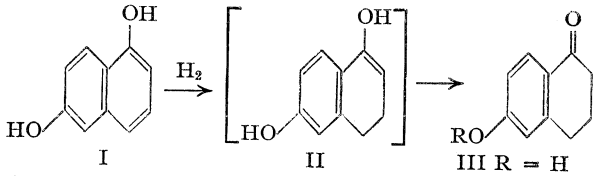
RECEIVED MAY 21, 1949

6-Methoxy-1-tetralone

BY DOMENICK PAPA

The selective hydrogenation of β-naphthol and β-naphthyl methyl ether[1] to the corresponding aryl-tetrahydro derivatives has been the most favored approach to the synthesis of 6-methoxy-1-tetralone[2] (IV). In addition, ring closure of γ-arylbutyric acids[2,3] and alkali fusion of tetralin-6-sulfonic acid[4] have given intermediates for the synthesis of IV.

Recently it has been reported[5] from these laboratories that 1,6-dihydroxynaphthalene (I) on treatment with Raney nickel–aluminum alloy in aqueous alkaline solution affords good yields of 6-hydroxy-1-tetralone (III). This reaction may be assumed to proceed either through the intermediate dihydro compound II, which rearranges to the tetralone III, or through the formation of 1,6-dihydroxytetralin (V) and subsequent dehydrogenation of V to III.[6]



I II III R = H IV R = CH_3

The failure of the alloy procedure to reduce III even after prolonged treatment with large excesses of nickel–aluminum alloy suggested that mild catalytic hydrogenation of I would yield III. Hydrogenation of I in 2% aqueous sodium hydroxide solution with Raney nickel catalyst at room temperature and a pressure of 2–3 atmospheres gave an uptake of one mole of hydrogen within one to one and one-half hours. The crude tetralone III was converted to IV with dimethyl sulfate in an over-all yield of 72%.

Preliminary experiments indicate that the noble metal catalysts give better yields of IV, as the semicarbazone, from I in acidic than in neutral or alkaline medium. As yet, we have not succeeded in isolating (IV) in pure form from the catalytic reduction with the noble metals. We are continuing our studies of the reduction of I and 6-methoxy-1-naphthol by cata ytic and chemical methods.

Experimental

Hydrogenation with Raney Nickel.—To a solution of 16.0 g. (0.1 mole) of 1,6-dihydroxynaphthalene[7] (m. p. 137–138°) in 300 cc. of 2% sodium hydroxide, there was added 5 cc. of Raney nickel catalyst.[8] The hydrogenation was carried out in the conventional Parr apparatus at room temperature at an initial pressure of 35–40 lb. After one and one-half hours[9] the hydrogen absorption ceased

(1) Stork, THIS JOURNAL, **69**, 576 (1947).
(2) Thomas and Nathan, *ibid.*, **70**, 331 (1948); refs. 1–6.
(3) Johnson and Glenn, *ibid.*, **71**, 1092 (1949).
(4) Burnop, Elliot and Linstead, *J. Chem. Soc.*, 727 (1940).
(5) (a) Papa, Schwenk and Breiger, *J. Org. Chem.*, **14**, 366 (1949); (b) Papa and Schwenk, U. S. Patent 2,475,781, July 12, 1949.
(6) Compare Schwenk, Papa, Whitman and Ginsberg, *J. Org. Chem.*, **9**, 1 (1944). Although this sequence of reactions is not very probable, the action of Raney nickel–aluminum alloy on V is being studied.
(7) Generous samples of 1,6-dihydroxynaphthalene have been obtained from National Aniline Division of Allied Chemical and Dye Corporation through the courtesy of Mr. B. M. Helfaer of the Buffalo plant.
(8) The Raney nickel catalyst was prepared at 50° essentially as described by Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1015 (1943), and was washed once with distilled water after decanting off the alkaline solution.
(9) In one instance the hydrogenation was quite sluggish, possibly due to the poisoning of the catalyst. In this case the nickel catalyst was filtered off and a fresh sample added. The hydrogenation then proceeded normally.

and corresponded to one mole of hydrogen. The alkaline solution was filtered to remove the nickel catalyst, diluted to 500 cc. with 25% sodium hydroxide solution. To this solution there was added 50 cc. of dimethyl sulfate and the methylation was carried out as usual. The alkaline solution was then extracted with two 100-cc. portions of ether and the combined ether extracts washed and dried. After removing the ether, the residue was distilled; yield 12.7 g. (72%), b. p. 135–139° (1 mm.), m. p. 75–77°. The semicarbazone, prepared in the usual manner, melted at 235.5–236.5° after recrystallization from aqueous alcohol.

Anal. Calcd. for $C_{12}H_{15}O_2N_3$: N, 18.01. Found: N, 18.06.

Reduction with Platinum Oxide Catalyst.—To 16.0 g. (0.1 mole) of 1,6-dihydroxynaphthalene in 150 cc. of acetic acid, there was added 200 mg. of Adams platinum oxide catalyst. The hydrogenation was carried out as described for the nickel catalyst and at the end of approximately three hours one mole of hydrogen had been absorbed. After filtering the platinum catalyst, the acetic acid was removed *in vacuo* and the residue dissolved in 300 cc. of 10% sodium hydroxide. Methylation of the crude hydroxy tetralone and isolation of the methylated product was carried out as described above. In this case, distillation yielded 6.8 g. of a pale yellow liquid, b. p. 130–144° (1 mm.) from which no crystalline material could be isolated. One gram of the distilled product was treated with semicarbazide hydrochloride and 0.16 g. of semicarbazone was isolated. The semicarbazone, after recrystallization from aqueous alcohol, melted at 230–232° and showed no depression on admixture with the product obtained by the nickel catalyst reduction. We are continuing our studies of this reduction procedure in order to establish the nature of the non-ketonic material.

CHEMICAL RESEARCH DIVISION
SCHERING CORPORATION
BLOOMFIELD, NEW JERSEY RECEIVED JUNE 22, 1949

Sulfanilamido-quinoxalines

BY BERTIE C. PLATT AND THOMAS M. SHARP

A paper by Wolf, Pfister, Beutel, Wilson, Robinson and Stevens[1] has appeared almost simultaneously with one by us[2] on sulfonamides derived from substituted quinoxalines. It is possible by inspection of the melting points quoted by Wolf,[1] *et al.*, to identify some of the compounds which were not fully identified by them.

In Table III[1] two 2-amino-6(or 7)-methylquinoxalines are described (a) m. p. 178–180° and (b) m. p. 171–173°. The former must be 2-amino-6-methylquinoxaline since it was prepared from 2-chloro-6-methyl-quinoxaline identified by Platt[3] by an unambiguous synthesis of 2-hydroxy-6-methylquinoxaline from 4-nitro-*m*-tolylglycine and conversion to the corresponding chloro and amino derivatives. The compound (b) m. p. 171–173° appears to be a mixture of 2-amino-6-methyl and 2-amino-7-methylquinoxalines since it was prepared from an impure 2-chloro-7-methylquinoxaline m. p. 56–57°. Pure 2-chloro-7-methylquinoxaline has m. p. 76° (Platt[3]). Platt[3] found 2-amino-6-methylquinoxaline, prepared by a method which could yield only one isomer, to have m. p. 181–182°, and 2-amino-7-methylquinoxaline, prepared in a similar manner to have m. p. 178–180°. A mixture of the two in approximately equal proportions had m. p. 172–174°. It is well known that mixtures of isomers in the quinoxaline series are very difficult to separate.

2-Chloro-5(or 8)-methylquinoxaline, m. p. 92–93°, of Table II[1] is identified as 2-chloro-5-methylquinoxaline which we[3] have synthesized rationally (m. p. 95°) and converted to 2-amino-5-methylquinoxaline (m. p. 201–2°). 2-Amino-5(or 8)-methylquinoxaline (m. p. 202–3°) of Table III[1] is therefore the 5-methyl isomer. (The isomeric 2-amino-8-methylquinoxaline we find to melt at 129°). The corresponding N^4-acetylsulfanilamide, m. p. 228–229°, and the N^1-sulfanilamide, m. p. 205–206° (Tables IV and V[1]) accordingly have the methyl groups in the 5-positions.

THE WELLCOME LABORATORIES OF TROPICAL MEDICINE
LONDON, N. W. 1, ENGLAND RECEIVED APRIL 26, 1949

(1) Wolf, Pfister, Beutel, Wilson, Robinson and Stevens, THIS JOURNAL, **71**, 6 (1949).

(2) *J. Chem. Soc.*, 2129 (1948).

(3) Platt, *ibid.*, 1310 (1948). This was recognized by Wolf, *et al.*, but by an unfortunate misprint they say ambiguous instead of unambiguous.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY,[1] PHILADELPHIA 18, PENNSYLVANIA]

2-(2-Chloroethoxy)-ethyl Acetate and 2-Chloroethyl Vinyl Ether

BY C. E. REHBERG

Dioxane is the principal impurity in the crude 2-chloroethyl vinyl ether prepared by the method of Cretcher.[2] Cretcher considered that the two formed an azeotrope which boiled at 107°. This azeotrope appeared remarkable in that its boiling point was between those of the two components of the azeotropic mixture.

In the work reported here, chloroethyl vinyl ether was prepared in 60% yield by Cretcher's method. When the crude product was distilled through a column having 60 theoretical plates, dioxane was obtained at 101–102°, a mixture of dioxane and ether at 102–108°, and finally, pure ether at 108°. Since both pure dioxane and pure ether were distilled from the mixture, it is evident that no azeotrope was formed.

The ether was also distilled at reduced pressure (120 mm.). Dioxane distilled at 52–53°, and chloroethyl vinyl ether at 59°; a mixture of variable composition was obtained between the pure components.

The following properties were observed with chloroethyl vinyl ether[3]: b. p., 108°, 59° (120 mm.); $n^{20}D$ 1.4378; d^{20}_4 1.0475.

(2-Chloroethoxy)-ethyl Acetate.—An effort was made to produce chloroethyl vinyl ether by

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) Cretcher, Koch and Pittenger, THIS JOURNAL, **47**, 1173 (1925).

(3) Cretcher reported b. p., 109° (740 mm.); d^{15}_{15} 1.0525; W. Chalmers reported b. p. 108°, $n^{20}D$ 1.4362; d^{20}_4 1.044 (*Can. J. Research*, **7**, 464 (1932)).

the pyrolysis of 2-(2-chloroethoxy)-ethyl acetate. Since the latter is a new compound, its preparation and pyrolysis are described. Diglycol chlorohydrin was acetylated with acetic anhydride, and the product (94% yield) was purified by distillation: b. p. 80° (1 mm.); d^{20}_4 1.1546; $n^{20}D$ 1.4398. Found: $M^{20}D$ 38.02; C, 43.3; H, 6.8. Calcd.: $M^{20}D$ 38.07; C, 43.3; H, 6.7. Pyrolysis over Pyrex glass at 500 and 550° (contact time, 8 sec.) decomposed 32 and 83%, respectively, of the ester but produced little if any chloroethyl vinyl ether. Most of the products were gases.

PHILADELPHIA 18, PA. RECEIVED MARCH 11, 1949

Alkoxy-*s*-triazines. III

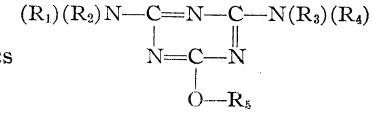
BY WILLIAM M. PEARLMAN, JACQUELINE DOWNS MITULSKI AND C. K. BANKS

In the search for antihistaminic compounds of the triazinyl ether type the alkyl 2,4-diamino-6-*s*-triazinyl ethers were found to have a peak of activity at the *n*-propyl compound.[1] A subsequent investigation of the methyl and butyl ethers of thirty substituted-aminotriazines disclosed no regular progression of activity as was noted in the first series.[2] Subsequently, an examination of the previously determined antihistaminic activities indicated that certain miscellaneous alkyl ethers should be prepared to determine if any products of appreciable activity had been overlooked. The ethers were prepared by previously described methods[1,2] from 2-chlorotriazines already described.[3]

The compounds were tested by Dr. Graham Chen and Mr. Charles Ensor of our laboratories by the histamine-aerosol technique of Dr. E. R. Loew.[2] The physical properties and effective antihistaminic values are recorded in the accompanying table.

TABLE I

ALKOXY-*s*-TRIAZINES



R_1, R_2	R_3, R_4	R_5	M. p., °C.	Yield, %	Recrystallization solvent[a]	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	A. H.[c] value (effective dose, mg./kg.)
H_2	H_2	C_5H_{11}[d]	181–183	30	Ch	48.7	48.7	7.7	7.4	25
H_2	H_2	C_5H_{11}[e]	170–172	30	B	48.7	48.7	7.7	7.3	50
H_2	H, CH_3	C_2H_5	170–171	79	H_2O-E	42.6	42.8	6.6	6.7	12.5
H_2	H, CH_3	*n*-C_3H_7	175–177	68	H_2O-P	45.9	46.1	7.2	7.2	12.5
H_2	H, CH_3	*n*-C_6H_{13}	166–168	75	H_2O-E	53.3	53.7	8.5	8.5	>50
H_2	H, CH_3	*c*-C_6H_{11}	232–234	64	H_2O-MC	54.0	54.2	7.7	7.5	12.5
H_2	H, CH_3	Phenyl	211–213	64	H_2O-D	55.3	55.5	5.1	4.9	>25
H, CH_3	H, CH_3	C_2H_5	171–173	61	H_2O-E	45.9	46.1	7.2	7.3	12.5
H_2	$(CH_3)_2$	C_2H_5	156–158	88	B	45.9	46.2	7.2	7.2	25
H, CH_3	$(CH_3)_2$	C_2H_5	173–175	80[f]	B	48.7	48.6	7.7	7.6	25
H, CH_3	$(CH_3)_2$	*c*-C_6H_{11}	154	75[f]	M	57.3	57.6	8.4	8.4	>25
H_2	H, C_5H_{11}	C_2H_5	103–105	55	H_2O-E	53.3	53.4	8.5	8.2	>25
H_2	H, C_5H_{11}	*n*-C_3H_7	92–95	46	H_2O-E	55.2	54.8	8.9	8.7	..
H, C_2H_5	H, C_2H_5	C_2H_5	116–118	44	H_2O-E	51.2	51.2	8.1	8.2	>25
H, C_2H_5	H, C_2H_5	*n*-C_3H_7	82–84	88	H_2O-E	53.3	53.5	8.5	8.4	..
H_2	C_2H_5O,[g] C_6H_5	C_2H_5	194–196 d.	83	H_2O-EC	56.7	56.7	6.2	6.1	50

[a] All compounds were colorless: B = benzene, Ch = chloroform, D = dioxane, E = ethanol, EC = Ethyl Cellosolve, M = methanol, MC = Methyl Cellosolve, P = propanol. [b] Analyses by our Microanalytical Department under the direction of Messrs. A. W. Spang and C. E. Childs. [c] See ref. 2. [d] 3-Methylbutyl. [e] 2-Methylbutyl. [f] Prepared by Mr. John Controulis. [g] Hydroxyethyl.

(1) Controulis and Banks, THIS JOURNAL, **67**, 1946 (1945).

(2) Pearlman and Banks, *ibid.*, **71**, 1128 (1949).

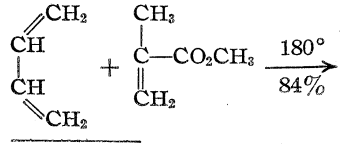
(3) Pearlman and Banks, *ibid.*, **70**, 3726 (1948).

RESEARCH LABORATORIES
PARKE, DAVIS AND CO.
DETROIT 32, MICH. RECEIVED MAY 19, 1949

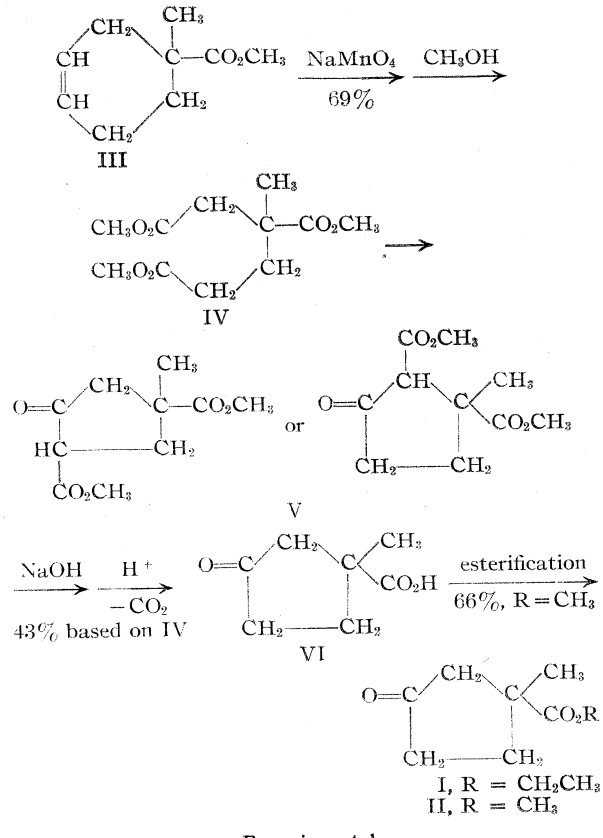
Synthesis of 3-Carbomethoxy-3-methylcyclopentanone

BY JOHN D. ROBERTS, A. K. JEYDEL AND ROSE ARMSTRONG

Ruzicka[1] has reported the preparation of 3-carbethoxy-3-methylcyclopentanone (I) through several steps from ethyl levulinate. In the present investigation, a shorter synthesis of the corresponding methyl ester (II) was achieved from the adduct of butadiene with methyl methacrylate by the following route.



(1) Ruzicka, *Ber.*, **50**, 1362 (1917).



Experimental

4-Carbomethoxy-4-methylcyclohexene (III).—A mixture of 100 g. (1.0 mole) of methyl methacrylate, 108 g. (2 moles) of butadiene and 1 g. of hydroquinone[2] was heated in a steel hydrogenation bomb at 180° for fifteen hours. The viscous product was distilled from a Claisen flask under reduced pressure to separate the polymeric materials and the distillate fractionated through a 2 × 40 cm. glass-helix packed column. The yield of III, b. p. 64–65° (10 mm.), $n^{20}D$ 1.4600, was 130 g. (84%).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.34; H, 9.28.

In other runs at 180° for five and six hours, the yields were 64 and 71%, respectively.

Hydrolysis of III with potassium hydroxide gave **4-carboxy-4-methylcyclohexene**, m. p. 78–79° after crystallization from ligroin.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.56; H, 8.63.

Dimethyl 3-Methyl-3-carbomethoxyadipate (IV).—A mixture of 145 g. (0.94 mole) of III and 2600 ml. of water was placed in a 12-l. flask equipped with a stirrer, dropping funnel and a thermometer extending close to the bottom of the flask. The contents of the flask were stirred vigorously and a solution of 457 g. (2.3 moles) of sodium permanganate trihydrate in 2600 ml. of water added during four hours. During the addition the reaction mixture was kept saturated with carbon dioxide by adding lumps of Dry Ice every few minutes. The temperature was kept below 50° by external cooling with an ice-bath. The manganese dioxide was reduced by passing in sulfur dioxide, the solution was filtered and extracted with ether in a large continuous extractor for five days. The ether was distilled from the extract and the residue was dried by distillation with benzene using a water separator. The viscous acid remaining after distillation of the benzene was refluxed for three days with 600 g. of methanol containing 2% of dry hydrogen chloride. The excess methanol was distilled, the residue dissolved in ether, and washed with water and sodium carbonate solution. The ethereal solution was dried over magnesium sulfate and distilled through a 30-cm. Vigreux column. The yield of IV was 145 g., b. p. 120–121° (0.7 mm.), $n^{25}D$ 1.4443. An additional 9 g. of IV was obtained by esterification of the tribasic acid recovered by acidification and extraction of the sodium carbonate washings of the crude ester. The total yield was 154 g. (70%).

Anal. Calcd. for $C_9H_{18}O_6$: C, 53.65; H, 7.37; sapon. equiv., 82.1. Found: C, 53.87; H, 7.26; sapon. equiv., 83.7.

3,5(or 2,3)-Dicarbomethoxy-3-methylcyclopentanone (V).—The following procedure gave better results than the one used by Ruzicka.[1] In a three-necked creased flask equipped with a stirrer, reflux condenser and dropping funnel was placed 100 ml. of dry toluene, 100 ml. of dry xylene and 3.6 g. (0.15 mole) of clean sodium. The flask was flushed with nitrogen, the contents heated to refluxing and 64 g. (2.0 moles) of methanol added dropwise. After all of the sodium had reacted, 50 ml. of the solvent was distilled to remove most of the excess methanol. To the hot reaction mixture was added 24.6 (0.1 mole) of IV over a forty-five-minute period. The mixture was heated under reflux for two hours, then cooled and 10 ml. of acetic acid added. The mixture was treated with 150 ml. of 1 *N* hydrochloric acid and the organic layer separated, washed with water, sodium carbonate solution and dried over magnesium sulfate. After distillation of the solvent under reduced pressure the residue was fractionated through a short Vigreux column. The yield of V (which may be a mixture of isomers) was 14.6 g. (68%); b. p. 145–151° (7 mm.); $n^{25}D$ 1.4628.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.35; H, 6.83.

3-Carboxy-3-methylcyclopentanone (VI) and 3-Carbomethoxy-3-methylcyclopentanone.—The over-all yield of VI, b. p. 140–145° (2 mm.), from IV by the previously reported procedure[1] was 43%. Esterification of VI with methyl iodide instead of ethyl iodide[1] gave 66% of II; b. p. 96° (7.5 mm.), $n^{25}D$ 1.4523.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.34; H, 8.03.

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASS. RECEIVED APRIL 27, 1949

(2) Much lower yields (20–55%) were obtained if no hydroquinone was used; *cf.* Shortridge, Craig, Greenlee, Derfer and Boord, THIS JOURNAL, **70**, 946 (1948), for similar observations.

The Catalytic Reduction of Dinitroneopentane[1]

BY JACK ROCKETT AND FRANK C. WHITMORE

The reduction of primary aliphatic nitro compounds has been found to yield, other than the primary amines, substances which are presumably reduction intermediates. These are the oxime,[2] the aldimine,[3] the nitrile,[3] and the N-hydroxylamine[4] corresponding to the nitro compound.

Among the products resulting from the hydrogenation of dinitroneopentane with Raney nickel catalyst, we have found the expected diaminoneopentane (67%) and, also, the diamide of dimethylmalonic acid (5%). The latter type substance has

(1) This work was completed by J. R. after the untimely death of Dean Frank C. Whitmore. Thanks are due to Dr. Thomas S. Oakwood who served as adviser after the death of Dean Whitmore.

(2) Johnson and Degering, THIS JOURNAL, **61**, 3194 (1939).

(3) Kohler and Drake, *ibid.*, **45**, 1286 (1923).

(4) Hoffman and Meyer, *Ber.*, **24**, 3528 (1891).

not previously been found to result directly from the reduction of a nitro compound.

The work of Paul[5] has demonstrated that aliphatic aldoximes in contact with Raney nickel will spontaneously rearrange upon gentle heating to the corresponding amides. It is therefore likely that some of the intermediate oxime (un-isolated) rearranged in the course of the present reduction

$$Me_2C(CH_2NO_2)_2 \xrightarrow[Ni]{H_2}$$

$$Me_2C(CH{=}NOH)_2 \longrightarrow \begin{cases} \longrightarrow Me_2C(CONH_2)_2 \\ \longrightarrow Me_2C(CH_2NH_2)_2 \end{cases}$$

It is possible that the reduction of a nitro compound or an oxime to an amine proceeds by way of the intermediate amide. However, the difficulty of reducing amides to amines[6] would indicate that this is probably not the most important reaction.

Experimental

Reduction of Dinitroneopentane.—A solution of 97.2 g. (0.6 mole) of dinitroneopentane in 750 ml. of absolute alcohol was placed in a hydrogenation bomb with 6 g. of Raney nickel catalyst. The hydrogenation proceeded at 1000 p. s. i. and 60°, requiring about two hours for completion. The contents of the bomb were placed in a beaker and allowed to stand at room temperature for twenty-four hours. The crystalline material and the catalyst were then filtered, and the crystalline material was removed from the mixture of extraction with hot water. Cooling the hot water solution gave white crystals, m. p. 268–269°, after one recrystallization from water. A second crop of the above compound was obtained by partly evaporating the alcohol from the original reaction mixture.

Anal. Calcd. for $C_5H_{10}O_2N_2$: C, 46.15; H, 7.69; N, 21.54. Found: C, 46.54; H, 7.84; N, 21.63.

The compound was shown to be the diamide of dimethylmalonic acid by comparison with a sample of that substance prepared from dimethylmalonic acid through the acid chloride, and subsequent treatment with liquid ammonia.

Diaminoneopentane.—The diaminoneopentane from the above reduction was obtained by treating the alcoholic solution above with anhydrous hydrogen chloride, which caused the separation of the di-hydrochloride. The hydrochloride was recrystallized from alcohol, m. p. 256–257°.

Anal. Calcd. for $C_5H_{16}N_2Cl_2$: Cl, 40.50. Found: Cl, 40.54.

This compound prepared in another way has been reported as having the m. p. 280–281°.[7] However, the picrate of the compound agreed with that prepared by these authors (m. p. 240°).

The recrystallized hydrochloride was dissolved in 300 ml. of methanol and methanolic potassium hydroxide was added. After filtering the potassium chloride formed, the diaminoneopentane was separated by distillation in an efficient column. It was a mobile water white liquid, fuming in moist air, b. p. 151–153° (737 mm.); $n^{20}D$ 1.4566.

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STATE COLLEGE, PENNSYLVANIA RECEIVED MAY 5, 1949

(5) R. Paul, *Bull. soc. chim.*, [5] **4**, 1115–1121 (1937).

(6) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937.

(7) Kommpa and Sevon, *C. A.*, **27**, 3914 (1933).

Evidence for a Solid Dihydrate of Hexafluoroacetylacetone[1]

BY BOYD G. SCHULTZ AND EDWIN M. LARSEN

In the final step in the production of hexafluoroacetylacetone according to the process of Staniforth[2] in which the solvent and product are separated by fractional distillation, we continually obtained a white crystalline residue with corresponding poor yields of the low boiling product.

The white crystalline product was very soluble in ether, slightly soluble in benzene and petroleum ether, and slowly soluble in water. The water solution of this compound was acid to litmus and slowly liberated carbon dioxide from a solution of sodium hydrogen carbonate. It had a pungent odor and was very volatile as evidenced by substantial sublimation occurring even at room temperature. No melting point was observed as the compound sublimed completely before reaching 115°. On the basis of the following experimental results we have concluded that the material obtained is the dihydrate of hexafluoroacetylacetone.

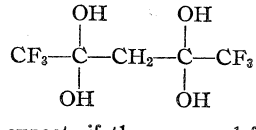
Experimental

For analysis the compound was recrystallized from ether, washed with benzene to remove any diketone present, and dried at room temperature under 0.1 mm. pressure. A qualitative elementary analysis confirmed the presence of carbon and fluorine, and the absence of any metallic elements. From the results of the quantitative analysis for carbon,[3] hydrogen[3] and fluorine, the empirical formula of the compound was calculated to be $C_5H_6O_4F_6$.

Anal. Calcd. for $C_5H_6O_4F_6$: C, 24.58; H, 2.47; F, 46.71. Found: C, 24.48; H, 2.54; F, 46.3.

The neutral equivalent of this compound as determined by titration of an aqueous solution with 0.1 *N* NaOH solution gave a value which corresponded to the molecular weight of the compound, $C_5H_6O_4F_6$: calcd. mol. wt., 244.10; exptl. neutral eq., 245.

Since the fluorine was all present in the starting material as trifluoromethyl groups, it was considered unlikely that the fluorine could be arranged in any other manner, and therefore on the basis of these data it was concluded that this compound was hexafluoroacetylacetone dihydrate



As one would expect, if the proposed formulation were correct, the dihydrate in ether solution was incapable of forming the copper chelate derivate directly. However, a small amount of the enol form must be present in both the ether and water solution of the dihydrate, because on standing in contact with a copper acetate solution for twenty-four hours, a greenish tint, characteristic of the copper chelate, was observed in the ether layer, and after several days the intensity of the coloration increased.

Additional experiments were conducted to test the possibility of dehydration as expressed in the reaction

$$CF_3C(OH)_2CH_2C(OH)_2CF_3 \rightleftharpoons CF_3C(OH){=}CH{-}CO(CF_3) + 2H_2O$$

(1) Based on research carried out under Task Order 4 of Contract N7onr-28504 between the Office of Naval Research and the University of Wisconsin.

(2) Henne, Newman, Quill and Staniforth, THIS JOURNAL, **69**, 1819 (1947).

(3) Analyses by Clark Microanalytical Laboratory, Urbana, Ill.

An ether solution of the dihydrate was treated with phosphorus pentoxide, and samples taken at intervals during a twenty-four-hour period were tested for the presence of hexafluoroacetylacetone.[4] Upon standing for a short time, no test for the hexafluoroacetylacetone was obtained, although after twenty-four hours an immediate test was obtained. The dehydration process progressed rapidly when an ether solution of the dihydrate was refluxed over phosphorus pentoxide for one hour, and then fractionally distilled. The fraction coming over above 35° gave an immediate test for the diketone.

Similarly, an increase in the *p*H of an aqueous solution resulted in a shift of the equilibrium to the right. Thus, an aqueous solution which had been brought up to a *p*H of 7 with 0.1 *N* sodium hydroxide, when treated with a copper acetate solution, gave immediately the ether extractable derivative.

The equilibrium could also be reversed as evidenced by the fact that when an ethereal solution of the hexafluoroacetylacetone was shaken with water, an immediate test for the diketone could not be obtained.

(4) The presence of hexafluoroacetylacetone was determined by shaking the test solution with aqueous copper acetate. The appearance of a green ethereal layer was taken as evidence of the formation of bis-(1,1,1,5,5,5 hexafluoro-2,4-pentanediono)-copper. This was confirmed by analyses of such copper derivatives recovered by evaporation of the ether solution. *Anal.* Found Cu, 13.4; F, 46.7; m. p. 114–116°. Calcd. Cu, 13.3; F, 47.8; m. p. 113–115°.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON 6, WISCONSIN

RECEIVED MAY 5, 1949

Resolution of DL-Tryptophan

BY A. C. SHABICA[1] AND MAX TISHLER

Although a number of excellent methods for the preparation of DL-tryptophan have been reported,[2] no equally satisfactory procedure for the resolution of the DL-mixture is known. We wish to report[3] a method of resolution developed by us several years ago which is simpler than the chemical procedures already reported.[4]

In this method N-acetyl-DL-tryptophan, an intermediate in a few of the recent syntheses, is resolved by brucine. The brucine salt of N-acetyl-D-tryptophan separates cleanly from ethanol and the L- form is obtained from the mother liquor. The N-acetyl enantiomorphs are hydrolyzed to the optically active amino acids by heating with 2*N* hydrochloric acid for about two hours. Both D- and L-tryptophan can be obtained in pure form and in good yields.

Brucine Salt of D- and L-N-Acetyltryptophan.—A mixture of 123 g. of N-acetyl-DL-tryptophan, 208 g. of brucine and 1750 cc. of absolute ethanol was boiled under reflux until solution was effected. After cooling, seeding and storing for twelve hours, the crystalline product was separated and slurried twice with small quantities of ethanol: Weight of dried product, 161 g.; $[\alpha]^{25}D$ — 16.5 ± 1°. Recrystallization from 320 cc. of hot ethanol gave 146 g. of pure brucine salt of N-acetyl-D-tryptophan ($[\alpha]^{25}D$ — 18.4°) as was indicated by its constant rotation when subjected to further recrystallization.

The brucine salt of N-acetyl-L-tryptophan was obtained from the resolution mother liquor by concentration of the solution to dryness under reduced pressure, dissolution of the residue in 320 cc. of hot methanol, charcoal treatment of the solution, dilution of the latter with 325 cc. of dry ether, seeding and storage of the mixture for several hours. The crystalline brucine salt was subjected again to the same recrystallization procedure whereby 139 g. of product was obtained; $[\alpha]^{25}D$ + 1.3 ± 1° (*c*, 1% in water). *Anal.* Calcd. for $C_{36}H_{40}O_7N_4$: C, 67.48; H, 6.29; N, 8.74. Found: C, 67.54; H, 6.13; N, 8.69.

L- and D-Tryptophan.—To a mixture of 49 g. of the recrystallized brucine salt of N-acetyl-L-tryptophan in 170 cc. of water was added 70 cc. of cold 1*N* sodium hydroxide solution. The salt dissolved readily and very soon brucine separated. After cooling in ice for a few hours, the mixture was filtered and the brucine washed with cold water. The combined filtrate and washings were neutralized with hydrochloric acid to *p*H 7.0, concentrated under reduced pressure to 140-cc. volume, treated with charcoal and finally acidified with hydrochloric acid *p*H 3.0. The N-acetyl-L-tryptophan was collected and slurried twice with cold water; weight 16.1 g. (85% yield); $[\alpha]^{25}D$ + 29° (*c*, 1% in H_2O + 1 equivalent NaOH).

A mixture of the product with 160 cc. of 2*N* hydrochloric acid was boiled under reflux for two and one-half hours and the resulting solution was concentrated under reduced pressure to dryness. The residue was dissolved in 40 cc. of hot water and the solution was treated with charcoal. A solution of 7 g. of sodium acetate in 20 cc. of water was added to the product solution and the mixture was stored at 5° for fourteen hours. The product was recrystallized by dissolution in 84 cc. of water containing 2.8 g. of sodium hydroxide, acidifying the warmed solution (at 70°) with 4.5 cc. of acetic acid and storing the mixture at 5° for fourteen hours. The pure L-tryptophan was collected and washed with small amounts of 50% ethanol followed by ethanol and then dry ether; weight, 10.9 g.; 82% yield; $[\alpha]^{25}D$ −31.90 (*c*, 1% in water + 1 equivalent of NaOH).

D-Tryptophan was obtained from the brucine salt of its N-acetyl derivative following the same procedure. The over-all yields were slightly better, however.

(1) Present address: Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

(2) Snyder and Smith, THIS JOURNAL, **66**, 350 (1944); Albertson, Archer and Suter, *ibid.*, **66**, 500; **67**, 36 (1945); Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945); Lyttle and Weisblat, *ibid.*, **69**, 2118 (1947); Warner and Moe, *ibid.*, **70**, 2765 (1948).

(3) The procedure is reported at this time because of a number of recent requests for our method of effecting resolution of DL-tryptophan.

(4) du Vigneaud and Sealock, *J. Biol. Chem.*, **96**, 511 (1932); Berg, *ibid.*, **100**, 79 (1933).

RESEARCH LABORATORIES
MERCK & CO., INC.
RAHWAY, NEW JERSEY

RECEIVED JULY 27, 1949

The Reduction of Methyl Cyclopropyl Ketone to Methylcyclopropylcarbinol

BY V. A. SLABEY AND P. H. WISE

In the course of an investigation of the syntheses of alkylcyclopropanes from methyl cyclopropyl ketone it was necessary to prepare a quantity of methylcyclopropylcarbinol. The reduction of methyl cyclopropyl ketone with sodium and ethanol[1] was found to be unsatisfactory because of the low yields of carbinol obtained. Methylcyclopropylcarbinol of good purity was obtained in good yield by the use of lithium aluminum hydride, but the method was abandoned because of the difficulties encountered in applying it to large-scale work.

Catalytic reductions were considered most desirable because of their applicability to preparations of any size. Consequently, reductions with hydrogen in the presence of Raney nickel and copper chromite catalysts were attempted. Hydrogenation with Raney nickel was found to yield nearly equal quantities of methylcyclopropylcarbinol and pentanol-2, as well as unconverted ketone. In the presence of a barium-promoted copper chromite catalyst, hydrogenation of the ketone at 150° and 1500 to 2000 p.s.i. of hydrogen gave a 76% yield of the desired carbinol which was contaminated with a close-boiling impurity believed to be pentanol-2. When the temperature was reduced to 100°, however, the yield of methylcyclopropylcarbinol increased to 90%, and ring cleavage to yield pentanol-2 was no longer evident. No difficulty was experienced in determining when the reaction was complete, because hydrogen consumption dropped to virtually nothing as soon as sufficient hydrogen to convert carbonyl to carbinol was absorbed (Fig. 1).

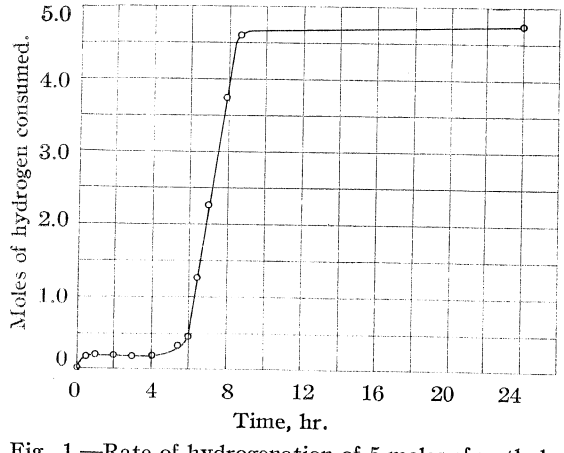


Fig. 1.—Rate of hydrogenation of 5 moles of methylcyclopropyl ketone at 100° in the presence of copper chromite catalyst.

The physical constants, carbon–hydrogen analysis, and infrared spectrum were determined on a center cut of the product obtained from the copper chromite reduction at 100°. These data are presented in Tables I and II.

TABLE I

PHYSICAL CONSTANTS AND C–H ANALYSIS OF METHYLCYCLOPROPYLCARBINOL

M. p., °C., −31.04; b. p., °C., at 760 mm., 122.51; $n^{20}D$, 1.43160; d^{20}, g./ml., 0.88860. Carbon, %, calcd. 69.7. Found: 69.8. Hydrogen, %, calcd. 11.7. Found: 11.8.

TABLE II

INFRARED ABSORPTION MAXIMA OF METHYLCYCLOPROPYLCARBINOL

λ, microns	% Transmission[a]	λ, microns	% Transmission[a]
2.98	38	8.62	66
3.38	39	9.05	23
4.90	65[b]	9.22	30
5.24	56[b]	9.53	28
6.08	60[b]	9.78	26
6.87	60	10.10	45
7.08	51	10.64	16
7.26	54	10.90	64
7.79	62	11.31	63
7.95	51	12.14	48[c]
8.36	68		

[a] 1:10 dilution in carbon tetrachloride. [b] Undiluted. [c] 1:10 dilution in carbon disulfide.

The use of copper chromite as a catalyst for 1,2-hydrogenation of "conjugated" cyclopropane systems appears to be generally applicable.[2] Copper chromite has previously been used to hydrogenate the "conjugate" isopropenylcyclopropane to isopropylcyclopropane.[3]

Experimental

The methyl cyclopropyl ketone[4] was fractionated and only center-cut material was used in this work ($n^{20}D$ 1.4250–1.4252).

Reduction with Sodium and Ethanol.—Fourteen gram atoms (322 g.) of sodium in 0.25-inch cubes was added piecewise to 5 moles (420 g.) of methyl cyclopropyl ketone, 1500 ml. of ethanol and 500 ml. of water in a 3-liter flask equipped with a mercury-seal stirrer and a reflux condenser. During the addition of the sodium the reaction mixture was cooled to 10 to 15° by means of an ice-bath. When the addition was completed, the reactants were allowed to warm to room temperature to permit complete dissolution of the sodium. The mixture was then hydrolyzed by slowly adding 2 liters of cold water. The products were extracted from the water layer with ether and dried over anhydrous sodium sulfate. The dried ether solution was fractionated to yield 181 g., 42% yield, of methylcyclopropylcarbinol, b. p. 120–122°.

Reduction with Lithium Aluminum Hydride.—Five moles of methyl cyclopropyl ketone was added to a solution of approximately 2 moles (76 g.) of lithium aluminum hydride in 2 l. of dry ether in accordance with a previously described procedure.[5] The reaction mixture was stirred overnight and then hydrolyzed by the addition of 200 ml. of water and subsequently 1800 ml. of 10% sulfuric acid

(1) Michiels, *Bull. Sci. Acad. Roy. Belgium*, 11 (1912).

(2) Unpublished work, this Laboratory.

(3) Slabey, Wise and Gibbons, THIS JOURNAL, **71**, 1518 (1949).

(4) U. S. Industrial Chemicals, Inc., 60 E. 42nd Street, New York, N. Y.

(5) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

solution. The ether layer was washed with saturated sodium bicarbonate solution, dried over "Drierite," and fractionated to yield 291 g. of carbinol, b. p. 121–122°. An additional 38 g. of carbinol was obtained by re-working the fore-run fractions; total yield was 76%.

Catalytic Reduction with Raney Nickel.—Five moles of methyl cyclopropyl ketone, 200 ml. of ethanol and approximately 25 g. of Raney nickel were sealed in a 1.25-l. rocking autoclave, and hydrogen was admitted to 1200 p. s. i. at room temperature. The reactants were gradually heated to 90° at which temperature hydrogenation began. Maximum temperature reached was 125°. The hydrogenation was stopped when the theoretical amount of hydrogen had been consumed. The product was fractionated to yield 46 g. of unconverted ketone, 131 g. of pentanol-2, and 145 g., 34% yield, of methylcyclopropylcarbinol, b. p. 120–122°.

Catalytic Reduction with Copper Chromite.—Three hydrogenations were run in essentially the same manner as follows with the exception of a difference in temperature: Five moles of methyl cyclopropyl ketone and 42 g. of a commercial barium-promoted copper chromite catalyst[6] were sealed into the previously mentioned hydrogenation vessel, and hydrogen was admitted to 1750 p. s. i. at room temperature. The reactants were heated to 100°, and after an induction period of about five hours, hydrogenation began. The reaction was completed within about four hours as indicated by the hydrogen consumption dropping to virtually nothing. With the exceptions of about 20 g. of fore-run the product consisted of 390 g., 90% yield of methylcyclopropylcarbinol, b. p. 121–122°. The 3,5-dinitrobenzoate was prepared, m. p. 88.5–89.0° (uncor.). *Anal.* Calcd. for $C_{12}H_{12}O_6N_2$: N, 10.00. Found: N, 9.86.

When the hydrogenation was carried out at 120°, the yield of carbinol was 374 g., or 87%. At 150° the yield was 326 g., 76% yield of carbinol, b. p. 118–120°. From the refractive index it was evident that a close-boiling impurity of lower index than methylcyclopropylcarbinol was present. The impurity was assumed to be pentanol-2.

(6) E. I. du Pont de Nemours, Ammonia Division, Wilmington, Delaware.

NATIONAL ADVISORY COMMITTEE FOR AERONAUTICS
LEWIS FLIGHT PROPULSION LABORATORY
CLEVELAND, OHIO
RECEIVED MAY 7, 1949

Preparation of Organopolysiloxanes from Sodium Trimethylsilanolate[1,2]

BY LEO H. SOMMER, LARRY Q. GREEN AND FRANK C. WHITMORE

The availability of trimethylsilanol in good yield and high purity from the controlled hydrolysis of trimethylfluorosilane, and its rapid and complete reaction with sodium to give sodium trimethylsilanolate,[3] led to a study of the latter as an intermediate for further synthesis.

In the present work sodium trimethylsilanolate was found to readily undergo Williamson type reactions with diethyldichlorosilane, ethyltrichlorosilane and silicon tetrachloride, according to the general equation

$$R_xSiCl_{4-x} + (4-x)(CH_3)_3SiONa \longrightarrow R_xSi[(CH_3)_3SiO]_{4-x} + (4-x)NaCl$$

By this method there were synthesized diethyldi-(trimethylsiloxy)-silane (I), ethyltri-(trimethylsiloxy)-silane (II), and tetra-(trimethylsiloxy)-silane (III). Alternate names by the siloxane nomenclature are somewhat more cumbersome, *i. e.*, 1,1,1,5,5,5-hexamethyl-3,3-diethyltrisiloxane (I).

$(C_2H_5)_2Si[OSi(CH_3)_3]_2$ (I) $\qquad$ $C_2H_5Si[OSi(CH_3)_3]_3$ (II)

$Si[OSi(CH_3)_3]_4$ (III)

Compounds I and II are new organopolysiloxanes of a type not readily obtained in good yields by other methods which comprise cohydrolysis of the appropriate pair of monomers. Compound III was previously prepared in 27% yield by the cohydrolysis of ethyl orthosilicate and trimethylethoxysilane with aqueous sodium hydroxide.[4]

In the present work compound III was also prepared by reaction of trimethylsilanol with ethyl orthosilicate in the presence of a small amount of sodium.

$$4\,(CH_3)_3SiOH + (C_2H_5O)_4Si \longrightarrow Si[OSi(CH_3)_3]_4 + 4\,C_2H_5OH$$

TABLE I

PHYSICAL PROPERTIES

Compound no.		I	II	III[a,b]
Calcd. mol. wt.		264.5	324.5	384.7
B. p., °C. (733 mm.)		187	206	220
Ref. index, $n^{20}D$		1.4005	1.3944	1.3895
Density in g./ml.	0°	0.8751	0.8756	0.8854
	20°	.8399	.8582	.8677
	60°	.8035	.8209	.8298
Mol. ref., found[c]		76.43	90.54	105.09
Mol. ref., calcd.[d]		76.90	90.75	104.80
Viscosity, centipoises	0°	2.020	2.723	4.235
	20°	1.441	1.896	2.868
	60°	0.841	1.067	1.503

[a] Melting point, *ca.* −60°. [b] Constants reported previously for compd. III (ref. 4) are $n^{25}D$ 1.3865, b. p. 91° (9 mm.). In a private communication Dr. M. J. Hunter informs us that the density given in ref. 4 should be changed to d^{25} 0.8630. [c] Calculated by the Lorentz-Lorenz equation. [d] Calculated by the method of Warrick, THIS JOURNAL, 68, 2455 (1946).

In Table I are listed the three organopolysiloxanes and some of their physical properties.

Comparison of compounds I and II with the previously reported octamethyltrisiloxane and methyl-(trimethylsiloxy)-silane,[5] respectively, shows that boiling points, densities and refractive indices are greater in compounds I and II by amounts approximating those to be expected from the substitution of ethyl for methyl.

A more interesting comparison is given by the highly-branched compound III and its linear isomer, dodecamethylpentasiloxane.[5] In compound III, boiling point, refractive index and density are

(1) XXIV in a series on organosilicon chemistry. For Paper XXIII see THIS JOURNAL, **71**, 3056 (1949).

(2) Taken in part from a thesis submitted by L. Q. Green to the Graduate School of The Pennsylvania State College in partial fulfillment of the requirements for the M.S. degree.

(3) Sommer, Pietrusza and Whitmore, THIS JOURNAL, **68**, 2282 (1946).

(4) Wright and Hunter, *ibid.*, **69**, 803 (1947).

(5) Patnode and Wilcock, *ibid.*, **68**, 358 (1946); Hunter, Warrick, Hyde and Currie, *ibid.*, **68**, 2284 (1946).

lower, and the melting point is higher. The differences are: b. p., 9°; $n^{20}D$ 0.0030; d^{20} 0.0078; m. p. 24°.

Viscosity measurements were similar to those of other organopolysiloxanes with respect to the temperature dependence of viscosity.

Experimental

Syntheses with Sodium Trimethylsilanolate.—The synthesis of tetra-(trimethylsiloxy)-silane will be described as representative of the procedure employed. In a 1-liter round-bottomed flask fitted with a reflux condenser there were placed 500 cc. of dry benzene and 110 g. (1.2 moles) of trimethylsilanol.[3] To this was added 30.1 g. (1.3 moles) of sodium cut into small pieces. Immediate reaction occurred, accompanied by evolution of hydrogen. Since a good deal of heat was evolved, the reaction flask was cooled externally in order to prevent the reaction from becoming too violent. After reaction had slackened heat was applied for two hours, causing a gentle reflux of benzene, in order to insure complete reaction. At this point the solution was slightly opalescent, but no sodium trimethylsilanolate separated. After cooling, the solution was decanted from the excess sodium into the flask in which the siloxane preparation was to be carried out. The remaining sodium was washed twice with small portions of benzene and the washings added to the bulk of the silanolate solution. The unreacted sodium weighed 2.3 g., indicating that the theoretical quantity, 27.8 g., had reacted with the silanol.

Reaction of the benzene solution of sodium trimethylsilanolate with silicon tetrachloride was performed in a 1-liter three-necked flask fitted with an efficient stirrer, reflux condenser and dropping funnel. The silicon tetrachloride, 42.5 g. (0.25 mole) was distilled directly into the dropping funnel, care being taken to exclude moisture. It was added to the silanolate during forty-five minutes while cooling the reaction flask in an ice-bath. After completion of the addition, the mixture was heated to reflux temperature for forty hours resulting in the separation of a considerable amount of sodium chloride. Sufficient water was then added to dissolve all solid material, the benzene layer separated, and the aqueous layer extracted with two 100-cc. portions of benzene. The benzene solution of the product was dried over anhydrous potassium carbonate and the benzene removed by distillation. Fractional distillation of the residue in a glass-helix packed column of about twelve theoretical plates gave 36.3 g. (0.095 mole) of tetra-(trimethylsiloxy)-silane, b. p. 96° (13 mm.), a yield of 38%. Table II gives pertinent data for the three syntheses.

TABLE II

Cpd.	Yield,[a] %	Mol. wt. Calcd.	Mol. wt. Found[b]	Si, % Calcd.	Si, % Found
I	52	264.5	264	31.8	31.8
II	44	324.5	327	34.6	34.3
III	38	384.7	386	36.5	36.2

[a] Yields are based on the quantity of chlorosilane, sodium trimethylsilanolate being present in approximately 20% excess. [b] Cryoscopically in benzene.

An attempted preparation of diethyldi-(trimethylsiloxy)-silane from the silanolate and diethyldichlorosilane in ethyl ether solution resulted in failure, thus indicating the need for a higher boiling solvent in these preparations.

Tetra-(trimethylsiloxy)-silane from Trimethylsilanol and Ethyl Orthosilicate.—A preliminary experiment indicated that ethanol and trimethylsilanol form an azeotropic mixture boiling in the range 62–70°. Since this would prevent the reaction from effectively being driven to completion by slow removal of ethanol, a large yield of tetra-(trimethylsiloxy)-silane was not expected.

In a 200-cc. round-bottomed flask were placed 41.7 g. (0.20 mole) of ethyl orthosilicate, 90 g. (1.00 mole) of trimethylsilanol, and a small amount (*ca.* 0.2 g.) of sodium. The mixture was heated at reflux temperature in a fractionating column for twenty-two hours. Fractionation in a glass-helix packed column of about twelve theoretical plates gave 14 g. of slightly impure tetra-(trimethylsiloxy)-silane, b. p. 215° at 732 mm. (uncor.), $n^{20}D$ 1.3889, mol. wt., 391 (calcd., 384.7), d^{20} 0.868, a yield of 18%. Other fractions obtained, b. 195–215°, 29.8 g., likely consist of products resulting from incomplete replacement of ethoxy groups by trimethylsiloxy groups.

Physical Properties.—Boiling points were determined in a modified Cottrell apparatus.[6] Densities were measured with pycnometers of about 5-cc. capacity. Viscosities were determined in Cannon–Fenske viscometers.[7]

Acknowledgment.—We thank Dr. F. Fischl of Standard Oil Development Co., Elizabeth, N. J., for the determination of the melting point of tetra-(trimethylsiloxy)-silane.

(6) Quiggle, Tongberg and Fenske, *Ind. Eng. Chem., Anal. Ed.*, **6**, 466 (1934).

(7) Cannon and Fenske, *ibid.*, **10**, 297 (1938).

THE WHITMORE LABORATORY
SCHOOL OF CHEMISTRY AND PHYSICS
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PA. RECEIVED FEBRUARY 25, 1949

Di-*t*-butyl-di-aminoalkyl Silicates[1]

BY PHILIP A. DI GIORGIO,[2] LEO H. SOMMER AND FRANK C. WHITMORE

Di-*t*-butoxydiaminosilane[3] reacts with amino alcohols to yield di-*t*-butyl-di-aminoalkyl silicates.[4] The following equation is illustrative of the reaction.

$$(t\text{-BuO})_2Si(NH_2)_2 + 2HOCH_2CH_2NH_2 \longrightarrow (t\text{-BuO})_2Si(OCH_2CH_2NH_2)_2 + 2NH_3$$

By this method we have synthesized six new di-*t*-butyl-di-aminoalkyl silicates whose properties are listed in Table I.

For the syntheses, generally a solution of one mole of di-*t*-butoxydiaminosilane and two moles of amino alcohol was refluxed for one to three hours at approximately 150–200°. After the theoretical weight of ammonia had been evolved, the crude product was purified by distillation under reduced pressure. The yields of di-*t*-butyl-di-aminoalkyl silicates ranged from 40 to 70%.

The products were viscous, water-white liquids having little or no odor. The 2-aminoethyl and 2-(β-aminoethylamino)-ethyl compounds were found to be very soluble in water, but the other compounds were substantially insoluble. Di-*t*-butyl-di-(2-aminoethyl) silicate dissolved readily in ligroin, benzene, carbon tetrachloride, 95% ethanol, ether, acetone and pyridine. This silicate did not react with molten sodium. Most of the

(1) Paper XXV in a series on organic silicon compounds. For the preceding paper see THIS JOURNAL, **71**, 3253 (1949).

(2) Present address: Research Laboratory, General Electric Co., Schenectady, New York.

(3) Miner, Bryan, Holysz and Pedlow, *Ind. Eng. Chem.*, **39**, 1368 (1947).

(4) Private communication from Dr. C. S. Miner, Jr., who, with his co-workers, first prepared and characterized di-*t*-amyl-di-(2-aminobutyl) silicate from the reaction of 2-amino-1-butanol with di-*t*-amoxydichlorosilane and with di-*t*-amoxydiaminosilane.

TABLE I

	Compound	Yield, %	B. p. uncor.[b] °C.	mm.	$n^{20}D$[b]	d^{20}[b]	% Nitrogen Calcd.	% Nitrogen Obs.	Equivalent wt.[c] Calcd.	Equivalent wt.[c] Obs.	MR_D[b] Calcd.	MR_D[b] Obs.
I	$(t\text{-BuO})_2Si(OCH_2CH_2NH_2)_2$	63	144	16	1.4269	0.9731	9.52	9.47[e]	147	150	77.30	77.69
II	$(t\text{-BuO})_2Si(OCH_2CH_2NEt_2)_2$	43[a]	197	33	1.4272	.909	6.89	6.82[e]	203	206	115.02	114.9
III	$(t\text{-BuO})_2Si[O\text{-}CH(CH_3)CH_2NH_2]_2$	72	107	1	1.4264	.9548	8.69	8.52[d]	163	162	86.56	86.61
IV	$(t\text{-BuO})_2Si[O\text{-}CH_2CH(NH_2)CH_2CH_3]_2$	47	133	1	1.4266	.9462	7.99	7.96[d]	...	...	95.82	95.04
V	$(t\text{-BuO})_2Si[O\text{-}CH_2C(CH_3)(NH_2)CH_3]_2$	47	126	4	1.4246	.9328	7.99	7.92[d]	175	173	95.82	96.01
VI	$(t\text{-BuO})_2Si(OCH_2CH_2NHCH_2CH_2NH_2)_2$	41	187	3	1.4495	.9911	14.73	14.75[d]	...	...	103.10	103.10

[a] The 100% excess amino alcohol used was recovered and in later runs was shown to be unnecessary. In a run which was stopped before it went to completion, there was isolated 70 g. of material boiling at 130° at 12 mm., $n^{20}D$ 1.4261, d^{20} 0.9180, MR_D 85.56, equivalent weight 154. Theoretical values for di-*t*-butoxy-(2-diethylaminoethoxy)-aminosilane, $(t\text{-BuO})_2(Et_2NCH_2CH_2O)SiNH_2$ are: equivalent weight 153 and MR_D 85.35. [b] These physical properties are those of a center fraction of the distillation flat which was taken as purified product. [c] Micro-Dumas by Mr. R. N. Walter. [d] Micro-Kjeldahl reported by Dr. P. M. Althouse as the average of three or more determinations with repeated cross-checks through tryptophan and urea standards. [e] A solution of the sample in aqueous methanol was titrated with 0.1 *N* hydrochloric acid to the methyl red end-point. [f] The calculated values were obtained by use of bond refractions given by Denbigh, *Trans. Faraday Soc.*, **36**, 936 (1940), and by Warrick, THIS JOURNAL, **68**, 2455 (1946). Similar results may be obtained by use of the method of Sauer, *ibid.*, **68**, 954 (1946). The average deviation was 0.26 ml. when the sign was disgarded and 0.04 ml. when the sign was considered. Molecular refractions calculated for the alternate structure having the amino alcohol residue attached to silicon through nitrogen with the hydroxyl free showed an average deviation of 0.39 ml. when the sign was disregarded and 0.31 ml. when the sign was considered.

compounds prepared were sufficiently basic to be titrated completely with hydrochloric acid using methyl red indicator.

It is very improbable that the amino alcohol residues were attached to silicon through nitrogen rather than through oxygen. The structures involving attachment through oxygen were assigned for the following reasons: (1) 2-diethylaminoethanol, which contains no hydrogen atoms attached to nitrogen, reacted with the diaminosilane in a manner analogous to other amino alcohols containing unsubstituted amino groups; and the product obtained with 2-diethylaminoethanol had properties analogous to those of compounds obtained with amino alcohols possessing free amino groups; (2) if the nitrogen were attached to silicon, it is unlikely that it would be sufficiently basic to be titrated quickly and completely with hydrochloric acid using methyl red indicator; (3) the inertness of the di-*t*-butyl-di-(2-aminoethyl) silicate toward molten sodium indicates the absence of free hydroxyl groups.

Experimental

Intermediates. A. Amino Alcohols.—Sharples Co. 2-ethylaminoethanol and Eastman Kodak Co. 2-aminoethanol, 2-diethylaminoethanol, and 2-amino-2-methylpropanol were distilled before use. Commercial Solvents 2-aminobutanol, Dow 1-amino-2-propanol, and Eastman 2-(β-aminoethylamino)-ethanol were used as received. The properties of the intermediate known amino alcohols as used are listed below.

Compound	B. p., uncor. °C.	Mm.	$n^{20}D$	d^{20}
$NH_2CH_2CH_2OH$	83–86	21	1.455	1.016
$C_2H_5NHCH_2CH_2OH$	165	740	1.4411	0.9162
$(C_2H_5)_2NCH_2CH_2OH$	56–57	15	1.4412	0.8921
$CH_3C(CH_3)(NH_2)CH_2OH$	75	16	1.4482	
$CH_3CH_2CH(NH_2)CH_2OH$			1.4524	
$CH_3CH(OH)CH_2NH_2$			1.4479	
$NH_2CH_2CH_2NHCH_2CH_2OH$			1.486	

B. Di-*t*-butoxydiaminosilane.—This intermediate was used as received from the Minnesota Mining and Manufacturing Co. The material had equivalent weight 107, $n^{20}D$ 1.4200 and d^{20} 0.9281. Distillation of a portion indicated over 95% purity. A center fraction had the following properties: b. p. 104° at 20 mm., $n^{20}D$ 1.4199, d^{20} 0.9276. The observed MR_D was 56.28 and the value calculated as indicated in Table I was 55.68.

Anal. Calcd. for $C_8H_{22}O_2N_2Si$: equivalent weight, 103; N, 13.58. Found: equivalent weight 106; N (Dumas), 13.58.

Synthesis of Di-*t*-butyl-di-aminoalkyl Silicates.—All six compounds were prepared in essentially the same manner. The following detailed description of the synthesis of di-*t*-butyl-di-(2-amino-1-methyl-ethyl) silicate (III) is representative of the method used. Yields, properties, and analyses of the six new compounds prepared may be found in Table I.

A solution of 231 g., 3.1 moles, of 1-amino-2-propanol and 309 g., 1.5 moles, of di-*t*-butoxydiaminosilane was refluxed for one hour in a two-liter, round-bottom flask equipped with water-cooled reflux condenser. Since at the end of this period the weight loss of the reactants corresponded to the theoretical weight of ammonia expected, the reaction was considered to have gone to completion. (Some of the other amino alcohols required a three-hour reflux period for completion of the reaction.) The equivalent weight of the crude product was 155, while the calculated equivalent weight of the expected product was 161. Distillation of the crude product at reduced pressure gave 345 g., 1.1 moles, of di-*t*-butyl-di-(2-amino-1-methyl-ethyl) silicate III.

Other compounds prepared by this method were: di-*t*-butyl-di-(2-aminoethyl) silicate I, di-*t*-butyl-di-(2-diethylaminoethyl) silicate II, di-*t*-butyl-di-(2-aminobutyl) silicate IV, di-*t*-butyl-di-(2-amino-2-methyl-propyl) silicate V, and di-*t*-butyl-di-[2-(β-aminoethylamino)-ethyl] silicate VI.

For a number of the syntheses the material balances on distillation were consistently low. In one run the volatile material lost was shown to be *t*-butyl alcohol by its melting point, boiling point, refractive index, water solubility, and conversion to *t*-butyl chloride with concentrated hydrochloric acid. Higher boiling fractions from a number of the syntheses had a high refractive index and low equivalent weight indicative of ester-interchange between *t*-butoxy groups and amino alcohol molecules.

The reaction of 2.0 moles of 2-ethylaminoethanol with 1.0 mole of di-*t*-butoxydiaminosilane repeatedly gave an anomalous result. The theoretical weight loss was attained in one and one-half hours; however, distillation of the crude product gave, as indicated by equivalent weights, an approximately equimolar mixture of di-*t*-butyl-di-(2-ethylaminoethyl) silicate, b. p. 165° at 16 mm. and $n^{20}D$ 1.423, and *t*-butyl-tri-(2-ethylaminoethyl) silicate, b. p. 185° at 19 mm. and $n^{20}D$ 1.435. The high refractive index of the higher boiling material precludes its being hexa-*t*-butoxydisilazane resulting from the condensation of di-*t*-

butoxy-diaminosilane. The presumed di-*t*-butyl-di-(2-ethylaminoethyl) silicate boiled at 285° at 740 mm. and did not decompose appreciably upon being refluxed at this temperature for one hour. Variation of conditions by adding the diaminosilane to the refluxing amino alcohol and *vice versa* appeared to give no improvement in eliminating or minimizing the formation of the side-product arising presumably by ester-interchange.

Acknowledgment.—Our thanks are due the Minnesota Mining and Manufacturing Co. and The Miner Laboratories for a research grant which made this work possible.

THE WHITMORE LABORATORY
SCHOOL OF CHEMISTRY AND PHYSICS
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PA. RECEIVED FEBRUARY 25, 1949

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Solubility and Specific Rotation of *l*-Ascorbyl Palmitate and *l*-Ascorbyl Laurate

BY DANIEL SWERN

Renewed interest in *l*-ascorbyl palmitate,[2] resulting from its recently reported antiscorbutic activity,[3] non-toxicity[4] and commercial availability[5] has prompted us to determine its solubility at 25° in some typical organic solvents, water, and cottonseed and peanut oils. For purposes of comparison, we also determined the solubility of *l*-ascorbyl laurate[2] in the two vegetable oils. We have also determined the specific rotation of both *l*-ascorbyl palmitate and laurate. With the exception of water and petroleum naphtha, the temperature coefficient of solubility is high. Benzene and ethyl acetate are two of the best crystallizing solvents for purifying the esters.

Experimental

Solubility Determinations.[6]—Solubility in petroleum naphtha, boiling range 63–70°, and water was determined on saturated solutions obtained by shaking the solvent with excess solute until equilibrium, ascertained by analysis, was attained. With all the other solvents, equilibrium was approached from the solution side by allowing excess solute to crystallize. Dissolved ester was determined either by titration with 0.1 *N* sodium hydroxide[2] or by evaporation of solvent. At least two determinations were run; precision of duplicates was about five parts per thousand. Solubility of *l*-ascorbyl palmitate in glycerol could not be determined because the solution was a thick gel. Its solubility, however, appeared to be low. Results are summarized in Table I.

Specific Rotation.—Specific rotation was determined with a Bellingham and Stanley Glass Seale polarimeter that could be read directly to 0.01°. A 5–10% solution of the ester in 95% alcohol and a 4.00-dm. tube were employed.

l-Ascorbyl palmitate: $[\alpha]^{25.5}D + 23.3°$ (8.086 g. per 100 ml. of 95% ethanol solution). *l*-Ascorbyl laurate: $[\alpha]^{25.5}D + 26.6°$ (5.014 g. per 100 ml. of 95% ethanol solution).

TABLE I

SOLUBILITY AT 25 ± 0.10°: *l*-ASCORBYL ESTERS

Solvent	Sol.[a] g./100 g.	Solvent	Sol.[a] g./100 g.
Palmitate		Palmitate	
Water[b]	0.56	Ethyl acetate	4.9
Petroleum naphtha[c]	0.00	Ethyl cellosolve[e]	>33.9
Ethanol 95%[d]	23.5	Peanut oil	0.18
Benzene	0.45	Cottonseed oil	0.22
Ethylene glycol	0.18	Laurate	
1,2-Propylene glycol	6.6	Peanut oil	0.11
Dioxane	19.0	Cottonseed oil	0.08

[a] By titration. [b] Solubility by evaporation 0.31 g./100 g. Small and probably variable quantities of solute emulsified, thus accounting for the poor duplication between the results by titration and by evaporation. [c] B. p. range 63–70°. Solubility by evaporation 0.01 g./100. [d] Solubility by evaporation 23.4 g./100. [e] Insufficient material to complete determination.

PHILADELPHIA 18, PENNA. RECEIVED JANUARY 26, 1949

Preparation of Fluorothiophene

BY ROBERT T. VANVLECK

Chloro- and bromothiophene are offered in the industrial market and iodothiophene is reported in the literature, but no reference has been made to fluorothiophene. This compound has been prepared in these Laboratories in small yields by the reaction of antimony trifluoride with iodothiophene in the presence of nitromethane as a solvent. The preparation of fluorothiophene from 2-iodothiophene indicates that the fluoro compound is the 2-isomer.

Nitroethane, nitropropane and *t*-butylthiophene were found not suitable as solvents for the reaction. Various other methods for preparing fluorothiophene proved unsuccessful; they include the reaction of antimony trifluoride with either chloro- or bromothiophene, the reaction of aluminum trifluoride with chlorothiophene, and the reaction of fluoboric acid with thiophene diazonium chloride. This last reaction was studied in an unsuccessful attempt to adapt Flood's synthesis of fluorobenzene[1] to the preparation of the thiophene analog. It is possible that the diazonium chloride was not obtained due to the instability of the aminothiophene.

Experimental

A mixture of 150 g. (0.72 mol) of iodothiophene and 43 g. (0.24 mole) of antimony trifluoride in 250 ml. of nitromethane was heated in a flask at reflux temperature (90–100°) for five hours; the product fluorothiophene distilled over through a small column as formed plus some

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Swern, Stirton, Turer and Wells, *Oil and Soap*, **20**, 224 (1943).

(3) Ambrose and DeEds, *Arch. Biochem.*, **12**, 375 (1947).

(4) Fitzhugh and Nelson, *Proc. Soc. Exptl. Biol. Med.*, **61**, 195 (1946).

(5) Chas. Pfizer and Company, New York, N. Y.

(6) Daniels, Mathews and Williams, "Experimental Physical Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1929, pp. 111 and 341.

(1) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 295.

solvent. The distillate was washed with thiosulfate solution to remove a small amount of free iodine, the organic layer separated and dried over calcium chloride. Distillation produced about a ten mole per cent. yield of the new compound, fluorothiophene, a water white liquid, boiling at 82° and having a refractive index of 1.4971, 20°/D.

Anal. Calcd. for C_4H_3SF: S, 31.37; F, 18.6. Found: S, 31.45; F, 18.0.

BEACON LABORATORIES
THE TEXAS COMPANY
BEACON, NEW YORK

RECEIVED MAY 13, 1949

Extraction of Cerium(IV) Nitrate by Butyl Phosphate[1a]

BY JAMES C. WARF[1b]

The extraction of inorganic compounds by organic solvents sometimes affords a unique method for rapidly and easily separating compounds of certain metals from common impurities. Well-known examples include the characteristic extraction of iron(III) chloride and the chlorides of a few other metals by ether, the extraction of uranyl nitrate by ether, the extraction of silver perchlorate by toluene,[2] and more recently the extraction of thorium nitrate by methyl isobutyl ketone and other solvents.[3] The extraction of cerium(IV) nitrate by ether was employed by Imre,[4] who observed that the solvent was attacked, generating heat and necessitating cooling, and that high nitric acid concentrations were required for efficient extraction. Pure ceria, however, could be produced.

A number of solvents expected to be resistant to the strong oxidizing action of cerium(IV) nitrate were tested, and nitromethane and tri-*n*-butyl phosphate found to be most satisfactory. The extent of removal of the cerium from the aqueous phase was also investigated.

Ammonium hexanitratocerate(IV) from the G. Frederick Smith Chemical Co. was employed. Tri-*n*-butyl phosphate from the Eastman Kodak Co. was vacuum distilled, the portion boiling at 145–150° (8 mm.) being collected separately; it was saturated with water before use.

The degree of stability of the solvent toward oxidation by the solute was established by permitting portions of solutions 0.5 *F* in ammonium hexanitratocerate(IV) and 1.0 *F* in nitric acid to stand at room temperature with the solvent for increasing periods of time, after which the cerium(IV) content was determined by titration with iron(II) sulfate solution using tris-(1,10-phenanthroline)-iron(II) sulfate as indicator.

The extent of extraction of the cerium(IV) nitrate was determined similarly by separating layers and titrating each immediately. The solvent layer was scrubbed several times with a solution 1.0 *F* each in nitric acid and ammonium nitrate before re-extraction of the cerium.

The rate of reduction of the cerium(IV) nitrate by butyl phosphate under the conditions described is indicated by the following results: After 1.6 hours, 1% of the total cerium(IV) was reduced; after 35 hours, 5%; after 120 hours, 10%; after 500 hours, 31%; and after 820 hours, 45%.

Conditions for favorable extraction were found to cover a wide range, 98–99% of the cerium entering the solvent when equal phase volumes were employed, regardless of the ammonium nitrate and nitric acid concentrations. The presence of nitric acid was found necessary to promote clean separation of the layers. At extreme dilution (0.001 *F* Ce(IV)) less favorable partition was observed, only 60–70% being extracted. Solutions of ammonium hexanitratocerate(IV) in 1.0 *F* nitric acid were used most frequently. Aqueous phases after extraction were colorless, and a few per cent. of the cerium(IV) was reduced to cerium(III) during the course of the operations. Addition of ammonium acetate or perchlorate to the aqueous phase had little effect on the degree of extraction, but ammonium sulfate caused serious interference.

Recovery of the cerium from the butyl phosphate by re-extraction with water or dilute nitric acid was slow and laborious, although the use of ammonium sulfate solutions was feasible. Generally the cerium(IV) was quickly and quantitatively re-extracted through reduction to cerium(III) by hydrogen peroxide; hydroxylamine, formaldehyde or glucose also were employed. Evaporation of aqueous solutions of the recovered cerium(III) salts and ignition yielded gray or black products, owing to the presence of pyrophosphates. This difficulty was avoided by washing the water phase thoroughly with benzene or carbon tetrachloride, to remove the small quantity of dissolved butyl phosphate, before evaporation or precipitation of cerium(III) oxalate. Cerium(IV) oxide resulting on ignition after such treatment was practically pure white, and contained negligible amounts of phosphorus.

Over 99.5% of the cerium could be removed from cerium(III) nitrate solutions by first oxidizing electrolytically as recommended by Smith, Frank and Kott,[5] in three steps, each followed by a butyl phosphate extraction. It was found more convenient to perform the oxidation chemically, using bromates in strong nitric acid solution, a procedure first employed by Schuman.[6] In order to realize quantitative removal of the cerium, a small continuous extractor was used.

A U-tube stirrer-extractor, described by Huzise,[7] was constructed. It was charged with 100–150 ml. of a solution 0.2 *F* in cerium(III) nitrate, 8–10 *F* in nitric acid, and 3 *F* in sodium nitrate. Small portions of solid sodium bromate were added over a period of two to three hours, using a total of 3 g., while butyl phosphate was run

(1a) Based on work done for the Manhattan District (Contract No. W-7405 eng-82), F. H. Spedding, Project Director. First recorded in Plutonium Project reports CC-2402 (April 3, 1945) and ISC-8 (August 7, 1947), by J. Warf.

(1b) Present address: Department of Chemistry, University of Southern California, Los Angeles 7, California.

(2) Hill and Miller, THIS JOURNAL, **47**, 2702 (1925).

(3) Rothschild, Templeton and Hall, *J. Phys. Colloid Chem.*, **52**, 1006 (1948).

(4) Imre, *Z. anorg. allgem. Chem.*, **164**, 214 (1927).

(5) Smith, Frank and Kott, *Ind. Eng. Chem., Anal. Ed.*, **12**, 268 (1940).

(6) Schuman, Plutonium Project Report CC-2739 (February 23, 1945).

(7) Huzise, *J. Chem. Soc. Japan*, **62**, 360 (1941).

through the extractor, a total of 300 ml. being employed. The solvent was well dispersed by the stirrer, and rose to form a static layer in the exit arm of the U-tube, from which it drained at the same rate at which fresh solvent was added. Qualitative tests showed no detectable cerium remaining in the water phase. The butyl phosphate extracted bromine as well as cerium.

Uranyl and thorium nitrates were observed to be readily extracted by butyl phosphate. These elements can be separated by extraction of cerium(III) solutions. The extraction of iron, zirconyl and lanthanum nitrates by butyl phosphate was also studied. The results showed that excellent separation from iron, fair separation from zirconium, and rather poor separation from lanthanum can be expected.

Iron(II) nitrate solutions, containing 1 mg. to 5 g. of iron per 100 ml., and 1.0 *F* in nitric acid, were extracted with butyl phosphate, the organic layer washed with ammonium nitrate–nitric acid solution, and re-extracted with hydrogen peroxide. The amount of iron thus recovered was determined spectrophotometrically with 1,10-phenanthroline and the ratio of the amount of iron in the original aqueous phase to the amount from the organic phase taken as a "separation factor." This factor varied from 2000 for low iron concentrations to 1.6×10^6 for the high concentrations. Similar experiments with zirconium, using a radioactive isotope (Zr^{95}, half-life 65 days) showed separation factors of 200 to 600, while with lanthanum (La^{140}, half-life 40 hours), factors of only 80 to 100 were observed. Lanthanum nitrate solution (500 mg. of La per 100 ml.) was extracted exhaustively by the stirrer U-tube technique described above, using sodium bromate, when 4 to 7% was found to be carried over.[8]

The high degree of extraction by butyl phosphate over a wide range of conditions suggested formation of a compound between the solvent and cerium(IV) nitrate.

Absorption spectra of aqueous and butyl phosphate solutions each 0.05 *F* in cerium(IV) nitrate were identical except for a slight shift toward the longer wave lengths for the non-aqueous solution. The absorption curves had no maxima, and both solutions were transparent for wave lengths above 580 mμ. The solvents were non-absorbing for wave lengths above 400 mμ. Kjeldahl analyses of the organic phase showed that no ammonium compound was present. Treatment of small known quantities of the solvent with a large excess of cerium(IV) nitrate solution, followed by extraction with carbon tetrachloride and determination of the Ce(IV) content, showed Bu_3PO_4/Ce ratios of 2.5 ± 0.1. Butyl phosphate extracts of ammonium hexanitratocerate(IV) from solutions containing no additional nitric acid were analyzed for nitrate by the nitron method,[9] and for cerium(IV), which gave NO_3/Ce ratios of 3.3 ± 0.2. While these values do not coincide with the ratios demanded by a simple formula, there was also no assurance of complete conversion of the reactants into a single compound. The analytical work was not pursued sufficiently to establish unambiguously the identity of the extracted substance or substances.

CONTRIBUTION NO. 53 FROM THE
INSTITUTE FOR ATOMIC RESEARCH
IOWA STATE COLLEGE
AMES, IOWA

RECEIVED APRIL 19, 1949

(8) Electrolytic oxidation is preferred to the use of bromates, for the latter seemed to permit greater extraction of iron, zirconium, and lanthanum. This may be attributable to the formation of bromides. It was observed that the behavior of zirconyl halides toward butyl phosphate extraction was quite different from that of the nitrate.

(9) Busch, *Ber.*, **38**, 861 (1905); Gutbier, *Z. angew. Chem.*, **18**, 494 (1905).

NEW COMPOUNDS

The Diacetate of 2-Methyl-1,3-pentanediol

Investigations in this Laboratory led to the preparation of the diacetate of 2-methyl-1,3-pentanediol. This new compound is of interest as it was reported by previous investigators[1] that the reaction of 2-methyl-1,3-pentanediol with acetic anhydride yields only the monoacetyl derivative.

Procedure.—One-half mole of 2-methyl-1,3-pentanediol and one-half mole of acetic anhydride were refluxed with a trace of sulfuric acid for three hours. At the end of this period, toluene was added to the reaction flask and a water-trap placed in the reflux system. The water from the reaction was then removed by refluxing with the toluene. The glycol diacetate was recovered in good yield after removal of the toluene and subsequent fractionation through a five-bulb Snyder column.

The physical constants of the diacetate of 2-methyl-1,3-pentanediol are: b. p., 225° (uncor.); d^{20}_4 1.0025; $n^{20}D$ 1.4253; *anal.* 99% ester content as the diacetate of 2-methyl-1,3-pentanediol; mol. ref. 51.68 found; 51.56 calcd.

PETROLEUM RESEARCH AND DEVELOPMENT LABORATORY
CELANESE CORPORATION OF AMERICA
CLARKWOOD, TEXAS GUILES FLOWER, JR.[2]

RECEIVED MARCH 9, 1949

(1) Kling and Roy, *Bull. soc. chim.*, [4] **1**, 698 (1907); Kling and Roy, *Compt. rend.*, **144**, 1112 (1907).

(2) Present address: Dictaphone Corporation, Bridgeport 5, Connecticut.

Esters of 5-Methyl-2-thenoic Acid

The esters of 5-methyl-2-thenoic acid listed in Table I were prepared by refluxing 10 g. (0.07 mole) of the acid[1] in an excess (125 ml.) of the required alcohol containing 6–7 ml. of concd. sulfuric acid. After refluxing for four hours, the esters were worked up in the usual manner, and vacuum-distilled.

TABLE I

ESTERS OF 5-METHYL-2-THENOIC ACID

Ester	B. p., °C. (5 mm.)	d^{20}_4	$n^{20}D$	Yield, %	Sulfur, %[b] Calcd.	Found
Methyl	77–79[a]	1.1736	1.5380	71	20.53	20.70
Ethyl	87–89	1.1234	1.5233	82	18.83	18.99
n-Propyl	95–98	1.0936	1.5075	80	17.40	17.47
i-Propyl	87–88	1.0766	1.5092	44	17.40	17.14
n-Butyl	106.5–108.5	1.0668	1.4955	88	16.17	16.18
i-Butyl	102–105	1.0610	1.5082	76	16.17	16.33
n-Amyl	116–118	1.0456	1.5054	64	15.10	15.29

[a] Rinkes reported a b. p. 102° (16 mm.) (*Rec. trav. chim.*, 52, 538 (1933)). [b] Analyses by Mrs. Betty Jarvis.

(1) Prepared by the method of Hartough and Conley, THIS JOURNAL, **69**, 3096 (1947), in an average of 69%.

INDIANA UNIVERSITY HERSCHEL G. GROSE
BLOOMINGTON, INDIANA E. E. CAMPAIGNE

RECEIVED MAY 21, 1949

3-(4- and 5-Methyl-2-pyridylamino)-acrylic Acids[1]

These two new derivatives of acrylic acid were prepared for biological testing at the request of the Chemical-Bio-

(1) This work was carried out under a Grant-in-Aid from the Research Corporation.

logical Coördination Center of the National Research Council. Preparation was accomplished by heating 5 g. of either the corresponding ethyl 2-pyridylaminomethylenemalonate (I)[2] or the 3-carbethoxy-2H-pyrido-1,2-a-pyrimidine-4-one (II)[2] with 250 ml. of 1% aqueous sodium hydroxide solution at 90° for five minutes with II or thirty minutes with I. The solution was filtered hot and made acid to congo red with dilute hydrochloric acid while still hot. The precipitated acid was twice recrystallized from pyridine.

3-(4-Methyl-2-pyridylamino)-acrylic Acid.—M. p. 238° with decarboxylation; yield from I 43%, from II 61%.

Anal. Calcd. for $C_9H_{10}O_2N_2$; N, 15.72; neut. equiv., 178. Found: N, 15.65[3]; neut. equiv., 176.

3-(5-Methyl-2-pyridylamino)-acrylic Acid.—M. p. 258° with decarboxylation; yield from I 36%, from II 67%.

Anal. Calcd. for $C_9H_{10}O_2N_2$: N, 15.72; neut. equiv., 178. Found: N, 15.74[3]; neut. equiv., 180.

(2) G. R. Lappin, THIS JOURNAL, **70**, 3348 (1948).

(3) Microanalysis by the Clark Microanalytical Laboratory, Urbana, Ill.

CHEMICAL LABORATORY
ANTIOCH COLLEGE
YELLOW SPRINGS, OHIO GERALD R. LAPPIN

RECEIVED MAY 16, 1949

Some Quaternary Salts of Carbamates of Amino Alcohols[1]

A series of compounds of the general formula $[R_3'N—A—OCONR_2]^+I^-$ has been prepared (Table I). The unsubstituted carbamates (both R = H) were prepared by method 1, the N-methylcarbamates (R = CH_3, and R = H) by method 2, and the N,N-dimethylcarbamates (both R = CH_3) by method 3.

(1) Reaction of a dialkylamino alcohol with phosgene gave the dialkylaminoalkyl chloroformate, which reacted with ammonia to give the urethan. Condensation with an alkyl iodide gave the quaternary salt.[2]

$$R_2N(CH_2)_nOH \xrightarrow{COCl_2} R_2N(CH_2)_nOCOCl \xrightarrow{NH_3}$$

$$R_2N(CH_2)_nOCONH_2 \xrightarrow{RI} [R_3N(CH_2)_nOCONH_2]^+I^-$$

(2) Reaction of a dialkylamino alcohol with methyl isocyanate gave a carbamate, which reacted with an alkyl iodide to give the quaternary salt.

$$R_2N(CH_2)_nOH \xrightarrow{CH_3NCO} R_2N(CH_2)_nOCONHCH_3 \xrightarrow{RI} [R_3N(CH_2)_nOCONHCH_3]^+I^-$$

(3) Reaction of a chloro alcohol and phosgene gave the chloroalkyl chloroformate, which was converted to the iodoalkyl carbamate by reaction first with dimethylamine and then with sodium iodide in acetone. Condensation of the iodoalkyl carbamate with a tertiary amine gave the quaternary salt.[3]

$$Cl(CH_2)_nOH \xrightarrow{COCl_2} Cl(CH_2)_nOCOCl \xrightarrow{(CH_3)_2NH}$$

$$Cl(CH_2)_nOCON(CH_3)_2 \xrightarrow{NaI} I(CH_2)_nOCON(CH_3)_2 \xrightarrow{R_3N} [R_3N(CH_2)_nOCON(CH_3)_2]^+I^-$$

(3) Sprinson, THIS JOURNAL, **63**, 2249 (1941).

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY L. KAPLAN
STANFORD, CALIF. C. R. NOLLER

RECEIVED APRIL 27, 1949

TABLE I

QUATERNARY SALTS OF CARBAMATES OF AMINO ALCOHOLS

Compound	M. p., °C.	Formula	Iodide analyses, % Calcd.	Found
2-Di-*n*-butylaminoethyl carbamate butiodide	99–100	$C_{15}H_{33}IN_2O_2$	31.70	31.47
3-Di-*n*-butylaminopropyl carbamate butiodide	122–123	$C_{16}H_{35}IN_2O_2$	30.62	30.64
3-Di-*n*-amylaminopropyl carbamate amyl iodide	108–110	$C_{19}H_{41}IN_2O_2$	27.80	27.40
2-Diethylaminoethyl N-methylcarbamate ethiodide	90–92	$C_{10}H_{23}IN_2O_2$	38.42	38.52
2-Di-*n*-butylaminoethyl N-methylcarbamate butiodide	100–101.5	$C_{16}H_{35}IN_2O_2$	30.62	30.43
2-Pentamethyleneaminoethyl N-methylcarbamate methiodide	103–105	$C_{10}H_{21}IN_2O_2$	38.66	38.99
3-Di-*n*-butylaminopropyl N-methylcarbamate butiodide	110.5–112	$C_{17}H_{37}IN_2O_2$	29.62	29.36
3-Di-*n*-amylaminopropyl N-methylcarbamate amyliodide	78–83	$C_{20}H_{43}IN_2O_2$	26.97	27.05
1-(3,4-Methylenedioxybenzyl)-2-[(3,4-methylenedioxybenzyl)-methylamino]-ethyl N-methylcarbamate methiodide	155–157	$C_{22}H_{27}IN_2O_6$	23.40	23.30
3-Dimethylamino-*d*-bornyl N-methylcarbamate methiodide	187–189	$C_{15}H_{29}IN_2O_2$	32.02	31.91
2-Diethylaminoethyl N,N-dimethylcarbamate ethiodide	106–107	$C_{11}H_{25}IN_2O_2$	36.86	37.08
Octahydro-N-[2-(dimethylcarbamyloxy)-ethyl]-2-methyl-pyrrocolinium iodide	150–151.5	$C_{14}H_{27}IN_2O_2$	33.19	33.23

(1) These compounds were prepared for the Office of Scientific Research and Development under Contract OEMsr-136 with Stanford University.

(2) Dalmer and Diehl, U. S. Patent 1,894,162; *C. A.*, **27**, 2533 (1933).

Stilbestrol Esters

Since a new series of testosterone esters[1] was found to have greater androgenic activity than testosterone propionate, similar stilbestrol esters have been prepared to determine whether these esters have any advantage over stilbestrol dipropionate. Two representative esters have been prepared.

Diethylstilbestrol Di-ethoxyacetate.—A solution of 1 g. of diethylstilbestrol (1 mole) in 15 cc. of dry ether and 6 cc. of dry pyridine was prepared. To this was added 2 cc. of ethoxyacetyl chloride (5 mole) in 10 cc. of dry ether. The reaction mixture was refluxed for one hour and 100 cc. more ether was added. This was poured into water and the ether layer separated, washed with dilute sulfuric acid, dilute sodium carbonate solution and water. Evaporation of the ether left 1.40 g. of reddish white powder, m. p. 129–136°. The product was taken up in a large amount of ether and filtered through activated alumina (Aluminum Ore Co. mm. 80 mesh). The red color was adsorbed on the alumina. Evaporation of the ether left a residue which was twice crystallized from 95% ethanol giving a product (1.05 g.) melting at 136.5–137.5°.

Anal. Calcd. for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32. Found: C, 71.16; H, 7.57.

(1) Mooradian and Lawson, in press.

Diethylstilbestrol Di-ethylmercaptoacetate.—This ester was prepared just as was the preceding ester. The purification was carried out by evaporating the ether extract to dryness and taking the residue up in 10 cc. of ether and 40 cc. of Skellysolve A. This solution was passed through activated alumina and the alumina was then extracted with 1:4 ether–Skellysolve A. The extract was evaporated and the absorption-elution process carried out twice more. Finally the crude product (1.05 g.) was crystallized once from Skellysolve B and twice from 95% ethanol giving a yellowish product 0.30 g., m. p. 99–101°.

Anal. Calcd. for $C_{26}H_{32}O_4S_2$: C, 66.04; H, 6.83; S, 13.57. Found: C, 66.01; H, 6.73; S, 13.83.

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E. J. LAWSON

RECEIVED MARCH 16, 1949

COMMUNICATIONS TO THE EDITOR

THE USE OF CADMIUM IODIDE IN STARCH–IODINE COLORIMETRIC PROCEDURES

Sir:

In the course of an investigation[1] on methods of analysis for trace amounts of selenium in water, it was found that cadmium iodide and starch form a stable solution which may be used as a colorimetric reagent for a number of oxidizing substances. The reduction potential of the iodide in such a solution is a function of the *p*H. By proper adjustment of the *p*H, the iodide may be "exposed" to oxidation by oxidizing agents for controlled periods of time and in this way it was found possible to determine one oxidizing agent in the presence of others.

Cadmium iodide crystals may have a brownish discoloration which is shown by reaction with starch to be free iodine. However, after an aqueous solution of cadmium iodide is boiled for ten or fifteen minutes, a colorless solution is obtained. This solution may be added to a solution of starch to give a mixture that is apparently stable indefinitely to atmospheric oxygen and diffused sunlight.

In neutral solution, only the very strongest oxidizing agents, such as chlorine or hypochlorite, are capable of oxidizing the iodide to iodine and producing the blue starch–iodine color. At lower *p*H values, weaker oxidizing agents are able to oxidize the iodide; *e. g.*, nitrous acid is capable of oxidizing the iodide if the *p*H is below about 4.0 but the *p*H must be in the neighborhood of 1.0 or lower before selenious acid is able to react. Dissolved oxygen attacks the cadmium iodide reagent only in the most highly acid solutions, and very slowly even then.

The linear starch "A-fraction" isolated by Schoch[2] gives the best results although commercial soluble starches can be used. The color of the A-fraction starch–iodine complex produced by selenious acid in concentrations from 0.1 to 2.0 p. p. m., as selenium, follows Beer's law quite closely. The absorption band is broad with maximum absorption occurring at about 615 mμ.

Cadmium iodide in aqueous solution has been shown to form one or more auto-complexes, the nature of which has been the subject of several investigations. The complex anion may be CdI_3^-, $CdI_4^=$ or $CdI_5^{\equiv}$, with the cation Cd^{++} or CdI^+.

This reagent is undergoing further investigation in connection with the development of colorimetric methods of determining traces of substances having oxidizing properties, particularly selenium as selenious acid.

We wish to thank T. J. Schoch of the Corn Products Refining Company for providing generous samples of the linear starch A-fraction.

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RECEIVED JULY 11, 1949

(1) This investigation is supported by a research grant from the National Institutes of Health.

(2) Schoch, THIS JOURNAL, **64**, 2957–2961 (1942); "Advances in Carbohydrate Chemistry," Vol. I, ed. by Pigman and Wolfrom, Academic Press Inc., New York, N. Y., 1945, pp. 247–277.

GERMIDINE AND GERMITRINE, TWO NEW ESTER ALKALOIDS FROM *VERATRUM VIRIDE*

Sir:

Recent evidence[1,2] indicates that powdered roots and rhizomes of *Veratrum viride* may produce marked reductions of arterial pressure in patients with essential hypertension. We have isolated from this material two new, highly active ester alkaloids derived from the alkamine germine, which we have named germidine and germitrine.[3]

(1) E. D. Freis and J. R. Stanton, *Am. Heart J.*, **36**, 723 (1948).

(2) E. D. Freis, *et al.*, *J. Clin. Investigation*, **28**, 353 (1949).

(3) Drs. E. D. Freis, J. A. Stanton and F. C. Moister of the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, have evaluated more than 100 of our individual alkaloidal fractions in patients with essential hypertension. Their results will be published elsewhere.

Preliminary fractionation of the benzene-extractable alkaloids by the excellent procedure of Jacobs and Craig[4] yielded the five known crystalline alkaloids and a large amorphous fraction; only the latter was active as a hypotensive agent at low dosage. Further fractionation of this material guided by assay[3] in hypertensive patients yielded a highly active concentrate, which on 24-plate Craig distribution, using 2 *M* acetate buffer at *p*H 5.5 and benzene as the immiscible phases, exhibited two discrete peaks. The material having a peak at tube 15 ($K = 1.67$) showed activity when administered orally in doses of 0.6–0.8 mg. per patient, while the material from the second peak, at tube 6 ($K = 0.35$), was active at about 4 mg. These fractions crystallized readily from methanol–water and ethanol–water respectively, yielding germidine (m. p. 220–223° (cor.); $[\alpha]^{25}D + 13°$ (*c*, 1.67 in chloroform)) and germitrine (m. p. 197–199° (cor.); $[\alpha]^{25}D + 11°$ (*c*, 1.54 in chloroform)).

Room temperature hydrolysis of germidine with 0.1 *N* aqueous methanolic alkali afforded germine ($C_{27}H_{43}O_8N$),[5] acetic acid and α-methylbutyric acid. The former was identified by rotation, analysis and conversion into monoacetonylgermine hydrochloride.[6] The acids, after conversion into the *p*-phenylphenacyl esters followed by chromatography on alumina, yielded *p*-phenylphenacyl α-methylbutyrate[7] (m. p. 71–72° (cor.)) and *p*-phenylphenacyl acetate[8] (m. p. 109–110° (cor.)). Analysis of the free base and the crystalline thiocyanate (m. p. 242–244° dec. (cor.)) indicates germidine to be an ester of germine with one mole each of the above acids.

Hydrolysis of germitrine yielded germine, α-methylbutyric acid and methyl-ethylglycolic acid. The phenylphenacyl ester of the latter (m. p. 119–120° (cor.); $[\alpha]^{25}D + 5°$ (*c*, 0.64 in chloroform)) was identical with an authentic sample.

Analysis of the free base and the thiocyanate (m. p. 228–231° dec. (cor.)) indicates that germitrine is probably a mono-α-methylbutyrate dimethylethylglycolate of germine.

The specific rotations of the branched-chain acids (isolated from the total amorphous fraction because of an insufficient supply of the crystalline alkaloids) showed these materials to be *l*-α-methylbutyric and *d*-methylethylglycolic acids. Germidine and germitrine, injected intravenously in doses of 0.6–0.8 γ per kg., markedly lowered the blood pressure of anesthetized dogs and cats.[9]

DIVISION OF ORGANIC CHEMISTRY JOSEF FRIED
SQUIBB INSTITUTE FOR MEDICAL RESEARCH HOWARD L. WHITE
NEW BRUNSWICK, NEW JERSEY O. WINTERSTEINER

RECEIVED AUGUST 9, 1949

(4) W. A. Jacobs and L. C. Craig, *J. Biol. Chem*, **160**, 555 (1945).
(5) W. Poethke, *Arch. Pharm.*, **275**, 571 (1937).
(6) L. C. Craig and W. A. Jacobs, *J. Biol. Chem.*, **148**, 57 (1943).
(7) F. Kögl and H. Erxleben, *Z. physiol. Chem.*, **227**, 70 (1934).
(8) N. L. Drake and J. Bronitsky, THIS JOURNAL, **52**, 3715 (1930).
(9) Dr. S. Krop of the Division of Pharmacology will report on these findings elsewhere.

THE BIO-OXYGENATION OF 11-DESOXYCORTICOSTERONE AT C-11[1]

Sir:

A number of chemical processes[2] have been elaborated for introducing an oxygen function at C_{11} in the partial synthesis of adrenal cortical hormones. We wish to report a biochemical process, different from any hitherto described, which leads to the production of corticosterone from 11-desoxycorticosterone.

Using methods previously reported,[3,4] it was found that after perfusing 11-desoxycorticosterone (DOC) through isolated adrenal glands the perfusate contained large amounts of glycogenic activity.[5] The method of assay employed was that of Olson, *et al.*[6] The increased glycogenic activity was observed whether plasma or blood was used as the perfusion medium, and in the absence of adrenocorticotrophic hormone (ACTH). The activity could not be accounted for in terms of DOC recovered from the perfusates. Neither perfusion of the gland in the absence of DOC and ACTH,[4] nor the circulation of DOC in the absence of the gland led to significant activity; nor was it possible to demonstrate a synergistic action of DOC upon the glycogenic steroids present in adrenal extracts (Upjohn).

These observations strongly suggested that the isolated adrenal introduced an 11-oxygen function into desoxycorticosterone. Further work has resulted in the isolation from these perfusates of corticosterone, m. p. 173.3–180° (178–180.5°),[7] $[\alpha]^{30}D +227°$ (*c*, 0.240, ethanol), as the principal crystalline transformation product. The identity was established conclusively by the melting point, 173–181°, of a mixture with an authentic sample of corticosterone (Upjohn), m. p. 173–179° (176.5–181°), and by the formation of an acetate, m. p. 150.5–152.5°, whose mixture with authentic corticosterone 21-acetate, m. p. 151.5–152.5°, melted at 150.5–152°.

Similar perfusion experiments employing 11-desoxycorticosterone 21-acetate also yielded corticosterone, the ester group apparently being hydrolyzed in the course of the perfusion.

These studies have been extended to a variety of steroids including progesterone, 4-androstene-3,17-dione, 17-hydroxyprogesterone, epi-androsterone, androsterone, 17-hydroxy-11-desoxycorticosterone and 5-pregnen-3-ol-20-one, and the

(1) The work described in this paper was supported by a grant from G. D. Searle and Company.
(2) For a comprehensive review of these processes, see L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," third edition, Reinhold Publishing Corp., New York, N. Y., p. 452, 1949.
(3) O. Hechter, *Endocrinology*, **42**, 285 (1949).
(4) O. Hechter, *Federation Proc.*, **8**, 70 (1949).
(5) O. Hechter and G. Pincus, unpublished observations.
(6) R. E. Olson, *et al.*, *Endocrinology*, **35**, 430 (1944).
(7) All comparison melting points were taken on powdered samples in open Pyrex capillaries. The melting points in parentheses were obtained for intact crystals whether determined in a capillary or on a Fisher–Johns block.

transformation products formed by the gland are being separated and identified.

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY, SHREWSBURY, MASSACHUSETTS, AND THE DEPARTMENT OF PHYSIOLOGY, TUFTS COLLEGE MEDICAL SCHOOL, BOSTON, MASSACHUSETTS
OSCAR HECHTER, ROBERT P. JACOBSEN, ROGER JEANLOZ, HAROLD LEVY, CHARLES W. MARSHALL, GREGORY PINCUS, VICTOR SCHENKER

RECEIVED JULY 29, 1949

THE CONFIGURATION OF THE 1,3-DICHLOROPROPENES

Sir:

Considerable interest has been shown[1] in the structure of the two isomeric 1,3-dichloropropenes and there has not been complete agreement as to which isomer should be assigned the *cis* configuration and to which the *trans* configuration. This difference of opinion has been caused, in part, by the lack of an unequivocal proof of structure. The configuration of each of the two isomers of 1,3-dichloropropene has now been determined by chemically transforming each isomer into a compound the configuration of which has been established.

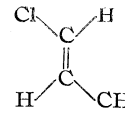
The low boiling isomer of 1,3-dichloropropene (b. p. 57.5° (150 mm.), $n^{25}D$ 1.4652, d^{25}_4 1.2048) was refluxed for four hours with sufficient lithium aluminum hydride in isopropyl ether[2] to replace one chlorine atom with a hydrogen atom. By this treatment there was obtained a 50% conversion with a 46% yield of *cis*-1-chloropropene-1 having the following constants: b. p. 32.5° (749 mm.), $n^{20}D$ 1.4054 (lit.[3] b. p. 32.0–32.2° (747 mm.), $n^{20}D$ 1.4053). Similar treatment of the high boiling isomer of 1,3-dichloropropene (b. p. 112.2° (760 mm.), $n^{25}D$ 1.4712, d^{25}_4 1.2139) gave a 56% conversion with a 50% yield of *trans*-1-chloropropene-1, b. p. 37.2° (750 mm.), $n^{20}D$ 1.4048 (lit.[3] b. p. 36.7° (747 mm.), $n^{20}D$ 1.4054). In neither reaction was there any indication of the formation of a mixture of *cis*- and *trans*-1-chloropropene-1.

From these experimental data it follows that the low boiling isomer of 1,3-dichloropropene has the following configuration



Low-boiling 1,3-dichloropropene — *cis*-1-Chloropropene-1

while the high boiling isomer has the remaining configuration



High-boiling 1,3-dichloropropene

This assignment of configuration is in agreement with that proposed by Andrews and Kepner[1b] and not that proposed by Hatch and co-workers.[1a,c]

This method of ascertaining configuration is also being applied to other allylic chlorides which yield compounds of known structure upon replacement of the allylic chlorine atom by a hydrogen atom.

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LEWIS F. HATCH, ROBERT H. PERRY, JR.

RECEIVED JULY 16, 1949

(1) (a) Hatch and Roberts, THIS JOURNAL, **68**, 1196 (1946); (b) Andrews and Kepner, *ibid.*, **69** 2230 (1947); (c) Hatch, Gordon and Russ, *ibid.*, **70**, 1093 (1948); (d) Smith and King, *ibid.*, **70**, 3528 (1948); (e) "Data Sheet" on the 1,3-dichloropropenes published by Shell Chemical Corporation, 8/4/47.

(2) Nystrom and Brown, *ibid.*, **70**, 3738 (1948).

(3) Kharasch, Englemann and Mayo, *J. Org. Chem.*, **2**, 288 (1938).

PREPARATION OF ADRENAL CORTICAL HORMONES

Sir:

We have made certain observations in the partial synthesis of adrenal cortical hormones which show that it is possible to introduce the 17α-hydroxy group in 11,20-diketo steroids. In addition we have studied the preparation of the dihydroxyacetone side-chain as exemplified by Reichstein's Compounds S and P. Since the reactions appear to be generally applicable, it is possible to prepare adrenal cortical hormones of both the 11-keto series such as Kendall's Compound E and its 11-desoxy analog, Reichstein's Compound S, both of current interest in their medical application.

When the dienol acetate derived from 3α-hydroxypregnane-11,20-dione (m. p. 200–201°; $[\alpha]^{33}D$ +105° (chloroform); $C_{27}H_{38}O_6$, calcd.: C, 70.71; H, 8.35; found: C, 70.80; H, 8.21) is treated with perbenzoic acid according to the procedure of Kritchevsky and Gallagher[1] the reaction product after saponification yielded 3α,17α-dihydroxypregnane-11,20-dione, m. p. 198–201°; $[\alpha]^{32}D$ +66° (acetone). The monoacetate of this compound, m. p. 202–204°, $[\alpha]^{34}D$ +81° (acetone), upon oxidation with chromic anhydride yielded 3α-acetoxyetiocholane-11,17-dione identical in all respects with the known compound. The enol of the 11-keto group therefore either does not react or reacts to such a negligible extent that isolation of the desired product in good yield is easily possible. This establishes the formation of a 17α-hydroxy derivative from a 20-keto steroid with an 11-keto group.

The preparation of the dihydroxy acetone side-chain characteristic of the most active adrenal hormones is illustrated by the reactions leading to the formation of Reichstein's Compounds P and S. Bromination of 3α-acetoxy-17α-hydroxyallopregnan-20-one with one mole of bromine yielded the 21-bromo derivative, m. p. 184–187°; $C_{23}H_{35}O_4Br$, calcd. Br, 17.76; found: Br, 17.47. Hydrolysis

(1) Kritchevsky and Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

with 0.05 *N* sodium hydroxide in 60% ethanol at room temperature in a nitrogen atmosphere for ten minutes resulted in replacement of halogen by a hydroxyl group. Acetylation yielded the diacetate of Reichstein's Compound P, m. p. 206–207°; $[\alpha]^{25}D$ +48° (chloroform).

The preparation of Reichstein's Compound S was achieved by the following reactions: 3α-formoxy-17α-hydroxypregnan-20-one (m. p. 184–185°; $[\alpha]^{34}D$ +68° (ethanol), $C_{22}H_{34}O_4$, calcd.: C, 72.89; H, 9.45; found: C, 73.00; H, 9.63) was brominated as in the preceding experiment yielding the 21-bromo compound as a solvate, m. p. 188–190°; $[\alpha]^{35}D$ +75° (ethanol). The formate was converted to the hydroxy compound, m. p. 202–204°, with methanol and dry hydrogen chloride at 5° for fourteen hours. Oxidation of 3α,17α-dihydroxy-21-bromopregnan-20-one with N-bromoacetamide yielded 17α-hydroxy-21-bromopregnan-3,20-dione, m. p. 203–204°; $[\alpha]^{33}D$ +81° (ethanol); $C_{21}H_{31}O_3Br$, calcd.: C, 61.31; H, 7.60; Br, 19.43; found: C, 61.02; H, 7.65; Br, 19.59. Hydrolysis of the halogen was accomplished by the procedure described above and, without isolation, the reaction product was acetylated, yielding 21-acetoxy-17α-hydroxypregnan-3,20-dione, m. p. 195–197°; $[\alpha]^{32}D$ +81° (ethanol). Bromination in acetic acid yielded the 4-bromo derivative (m. p. 196–203°; $[\alpha]^{36}D$ +83° (chloroform); $C_{23}H_{33}O_5Br$, calcd.: Br, 17.03; found: Br, 17.62) which was dehydrobrominated by a modification of the Mattox and Kendall[2] procedure to yield Reichstein's Compound S acetate, m. p. 237–241°; $[\alpha]D$ +116° (acetone); ϵ_{2410} = 17,400 (methanol).

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RECEIVED AUGUST 19, 1949

(2) Mattox and Kendall, THIS JOURNAL, **70**, 882 (1948).

(3) Visiting investigator from the University of New Brunswick, Fredericton, N. B.

SEPARATION OF ZIRCONIUM AND HAFNIUM WITH ANION EXCHANGE RESINS[1]

Sir:

During the course of an investigation of the behavior of negatively charged metal complexes on anion exchange resins, an attempt was made to separate zirconium and hafnium. These elements are generally considered to form negatively charged complexes[2] with certain complexing agents, particularly fluoride and oxalate ions. These elements, furthermore, are generally believed to be in true solution (rather than colloidal solutions) only if they are in the form of ionic complexes.

A separation based on their ability to form negatively charged complexes thus would have the advantage of being specifically designed for operation under conditions where true solution is most probable and complications due to hydrolysis (colloid formation or precipitation) minimized.

The experiments which have been carried out have demonstrated that separation of Zr(IV) and Hf(IV) by anion exchange is feasible, although the separation achieved is by no means at its optimum. Experiments are now under way to improve the efficiency of separation.

Partial separation of Zr(IV) and Hf(IV) at room temperature was achieved using a 107-cm. column of 200–230-mesh Dowex-1 (a quaternary amine anion exchanger) of 0.0226 sq. cm. cross section, and a mixture of 0.5 *M* hydrofluoric acid–1.0 *M* hydrochloric acid as eluent. Flow rates of *ca.* 0.3 ml./sq. cm./min. were used. Under these conditions elutions are relatively rapid (complete elution in *ca.* one and one-half days). The experiments were carried out with tracer concentrations of zirconium and 0.2 mg. of hafnium, using Zr^{95} (β-emitter, $T_{1/2}$ = 65 days[3]) and Hf^{181} (β-emitter, $T_{1/2}$ = 55 days[3]) as tracers. Zirconium and hafnium were identified radiochemically and in particular the hafnium content of the various elution fractions was determined by delayed coincidence counting taking advantage of the metastable daughter Ta^{181} (γ-emitter, $T_{1/2}$ = 20μsec.[4]) of Hf^{181}.[5]

The results of a typical experiment are shown in Table I. It may be noticed that the earlier fractions are highly depleted of hafnium, while the last fractions are practically pure hafnium.

TABLE I

SEPARATION OF ZIRCONIUM AND HAFNIUM IN 1.0 *M* HCl–0.5 *M* HF

Column length 107 cm., average flow-rate 0.29 ml. cm.$^{-2}$ min.$^{-1}$

No.	Vol., ml.	Spec.[a] act.	Rate[b]	% Hf[c]	No.	Vol., ml.	Spec.[a] act.	Rate[b]	% Hf[c]
4	2.20	16.8	0.08	0.4	9	0.29	510	17	79
5	0.40	290	0.7	3	10	.31	321	22[d]	>95
6	.32	580	1.9	9	11	.31	147	21	>95
7	.27	616	6.6	31	12	.43	30.7	24	>95
8	.31	609	12	56	13	.45	3.3	19[d]	>95

[a] *c*/min./λ. [b] Coincidence rate per 1000 c./min. [c] Calculated on an activity basis. The initial solution had approximately equal activities of zirconium and hafnium. [d] Radiochemical analyses by S. A. Reynolds did not show presence of Zr^{95}. Estimated purity of the hafnium fractions according to these analyses is better than 95%.

OAK RIDGE NATIONAL LABORATORY
OAK RIDGE, TENNESSEE

KURT A. KRAUS
GEORGE E. MOORE

RECEIVED JULY 25, 1949

(1) This document is based on work performed under Contract No. W-7405 eng. 26 for the Atomic Energy Commission at Oak Ridge National Laboratory.

(2) Gmelin's "Handbuch der anorganischen Chemie, Hafnium," Verlag Chemie, Berlin, 1941.

(3) Information from G. T. Seaborg and I. Perlman, "Table of Isotopes," *Rev. Mod. Phys.*, **20**, 585 (1948).

(4) S. DeBenedetti and F. K. McGowan, *Phys. Rev.*, **70**, 569 (1946).

(5) We are indebted to Mr. F. K. McGowan for asssistance in the coincidence counting and for the use of his delayed coincidence circuit.

SYNTHETIC CURARE SUBSTITUTES FROM ALIPHATIC DICARBOXYLIC ACID AMINOETHYL ESTERS

Sir:

The recent publication by Bovet and co-workers[1] of extensive work on synthetic curare substitutes derived from aliphatic dicarboxylic acid aminoethyl esters leads us to record briefly at this time results obtained in these laboratories simultaneously and independently.

Stimulated by the work of Barlow and Ing,[2] and of Paton and Zaimis[3] in discovering powerful curare-like activity in a series of straight-chain polymethylene bis-quaternary ammonium salts we sought to produce compounds of similar activity by duplicating the favorable chain length, found by them to be ten atoms, between the quaternary nitrogens. We did this first by making a series of bis-(β-dimethylaminoethyl) esters of aliphatic dicarboxylic acids, the bis-amino esters then being converted to bis-quaternary salts by reaction with the appropriate alkyl iodide.

The amino esters were obtained in poor or moderate yields by ester exchange reactions of the corresponding methyl or ethyl esters with a small excess of β-dimethylaminoethanol in the presence of a trace of dissolved sodium. The quaternary salts were best made in an inert solvent such as ether or acetone, as use of an alcohol solvent gave poor yields usually, probably because of reversal of the ester exchange process under these conditions.

bis-Dimethylaminoethyl succinate (b. p. 130–135° at 1 mm.); its bis-methiodide (m. p. 254–255°; calcd.: C, 30.87; H, 5.55. Found: C, 30.82; H, 5.45); bis-ethiodide (m. p. 203–204°; calcd.: C, 33.55; H, 5.99. Found: C, 33.56; H, 6.00); bis-*n*-propiodide (m. p. 132–133°; calcd.: C, 35.98; H, 6.38. Found: C, 36.47; H, 6.40); bis-dimethylaminoethyl glutarate (b. p. 145–150° at 1 mm.); its bis-methiodide (m. p. 214–217°; calcd.: C, 32.24; H, 5.79. Found: C, 32.52; H, 5.85); bis-ethiodide (m. p. 151–153°; calcd.: C, 34.79; H, 6.19. Found: C, 35.07; H, 6.10); and bis-dimethylaminoethyl adipate (b. p. 153–158° at 1 mm.) and its bis-methiodide (m. p. 138–139°; calcd.: I, 44.35. Found: I, 42.50) were prepared in this way.

The first compound made, the bis-dimethylaminoethyl succinate bis-methiodide, has ten atoms interposed between the quaternary salt groups, and showed a curariform activity equal in intensity to that of *d*-tubocurarine chloride as determined by its ability to block neuro-muscular transmission in the cat, but the effect was of much shorter duration than that produced by *d*-tubocurarine. This shorter duration of action was tentatively attributed to the action of choline esterases based on the similarity between this substance and two molecules of acetylcholine coupled at the α-carbon. Independent investigations by the pharmacological group of our laboratories confirm the findings of Bovet and co-workers[1] and further work is being carried on with the most active members of this series.

(1) Bovet, *et al.*, *Rend. Ist. Super. Sanità*, **12**, 1 (1949).
(2) Barlow and Ing, *Nature*, **161**, 718 (1948).
(3) Paton and Zaimis, *ibid.*, **161**, 718 (1948).

THE WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK ARTHUR P. PHILLIPS

RECEIVED JULY 11, 1949

THE TETRAMETHYLPLATINUM–BENZENE COMPLEX

Sir:

Tetramethylplatinum forms a crystalline benzene complex.[1] Since Pt(IV) has six low energy orbitals and forms six interatomic links even in tetramethylplatinum,[1] it seemed possible that benzene was acting as a Lewis base, bonded to platinum, perhaps in the manner suggested by Winstein and Lucas for the silver perchlorate–benzene complex.[2] The nature of such a linkage has not been demonstrated, but is currently interesting due to speculation on π-bonding in organic reaction mechanisms, particularly by Dewar.[3]

Crystals of the benzene complex have the composition $(CH_3)_4Pt\cdot{}^1/_2C_6H_6$, as determined by loss of weight in going to the unsolvated form. A composition $(CH_3)_4Pt\cdot 2C_6H_6$ would be expected if benzene satisfied all platinum orbitals. Evidence, outlined below, indicates that the complex contains the tetramer, $(CH_3)_{16}Pt_4$, with molecular configuration unaltered.[1] There are then two benzene molecules per tetramer.

The tetramer configuration permits only methyl–benzene contacts, suggesting that the complex is held together by van der Waals forces, probably augmented by good crystal packing of these highly polarizable molecules.

Molecular Weight in Benzene.—The cryoscopically determined molecular weight in benzene is 1070 ± 100, *versus* 1021 expected for the tetramer. If benzene were bonded to platinum it would be expected that the methyl bridges of the tetramer would be broken, leading to a lower molecular weight.

Ultraviolet Absorption in Benzene and Cyclohexane.—The ultraviolet absorption of tetramethylplatinum in benzene and cyclohexane solutions, determined with a Beckmann spectrophotometer, are identical. Presumably the absorption would be considerably altered by any significant interaction of benzene with platinum.

Crystal Structure.—The benzene complex is orthorhombic, $a_0 = 16.83$, $b_0 = 21.08$, $c_0 = 8.92$ kX. ρ (obsd.) = 2.4, 16 $(CH_3)_4Pt$ and 8 benzenes per unit, with space group, as determined by Weissenberg and procession diagrams, C_{2v}^9–Pn2a or D_{2h}^{16}–Pnma. If the higher space group, Pnma,

(1) R. Rundle and J. H. Sturdivant, THIS JOURNAL, **69**, 1561 (1947).
(2) S. Winstein and H. J. Lucas, *ibid.*, **60**, 836 (1938).
(3) M. J. S. Dewar, *J. Chem. Soc.*, 777 (1946).

is correct, and if the molecular configuration of the tetramethylplatinum tetramer is unaltered,[1] y-parameters of all platinum positions are determined. Intensities of (0k0) reflections can then be calculated, and are in good agreement with observation (Table I). One could not achieve this agreement if the molecular structure of the tetramer were seriously altered by complexing with benzene.

TABLE I

INTENSITIES OF (0k0) REFLECTIONS

k	Intensity Obsd.	Intensity Calcd.	k	Intensity Obsd.	Intensity Calcd.
2	S	1475	16	M$^-$	75
4	M$^+$	641	18	O	0
6	O	0	20	O	12
8	W	173	22	M$^-$	325
10	S	1178	24	M$^+$	573
12	VS	1575	26	M$^+$	630
14	S$^+$	722			

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE R. E. RUNDLE
AMES, IOWA E. JEANNE HOLMAN

RECEIVED JULY 25, 1949

HYDROLYSIS OF THE α-1,6-GLUCOSIDIC LINKAGE IN ISOMALTOSE BY CULTURE FILTRATE OF *ASPERGILLUS NIGER* NRRL 330

Sir:

The α-1,6-glucosidic linkage in the amylopectin fraction of starch is resistant to hydrolysis by the action of the more common amylolytic enzymes. Inasmuch as the linkage between the two glucose residues in isomaltose is of the α-1,6 type, it was of interest to test the ability of a culture filtrate of *Aspergillus niger* NRRL 330 to hydrolyze this disaccharide. Isomaltose is now available in crystalline form. The sample of sugar used in these experiments was prepared from starch by the method of Montgomery, Weakley and Hilbert[1] and characterized as 6-(α-D-glucopyranosyl)-α-D-glucose monohydrate, rotating +120° in water (anhydrous). This particular strain of *A. niger* was selected because it elaborates, when grown in submerged culture, an enzyme capable of hydrolyzing maltose in large amounts.

To 20 ml. of 0.06 M isomaltose monohydrate, buffered at pH 4.4 (acetate buffer, 0.3 M), was added 10 ml. of culture filtrate. The reaction mixture was held at 50°. The extent of hydrolysis was measured at two and five hours by the increase in reducing power as determined by the method of Somogyi.[2] The glucose formed in the reaction mixture after five hours was identified biologically by "fermentation" at pH 8.8 with an excess of yeast by the procedure of Somogyi.[3] A collection of some of our experimental data is given in Table I.

(1) Edna M. Montgomery, F. B. Weakley and G. E. Hilbert, THIS JOURNAL, **71**, 1682 (1949).
(2) M. Somogyi, *J. Biol. Chem.*, **160**, 61 (1945).
(3) M. Somogyi, *ibid.*, **119**, 741 (1937).

TABLE I

Reaction mixture no.		1	2	3
Culture filtrate diluted		Un-	1:1 50%	1:3 25%
Two hr.	Isomaltose hydr./ml. culture filt., mg.	27.4	19.4	14.3
	Hydrolysis, %	63.4	44.9	33.1
Five hr.	Isomaltose hydr./ml. culture filt., mg.	39.0	35.1	29.0
	Hydrolysis, %	90.2	81.2	67.1
"Fermentable" glucose per ml. cult. filt., mg.		37.5	33.0	25.7

It will be noted that the undiluted culture filtrate hydrolyzed 90.2% or 39.0 mg. of the isomaltose per ml. of culture filtrate in five hours. The amount of fermentable glucose produced, 37.5 mg., per ml. of culture filtrate checks reasonably well with this figure. (The hydrolysis of isomaltose proceeds more slowly than the hydrolysis of maltose as indicated by the fact that 38.2 mg. of maltose is hydrolyzed per ml. of culture filtrate in one hour at 30°). In addition, the sugar formed in a reaction mixture identical to No. 1 in Table I, but incubated for six hours, was isolated as crystalline α-D-glucose monohydrate; $[\alpha]^{25}D$ +47.8° (c, 4 in water); m. p., 82.8°[4]; yield, 83.4%.

Further work on characterization of the enzyme system responsible for the hydrolysis of isomaltose is in progress.

(4) *Cf.* Nat. Bur. Stand. Circ. No. C440, p. 728.

CORN INDUSTRIES RESEARCH FOUNDATION
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NORTHERN REGIONAL RESEARCH LABORATORY
BUREAU OF AGRIC. AND IND. CHEM. HENRY M. TSUCHIYA
UNITED STATES DEPT. OF AGRIC. EDNA M. MONTGOMERY
PEORIA, ILLINOIS JULIAN CORMAN

RECEIVED MAY 31, 1949

DERIVATIVES OF DIBORINE

Sir:

Although tetrachlorodiborine, B_2Cl_4, first prepared by Stock, Brandt and Fischer (*Ber.*, **58**, 855 (1925)) by striking an arc across zinc electrodes immersed in liquid boron trichloride, is a compound of considerable potential interest, the original preparative method gave such poor yields (about 1%) of material of such low purity (less than 90%) that detailed study of the compound was not feasible.

Much better results have now been obtained by passing gaseous boron trichloride at 1 to 2 mm. through a glow discharge established between mercury electrodes. The mercurous chloride and other non-volatile products remain in the discharge tube; the volatile material is passed through a −78.5° trap, which retains the tetrachlorodiborine and allows the unchanged trichloride to pass. The latter is repeatedly subjected to the action of mercury in the discharge tube, since the amount converted per pass is small. The yield, however, is approximately 50%. There is evidence that other less volatile boron–chlorine compounds are obtained.

Tetrachlorodiborine is completely hydrolyzed by aqueous sodium hydroxide at 70°.

$$B_2Cl_4 + 6NaOH \longrightarrow 2NaBO_2 + 4NaCl + 2H_2O + H_2$$

Determination of the amounts of hydrogen, boron and chlorine in the hydrolysate of an unweighed sample by the usual methods gave the following results: H, 74.64 cc.; B, 0.0727 g.;

Cl, 0.481 g., corresponding to the atomic ratio H:B:Cl = 1.98:2.00:4.03. A 0.0995-g. sample gave 0.0131 g. of boron and 0.0878 g. of chlorine, a total of 0.1009 g. The vapor density corresponds to a molecular weight of 163 (calcd., 163.5). The vapor tensions, measured between −63.5 and 22.5°, are satisfactorily reproduced by the equation: $\log P_{(mm.)} = -1753/T + 8.057$.

Liquid tetrachlorodiborine at room temperature for seventy-two hours undergoes 21% decomposition, yielding boron trichloride, a very slightly volatile red substance and a white solid. The latter two must be hitherto unknown boron chlorides of as yet undetermined composition. At 0° the decomposition is much slower.

The following reactions of tetrachlorodiborine have been studied in preliminary fashion. (1) It yields the hitherto unknown *tetrabromodiborine* by treatment with boron tribromide, but does not react with boron trifluoride. (2) With dimethyl or diethyl ether it forms a liquid monoetherate and a solid dietherate. The latter has an appreciable dissociation pressure and is somewhat soluble in the ether. (3) It yields the corresponding tetramethoxy and tetraethoxy derivatives on treatment with the appropriate alcohols. (4) It reacts with lithium borohydride and aluminum borohydride to give boron hydrides among which diborane and dihydrotetraborane (B_4H_{10}) have been definitely identified; pentaboranes and decaboranes are probably present. It does not seem to react with lithium aluminum hydride at 0°. (5) It absorbs hydrogen at room temperature, by which reaction all of the chlorine is converted to boron trichloride, and the residue is a compound or mixture of the approximate composition $BH_{1.37}$ ($B_{10}H_{14}$?). (6) It reacts with ammonia in complex fashion. These and other reactions, as well as the preparative method, will receive further intensive study.

We gratefully acknowledge the interest and financial support of the Office of Naval Research and the Naval Research Laboratory.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF CHICAGO
CHICAGO, ILLINOIS

THOMAS WARTIK
R. MOORE
H. I. SCHLESINGER

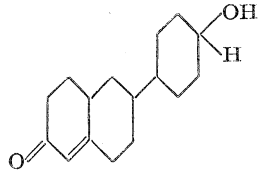
RECEIVED JULY 18, 1949

SYNTHESIS OF PHYSIOLOGICALLY ACTIVE ANALOGS OF TESTOSTERONE

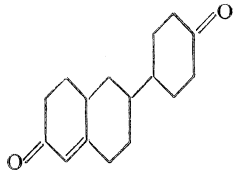
Sir:

The discovery of several hundred compounds possessing the physiological activity of the estrogenic hormones has prompted a number of investigators to search for synthetic analogs having activity similar to the other steroid hormones. While some claims of activity for such analogs have been made, particularly in patents, so far as we are aware no such claim has yet been substantiated [*cf.*, for example, the reported androgenic activity for certain reduction products related to diethylstilbestrol, apparently irrespective of configuration, Schoeller, Inhoffen, Steinruck and Höss, U. S. Patent 2,392,864 (Jan. 15, 1948)].

Since 1941 we have directed efforts toward the synthesis of analogs of the non-aromatic steroid hormones lacking ring C, and wish to report now the synthesis of two such analogs of the androgens: I, comparable to testosterone, and II, to androstenedione.



I



II

These α,β-unsaturated ketones were synthesized using the Robinson–Mannich base method [du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937)] with some modifications. Hydrogenation of 4,4′-dihydroxybiphenyl gave the three possible perhydro derivatives (m. p.'s 215–216°, 176.5–177° and 194–195°, all m. p.'s cor.). Half-oxidation of the first two stereoisomers with chromium trioxide afforded the same 4-(4′-hydroxycyclohexyl)-cyclohexanone (III, probably *trans*), m. p. 129–130°. *Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3. Found: C, 73.6; H, 10.1. When sufficient 195° diol becomes available, it will presumably lead to the other possible isomer. More complete oxidation gave 4-(4′-ketocyclohexyl)-cyclohexanone (IV), m. p. 115–116° *Anal.* Calcd. for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3 Found: C, 74.3; H, 9.2.

Formylation of the keto alcohol (III) with ethyl formate and sodium methoxide, reaction of the derivative with the methiodide of 1-diethyl aminobutanone-3 and cyclization with *ca.* 4% methanolic potassium hydroxide at room temperature gave 6-(4′-hydroxycyclohexyl)-Δ^{1-9}-octalone-2 (I), purified by chromatography on alumina and recrystallization from cyclohexane–ethyl acetate, m. p. 127–127.5°; max. 238.5 mμ (E_{molar} = 16,870). *Anal.* Calcd. for $C_{16}H_{24}O_2$: C, 77.4 H, 9.7. Found: C, 77.7; H, 9.8. The semicarbazone melted at 235–236° (dec.). *Ana* Calcd. for $C_{17}H_{27}N_3O_2$: C, 66.9; H, 8.9. Found C, 67.0; H, 8.7.

Similarly, monoformylation of the diketone (IV), reaction with the Mannich base methiodide and cyclization gave 6-(4′-ketocyclohexyl)-Δ^{1-} octalone-2 (II), also obtained in small yield by oxidation of I (as the dibromide), m. p. 88.–89.5°; max. 238 mμ (E_{molar} = 16,400). *An* Calcd. for $C_{16}H_{22}O_2$: C, 78.0; H, 9.0. Four C, 77.9; H, 8.7. The disemicarbazone decomposed at 256–257°. *Anal.* Calcd. for $C_{18}H_{28}N_6$ C, 60.0; H, 7.8. Found: C, 59.9; H, 7.5.

Preliminary assays in day-old chicks, under the direction of Drs. R. K. Meyer and Elva G. Sh

ley of the Department of Zoology, have indicated androgenic activity for the diketone II at a total dose of 2.5 mg. (26 to 83% increase in comb weight over the controls). A total dose of 0.012 mg. of testosterone propionate resulted in 40% increase. The keto alcohol I has given inconclusive results. Further investigation of physiological effects in other species awaits the preparation of additional material.

DEPARTMENT OF CHEMISTRY
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A. L. WILDS
CLIFFORD H. SHUNK
CARL H. HOFFMAN

RECEIVED JULY 20, 1949

SYNTHESIS OF VITAMIN A

Sir:

The appearance of an article by Schwarzkopf and collaborators[1] on the synthesis of vitamin A by the reduction of vitamin A esters with lithium aluminum hydride prompts us to record experimental work carried out in these laboratories.

Ethyl β-ionylidene acetate[2] was reduced with lithium aluminum hydride in 85% yield to β-ionylidene ethyl alcohol following the method of Milas and Harrington[3] [b. p. 112–114° at 0.4 mm.; $\lambda_{max.}^{isooctane}$ 2840 Å., $E_{1\,cm.}^{1\%}$ 1205]; *trityl ether* (m. p. 132–134°) *anal.* Found: C, 88.13; H, 8.47; $\lambda_{max.}^{isooctane}$ 2850 Å., $E_{1\,cm.}^{1\%}$ 733.

Oxidation of β-ionylidene ethyl alcohol with manganese dioxide by the method used to convert vitamin A to the aldehyde[4] produced a mixture of two stereoisomeric β-ionylideneacetaldehydes in 60% yield separable by chromatography into essentially equal amounts of *nor*-β-ionylideneacetaldehyde[5] [b. p. 90–95° at 10^{-2} mm.; $n^{25}D$ 1.5780; $\lambda_{max.}^{isooctane}$ 2650 Å., $E_{1\,cm.}^{1\%}$ 567 and 3150 Å., $E^{1\%}$ 760, *anal.* Calcd. for $C_{15}H_{22}O$: C, 82.57; H 10.09. Found: C, 82.14; H, 10.36. *Semicarbazone:* m. p. 195–196°; $\lambda_{max.}^{chloroform}$ 3230 Å., $E_{1\,cm.}^{1\%}$ 1330; *anal.* Found: C, 69.56; H, 8.82; N, 15.29][6] and *iso*-β-ionylidene acetaldehyde[5] [b. p. 80–85° at 10^{-2} mm.; $n^{25}D$ 1.5780; $\lambda_{max.}^{isooctane}$ 3180 Å., $E_{1\,cm.}^{1\%}$ 904. *Anal.* Found: C, 82.14; H, 10.33. *Semicarbazone:* m. p. 175–176°, $\lambda_{max.\ 3175}^{chloroform}$ $E_{1\,cm.}^{1\%}$ 1000. *Anal.* Found: C, 70.16; H, 9.07; N, 15.03].

nor-β-Ionylideneacetaldehyde was condensed with acetone in the presence of aluminum *t*-butoxide whereby the previously described C_{18}-ketone was obtained[7] in 80–85% yield; $\lambda_{max.}^{isooctane}$ 3360 Å.; *semicarbazone:* m. p. 186–188°; $\lambda_{max.}^{chloroform}$ 3490 Å., $E_{1\,cm.}^{1\%}$ 1680. The C_{18}-ketone was converted by the Reformatsky reaction to the C_{20}-hydroxyester which was dehydrated by iodine to vitamin A ester and the latter saponified to vitamin A acid, m. p. 179–180°; $\lambda_{max.}^{ethanol}$ 3500 Å., $E_{1\,cm.}^{1\%}$ 1415. From *iso*-β-ionylideneacetaldehyde there was obtained a more difficultly characterizable C_{18}-ketone exhibiting a broad band at 3340–3370 Å. indicating a mixture of the *nor* and *iso* forms. This ketone afforded vitamin A acid in the same yield as that obtained from the *nor* series (25%); m. p. 180.5–181.5°; $\lambda_{max.}^{ethanol}$ 3530 Å., $E_{1\,cm.}^{1\%}$ 1510; mixed m. p. with acid from *nor* series, 180–181°. Both vitamin A acids on reduction with lithium aluminum hydride gave vitamin A exhibiting a single, well-defined maximum at 3260 Å., $E_{1\,cm.}^{1\%}$ 1330 (80% yield) as measured in isooctane.

(1) Schwartzkopf, Cahnmann, Lewis, Swindinsky and Wuest, *Helv. Chim. Acta*, **32**, 443 (1949).

(2) Karrer, Salomon, Morf and Walker, *ibid.*, **15**, 878 (1932).

(3) Milas and Harrington, THIS JOURNAL, **69**, 2247 (1947).

(4) Ball, Goodwin and Morton, *Biochem. J.*, **42**, 516 (1948).

(5) The names *nor*- and *iso*-β-ionylideneacetaldehyde denote stereochemical relationships to β-carotene. The *nor* (normal) aldehyde is obtainable from β-carotene by oxidation—Wendler, Rosenblum and Tishler, THIS JOURNAL, in press.

(6) The β-ionylidenealdehydes semicarbazones prepared by Kuhn and Morris, *Ber.*, **70**, 853 (1937), and by van Dorp and Arens, *Rec. trav. chim.*, **67**, 459 (1948), apparently have the *nor* configuration.

(7) Arens and van Dorp, *Rec. trav. chim.*, **65**, 338 (1946); Heilbron, Jones and O'Sullivan, *J. Chem. Soc.*, 866 (1946); Karrer, Jucker and Schick, *Helv. Chim. Acta*, **29**, 704 (1946).

RESEARCH LABORATORIES
MERCK & CO., INC.
RAHWAY, NEW JERSEY

N. L. WENDLER
H. L. SLATES
M. TISHLER

RECEIVED JULY 7, 1949

NEW BOOKS

Oxidation–Reduction Potentials in Bacteriology and Biochemistry. By L. F. HEWITT, Ph.D., B.Sc., F.R.I.C., Acting Director, Serum Research Institute, Carshalton, Surrey. Fifth Edition. Published by the London County Council, 1948, and may be purchased, either directly or through any Bookseller, from Staples, Ltd., 14, Great Smith Street, Victoria Street, Westminster, S.W.1. 130 pp. 17 × 25 cm. Price, 4s. 6d. By post, 4s. 10d.

The last previous edition of this small monograph was published in 1936. The present fifth edition follows the pattern of earlier ones. The first chapter contains a brief outline of the theory of oxidation–reduction reactions and the mathematical expressions relating oxidation–reduction potentials to the components of the reactions. The second chapter describes the methods for measuring oxidation–reduction potentials and gives tables of oxidation–reduction indicators. The third chapter deals with oxidation–reduction systems of biological interest. In the fourth chapter, the bacteriological applications of oxidation–reduction studies are described. This fourth chapter is the most important in the monograph, since it constitutes the best review of the work in this particular field—a field to which the author himself has made many contributions. The monograph concludes with two short

chapters, one on the polarograph and one entitled, "General Conclusions."

An excellent bibliography covering about twenty-four pages further increases the value of this monograph. The number of new contributions made in this field during the last decade is, however, conspicuously small and is probably in part due to a diversion of interests during the war years.

ERIC G. BALL

Kinetics of Chemical Change in Solution. By EDWARD S. AMIS. Formerly Associate Professor of Chemistry, Louisiana State University; also Senior Research Chemist, Carbide and Carbon Chemicals Corporation, Oak Ridge, Tenn. At present Professor of Chemistry, University of Arkansas. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1949. ix + 332 pp. illustrated. 14 x 21.5 cm. Price, $5.00.

Amis presents a very good summary of his book in the preface. After discussing the order of reactions, he considers the Arrhenius equation. Because molecules often are polar and sometimes ionize, dielectric behavior is treated at length and chapter three which discusses the work in this field by Debye, Onsager, Kirkwood, Jaffé and others is a useful summary. Absolute rate theory is developed after a detailed presentation of earlier treatments. Photochemistry, chain reactions, homogeneous and heterogeneous catalysis are treated in the concluding chapters. A visit to the library verified the supposition that Lewis in the index meant G. N., W. K. or J. R., although by reading the text I could only find out that there was a G. N., which I knew before. Reaction kinetics shows almost infinite variety so that any treatment hits the high spots only. Amis has chosen a very interesting set of reactions to treat and has done the job well. This book is a valuable addition to the literature of reaction kinetics.

HENRY EYRING

An Introduction to the Chemistry of Carbohydrates. By JOHN HONEYMAN, Lecturer in Organic Chemistry, University of London, King's College. Oxford University Press, 114 Fifth Ave., New York 11, N. Y., 1949. 143 pp. 14.5 × 23 cm. Price, $4.50.

This small book serves as an excellent though brief textual summary of the present status of the chemistry of the carbohydrates. Most of the modern methods and techniques are delineated. It is intended to meet the needs of English students "reading for an Honours degree in Chemistry" but it should also be useful for others desiring to keep abreast of recent developments through a rapid survey of this field.

M. L. WOLFROM

BOOKS RECEIVED

July 10, 1949–August 10, 1949

MANSON BENEDICT AND CLARKE WILLIAMS, Editors, "Engineering Developments in the Gaseous Diffusion Process." First Edition. McGraw-Hill Book Company, Inc., 330 West 42nd. Street, New York 18, N. Y. 1949. 129 pp. $1.25.

A. V. BLOM. "Organic Coatings in Theory and Practice." (Elsevier's Polymer Series.) Elsevier Publishing Company, Inc., 215 Fourth Avenue, New York 3, N. Y. 1949. New York, Amsterdam, London, Brussels. (Printed in the Netherlands by N. V. Drukkerij and G. J. Thieme Nijmegen.) 298 pp. $6.00.

RAY Q. BREWSTER. "Organic Chemistry." Prentice-Hall, Inc., 70 Fifth Avenue, New York 11, N. Y. 1949. 409 pp. $6.00.

G. CHARLOT AND D. BEZIER. "Methodes Modernes D'Analyse Quantitative Minerale." Second Edition, Revised. Masson et Cie. Editeurs, 120, Boulevard Saint-Germain, Paris VIe. 685 pp.

FRITZ FEIGL. "Chemistry of Specific, Selective and Sensitive Reactions." Translated by Ralph E. Oesper. Academic Press, Inc., 125 East 23rd. Street, New York, N. Y. 1949. 740 pp. $13.50.

ROSS AIKEN GORTNER. "Outlines of Biochemistry." Third Edition. Edited by Ross Aiken Gortner, Jr. and Willis Alway Gortner. Chapman and Hall, Limited, London. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1949. 1078 pp. $7.50.

R. H. GRIFFITH. "The Practice of Research in the Chemical Industries." Oxford University Press, 114 Fifth Avenue, New York 11, N. Y. 1949. 184 pp. $3.25.

P. H. HERMANS. "Physics and Chemistry of Cellulose Fibres." (Elsevier's Polymer Series.) Elsevier Publishing Company, Inc., 215 Fourth Avenue, New York 3, N. Y. 1949. 534 pp. $9.50.

R. HOUWINK, Editor. "Elastomers and Plastomers. Manufacture, Properties, and Applications." (Elsevier's Polymer Series. Vol. II.) Elsevier Publishing Company, Inc., 215 Fourth Avenue, New York 3, N. Y. 515 pp. $9.00.

HENRY A. LARDY, Editor. "Respiratory Enzymes." Revised Edition. Burgess Publishing Company, 426 South Sixtieth Street, Minneapolis 15, Minnesota. 1949. 290 pp. $4.50.

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Polarographic Studies of Metal Complexes. I. The Copper(II) Tartrates

BY LOUIS MEITES

The first study of the polarographic behavior of copper(II) in a tartrate supporting electrolyte was made by Suchy,[1] who found a single wave, with a half-wave potential of −0.14 v. *vs.* the saturated calomel electrode, in a 10% (0.35 *M*) potassium sodium tartrate solution of unstated *p*H. Kolthoff and Lingane[2] found, in 0.5 *M* tartrate, $E_{1/2}$ = −0.10 v., again at an unspecified *p*H value, and stated that the wave height corresponded to reduction to the metal. More recently, Lingane[3] has shown that the polarographic behavior of the system is significantly dependent on the *p*H: in particular, he found that the half-wave potential is displaced to very negative potentials in strongly alkaline solutions containing gelatin, in agreement with the earlier observation of Kolthoff and Lingane.[2]

Inasmuch as some preliminary experiments with alkaline tartrate solutions were in sharp disagreement with previous data, it was deemed desirable to make a complete study of the effects of *p*H and tartrate concentration on the system.

Experimental

The polarographic apparatus used was that described by Meites and Meites.[4] All measurements were made at 25.00 ± 0.02° in a water thermostat. The cell is a modification of the H-cell described by Lingane and Laitinen.[5] The solution compartment of this cell has a capacity of about 450 ml.; it is fitted with a no. 14 rubber stopper, through which are inserted the dropping electrode, a tube for leading oxygen-free hydrogen over the solution, the tips of two calibrated 10-ml. microburets, and the glass and calomel electrodes of a Beckman Model G *p*H meter. A known volume of air-free acid or base is added to the solution, which is then stirred briefly by a stream of gas, the *p*H is measured, and the polarogram is recorded; or, alternatively, one of the microburets may be filled with a standard solution of the metal ion and the diffusion current constant[6] measured by the technique previously described.[7-9] The entire time consumed is very little more than that required by the polarographic measurements themselves.

The Beckman *p*H meter used was set to read 3.57 in a saturated potassium hydrogen tartrate solution at 25°.[10] All *p*H values above 10 were measured with a Type E glass electrode, using as standard a potassium borate–boric acid buffer whose *p*H had been checked against the National Technical Laboratories buffer of *p*H 10.00. Suitable corrections for the alkali errors of the glass electrode have been made: they were minimized by the use of potassium hydroxide instead of sodium hydroxide.

Oxygen was removed from the tank hydrogen used by a vanadous sulfate wash train.[11]

Results and Discussion

Typical polarograms of copper(II) in potassium sodium tartrate solutions at varying *p*H values in the absence of gelatin are shown in Figs. 1, 2 and 3. In solutions containing the hydrogen tartrate ion at concentrations considerably greater than that of the copper(II), only a single wave is found. It is characterized by a very sharp maximum whose relative height decreases with increasing *p*H, but the plateau finally attained is very well defined. Lingane's data[3] indicate that the maximum in this wave is suppressed by as little as 0.005% gelatin.

The half-wave potential of this wave is only slightly affected by changes in *p*H: in 0.1 *M* tartrate $E_{1/2}$ is −0.003 v. at *p*H 1.70 and −0.084 v. at *p*H 5.73 (all potential measurements are referred to the saturated calomel electrode), and they are

(1) K. Suchy, *Coll. Czechoslov. Chem. Commun.*, **3**, 354 (1931).

(2) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941, p. 280.

(3) J. J. Lingane, THIS JOURNAL, **65**, 866 (1943).

(4) L. Meites and T. Meites, to be submitted.

(5) J. J. Lingane and H. A. Laitinen, *Ind. Eng. Chem., Anal. Ed.*, **11**, 504 (1939).

(6) J. J. Lingane, *ibid.*, **15**, 543 (1943).

(7) J. J. Lingane and L. Meites, *ibid.*, **19**, 159 (1947).

(8) L. Meites, Ph.D. Thesis, Harvard University, 1947.

(9) L. Meites, *Anal. Chem.*, **20**, 895 (1948).

(10) J. J. Lingane, *Ind. Eng. Chem., Anal. Ed.*, **19**, 810 (1947).

(11) L. Meites and T. Meites, *Anal. Chem.*, **20**, 984 (1948).

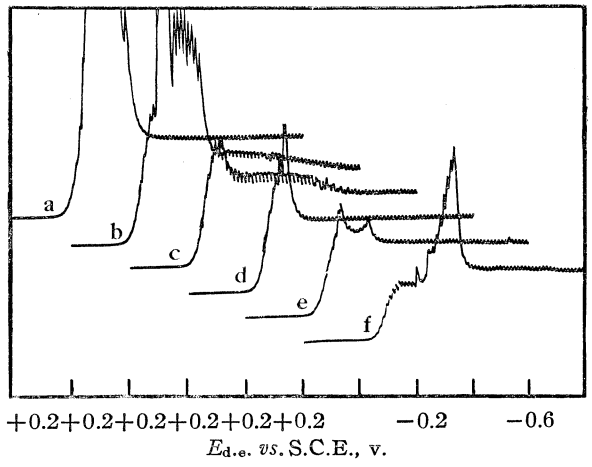

Fig. 1.—Polarograms of 3.23 millimolar copper (II) in 0.5 *M* potassium sodium tartrate at *p*H (a) 1.74, (b) 2.70, (c) 3.71, (d) 4.80, (e) 5.62, and (f) 6.27.

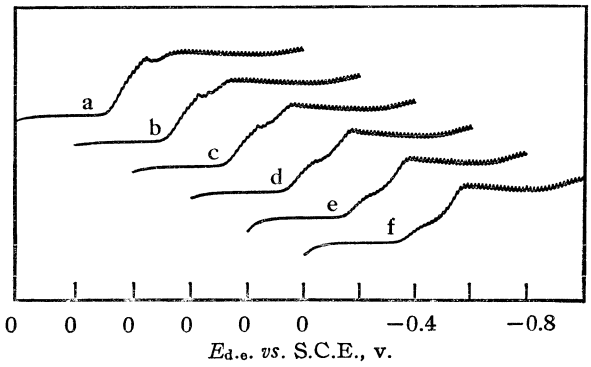

Fig. 2.—Polarograms of 3.23 millimolar copper (II) in 1.0 *M* potassium sodium tartrate at *p*H (a) 7.02, (b) 7.24, (c) 7.47, (d) 7.69, (e) 7.93, and (f) 8.12.

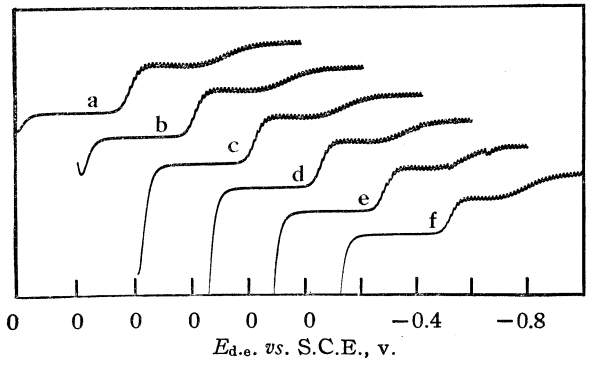

Fig. 3.—Polarograms of 3.23 millimolar copper (II) in 1.0 *M* potassium sodium tartrate at *p*H (a) 11.78, (b) 12.07, (c) 12.38, (d) 12.72, (e) 13.12, and (f) 13.50.

almost exactly the same in 0.5 or 1.0 *M* tartrate. This is in accordance with the fact that, in this *p*H range, the composition of the solution is determined, not by the total amount of tartrate present in the cell, but by the solubilities of sodium and potassium hydrogen tartrates. The presence of the maximum makes it impossible to attach any thermodynamic significance to the measured half-wave potentials.

As the *p*H is increased above about 6, the former single wave splits quite sharply into two waves. The first of these is fairly well defined, but the second has a maximum, sharper in 0.1 and 0.5 *M* tartrate than in 1 *M* tartrate (*cf.* curve *f*, Fig. 1, and Fig. 2), which again is suppressed by increasing *p*H. Concurrently, the height of the first wave is decreased, while that of the second increases. The sum of these two waves, at *p*H values near the bottom of this range, is about 10% smaller than the total wave height in more acid solutions where only one wave appears. The variation with *p*H of the relative heights of these waves in 0.5 *M* tartrate is shown in Fig. 4.

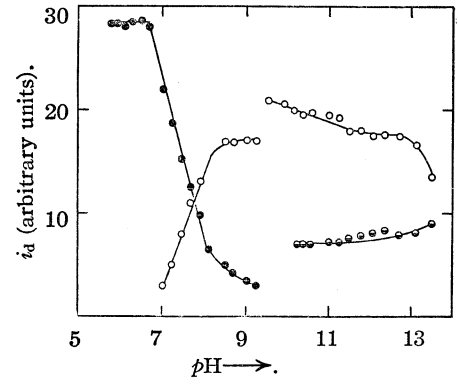

Fig. 4.—Effects of *p*H on the diffusion currents of the copper (II) waves in 1.0 *M* potassium sodium tartrate. Solid circles represent the first wave, open circles the second, and half-solid circles the third.

From Figs. 4, 5 and 6, which show the effect of *p*H on the half-wave potential of copper in tartrate solutions of various concentrations, the first indication of the appearance of two waves is found at *p*H 5.5 in 0.1 *M* tartrate, *p*H 6.3 in 0.5 *M* tartrate, and *p*H 6.7 in 1.0 *M* tartrate. The concentration of copper in all of these solutions was 3.23 millimolar, and from this datum and the values of K_1 and K_2 for tartaric acid given by Jones and Soper,[12] one calculates that the concentration of free hydrogen tartrate ion becomes equal to four times the copper concentration at *p*H 5.7 in 0.1 *M* total tartrate, at *p*H 6.4 in 0.5 *M* tartrate, and at *p*H 6.7 in 1.0 *M* tartrate. This appears to constitute conclusive proof that the complex formed in these acidic solutions has the formula $Cu(H\ Tart)_4^{=}$, a deduction further supported by the results of an amperometric titration shown in Fig. 7.

The second of these two waves increases in height at the expense of the first as the concentration of the hydrogen tartrate ion decreases with increasing *p*H until only a single wave is observed. Over a *p*H range whose lower limit is the first appearance of a double wave and whose upper limit is the point at which the wave begins a grad-

(12) I. Jones and F. G. Soper, *J. Chem. Soc.*, **136**, 1836 (1934).

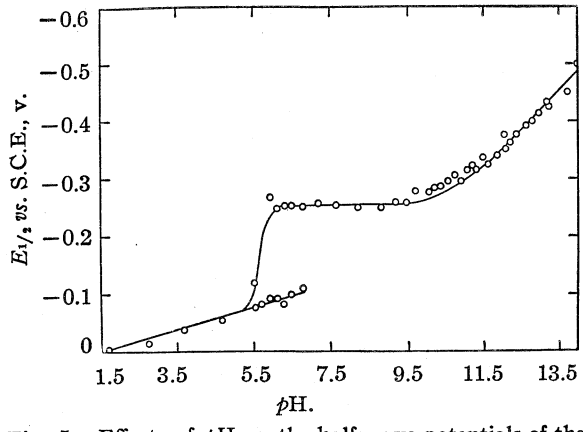

Fig. 5.—Effects of pH on the half-wave potentials of the copper (II) waves in 0.10 M potassium sodium tartrate.

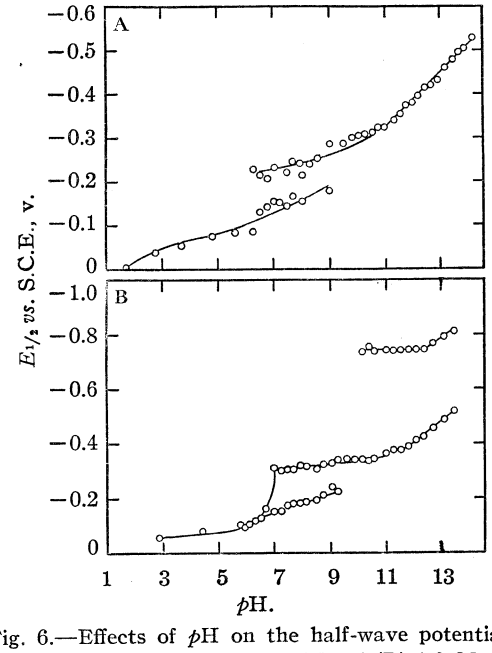

Fig. 6.—Effects of pH on the half-wave potentials of the copper(II) waves in (A) 0.50 M and (B) 1.0 M potassium sodium tartrate.

ual continuous shift to more negative values, the half-wave potential of this wave is fairly constant.

From measurements of the relative heights of the two waves in a similar critical region, Lingane[13] was able to establish the formula of the ferric hydrogen tartrate complex in solution as Fe(H Tart)$_3$, and theoretically it should also be possible, if the tartrate and hydrogen tartrate complexes were sufficiently slowly interconvertible, to calculate the ratio of their dissociation constants from such diffusion current measurements. In the present case, however, the ratio secured exhibits a consistent trend with pH: this is the behavior which would be expected if the two species were in moderately rapid equilibrium at the surface of the drop.

(13) J. J. Lingane, THIS JOURNAL, **68**, 2448 (1946).

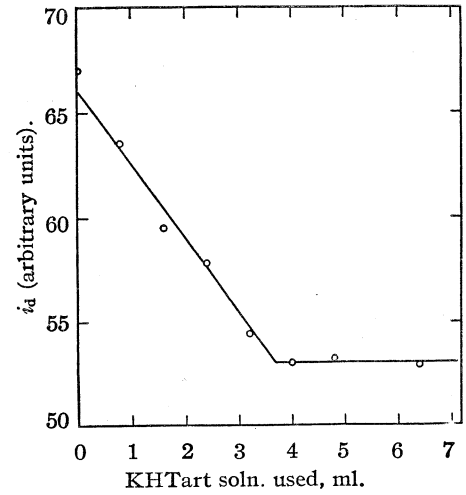

Fig. 7.—Amperometric titration of 250 ml. of 0.400 millimolar copper (II) in an 0.5 M acetate buffer of pH 3.59 with 20 millimolar potassium hydrogen tartrate, at $E_{d.e.} = -0.50$ v.

As the pH is further increased so that the concentration of hydroxyl ion becomes significant in comparison with the copper concentration, the wave begins the slow shift to more negative potentials described above. This shift is first observed at pH 9.0 in 0.1 M tartrate, at pH 9.5 in 0.5 M tartrate, and at pH 10.5 in 1.0 M tartrate. It is surprising that the hydroxyl ion concentration in every case is much too small to correspond to conversion of an appreciable fraction of the copper into a hydroxytartrate complex. Nevertheless, the waves observed in this region are very well defined and show, on mathematical analysis, none of the phenomena frequently observed[9,14] in systems where other evidence points to the co-existence of two ionic species in moderately slow equilibrium.

A comparison of the half-wave potentials of this wave at a constant hydroxyl ion activity gives results typified by those at pH 12, which are −0.346 v. in 0.1 M tartrate, −0.378 v. in 0.5 M tartrate, and −0.409 v. in 1.0 M tartrate. Applying to these data the theoretical equation for the reduction of metal complexes derived by Lingane,[15,16] one calculates that, in the generalized equation for the reduction

$$[Cu(OH)_p(Tart)_q]^{2-(p+2q)} + ne \longrightarrow Cu^{(2-n)}(OH)_r(Tart)_s^{2-(n+r+2s)} + (q-s)\,Tart^{=} + (p-r)OH^- \quad (1)$$

$(q - s)$ is equal to n. Lingane[3] and Kolthoff and Lingane[17] are agreed that the reduction of copper from these solutions proceeds all the way to the metal. In confirmation of this, the slopes of plots of $-E_{d.e.}$ against $\log[i/(i_d - i)]$ for the waves given by these solutions are uniformly 36 ± 2 mv., cor-

(14) J. J. Lingane and L. Meites, *ibid.*, in press.
(15) J. J. Lingane, *Chem. Rev.*, **29**, 1 (1941).
(16) Ref. 2, pp. 161–165.
(17) Ref. 2, p. 280.

responding approximately to the expected value for a thermodynamically reversible two-electron reduction.[16] Therefore equation (1) becomes

$$[Cu(OH)_p(Tart)_2]^{-(2+p)} + 2e \longrightarrow Cu(Hg) + 2\ Tart^{=} + p\ OH^{-} \quad (2)$$

Now the rate of change of the half-wave potential with pH in this region is shown by Figs. 5 and 6 to be nearly linear, and from them the average values of $\Delta E_{1/2}/\Delta(p\mathrm{H})$ are estimated to be -50 mv. in 0.1 M tartrate, -60 mv. in 0.5 M tartrate, and -63 mv. in 1.0 M tartrate. The differences in these values may well be due to the effects of the changing ionic strength on the activity coefficients of the various species involved in the equilibrium. However, they are all in satisfactory agreement for the predicted effect of pH on the half-wave potential for $p = 2$ in equation (2), so that, finally

$$Cu(OH)_2(Tart)_2^{-4} + 2e \longrightarrow Cu(Hg) + 2\ Tart^{=} + 2OH^{-} \quad (3)$$

At pH 14.0, and at a total tartrate concentration of 1.0 M, the half-wave potential is -0.563 v. Then, neglecting, perforce, activity effects, we write, using the value for $E_{1/2}$ of the aquo-cupric ion given by Kolthoff and Lingane[18]

$$K = \frac{[Cu^{++}][OH^{-}]^2[Tart^{=}]^2}{[Cu(OH)_2(Tart)_2^{-4}} = 1.4 \times 10^{-10}$$

and, for the standard potential of the reduction corresponding to equation (3), by combining this value for K with the E_0 for the copper–cupric ion couple given by Lewis and Randall,[19] we secure

$$Cu + 2OH^{-} + 2\ Tart^{=} \longrightarrow Cu(OH)_2(Tart)_2^{-4} + 2e;\ E^0 = +0.24\ \text{v.}$$

corresponding to a standard free energy change of 13.4 kcal.

Jellinek and Gordon[20] report, from potentiometric measurements, that $K = [Cu^{++}][OH^{-}]^4$.

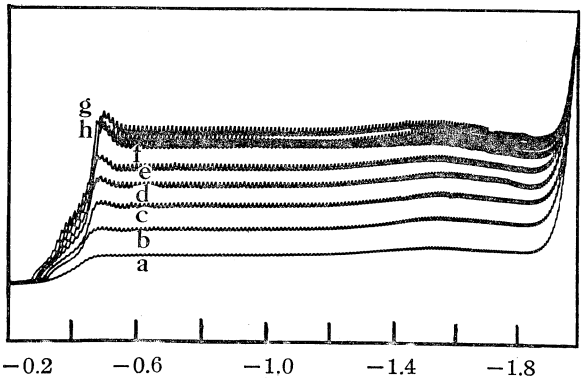

Fig. 8.—Polarograms of (a) 0.385, (b) 0.741, (c) 1.071, (d) 1.380, (e) 1.667, (f) 2.064 (g) 2.424, and (h) 2.86 millimolar copper (II) in 1.00 M potassium hydroxide.

(18) Ref. 2, p. 279.

(19) G. N. Lewis and M. Randall, "Thermodynamics," McGraw-Hill Publishing Co., New York, N. Y., 1923, p. 433.

(20) K. Jellinek and H. Gordon, *Z. physik. Chem.*, **112**, 207 (1924).

$[Tart^{=}]^2/[Complex]$ and state that $[Cu^{++}] = 10^{-15}\ M$ when $[OH^{-}] = 1\ M$ and the concentration of the complex is $10^{-3}\ M$. Latimer[21] has called attention to the uncertainty regarding the formula of the complex ion.

The second wave visible on the curves of Fig. 4 appears only at pH values above about 10. Since its height, although to some extent a function of the tartrate concentration, is never quite equal to that of the first wave, and in 1 M tartrate is only about one-third of the height of the first wave, it cannot indicate stepwise reduction of the copper, but must be due to the presence of a second complex in very slow equilibrium with the first. Its height is quite insensitive to gross changes in pH, and its half-wave potential is similarly independent of pH ($E_{1/2} = -0.744 \pm 0.004$ v. *vs.* the S.C.E. in 1.0 M tartrate) up to pH 12.5. Because it was thought that this wave might be due to the reduction of a cuprate ion, the polarograms shown in Fig. 8 were recorded. At low concentrations (0.4 millimolar) only a single wave, with a half-wave potential of -0.410 v., is observed. The value of $E_{3/4} - E_{1/4}$ for this wave is -42 mv., showing that the two-electron reduction to the metal proceeds somewhat irreversibly from these solutions. As the total copper concentration is increased, the wave appears to divide into two poorly separated waves nearly equal in height, of which the second is much more nearly reversible than the first, and at the same time a small maximum develops. These facts strongly indicate that the cuprate species which predominates in these solutions is reduced to the metal *via* an intermediate cuprite ion. At copper concentrations above 2.5 millimolar, a dark brown solid phase, presumably cupric oxide, separates, and further additions of copper then have little effect on the diffusion current observed. The complexity of the wave form does not appear to affect the constancy of i_d/C, as shown in Fig. 9, which shows a sharply defined limiting concentration of dissolved +2 copper of $2.18 \times 10^{-3}\ M$. This is considered more reliable than the solubility computed by Latimer.[22]

$$Cu(OH)_2 + 2OH^{-} \longrightarrow CuO_2^{=} + 2H_2O;\ K = 1.2 \times 10^{-3}$$

For the moment, we can at least conclude that the wave at -0.744 v. is not due to the reduction of a cuprate ion, but no better explanation has as yet suggested itself.

Lingane,[3] working with solutions containing 0.01% gelatin, found that the copper wave in 0.5 M tartrate containing 0.1 M sodium hydroxide was shifted to a very negative potential ($E_{1/2} =$ *ca.* $-$ 1.6 v.), while a small "pre-wave" was observed starting at about -0.4 v. He considered the "pre-wave" to be produced by the same species present in the neutral and slightly acid solutions, which, on the basis of the present discussion, is plainly impossible. The appearance of the main

(21) W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938, p. 175.

(22) Ref. 21, p. 174.

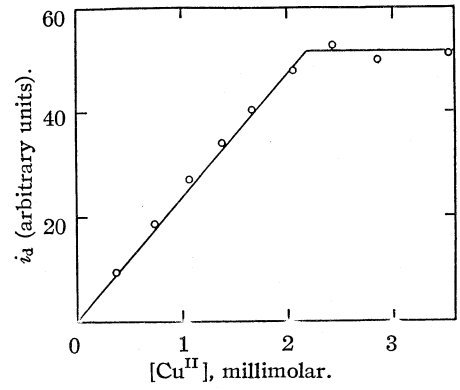

Fig. 9.—The diffusion current of copper (II) in 1.00 *M* potassium hydroxide. $E_{d.e.} = -0.80$ v.

wave at −1.6 v. is also in contradiction of the present data. The apparent controversy is resolved by Fig. 10, which shows the effect of adding 0.010% gelatin to a solution of +2 copper in 0.5 *M* tartrate containing 1 *M* potassium hydroxide. Similar effects are caused by the addition of gelatin to every other system discussed in this paper: a discussion of these effects is now in preparation. Once again it must be stressed that the indiscriminate addition of gelatin to a solution except for the specific purpose of suppressing a maximum, and then only in an amount barely sufficient to accomplish this purpose, is to be looked upon with the gravest suspicion.

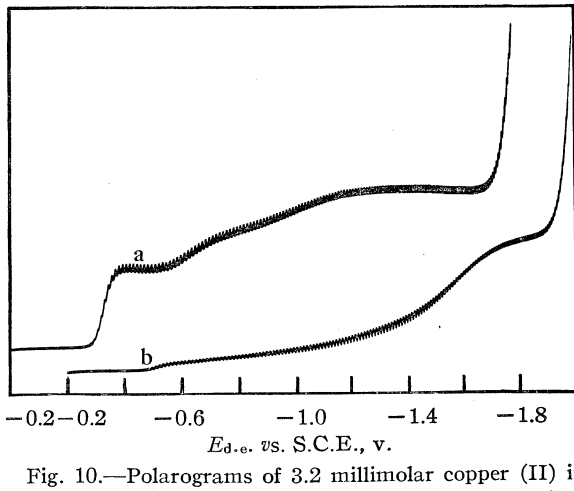

Fig. 10.—Polarograms of 3.2 millimolar copper (II) in 0.50 *M* potassium sodium tartrate and 1.0 *M* potassium hydroxide, (a) without gelatin, (b) with 0.010 % gelatin.

Figures 11, 12 and 13 show the effect of *p*H on the reduction of +2 copper from ammoniacal ammonium tartrate solutions: the values of $E_{1/2}$ are plotted in Fig. 14 as functions of the *p*H. Below *p*H 5.6 there appears to be no difference between the waves in these solutions and those in solutions containing only alkali metal ions, except that the maximum seems to be somewhat accentuated. The appearance of a double wave at *p*H

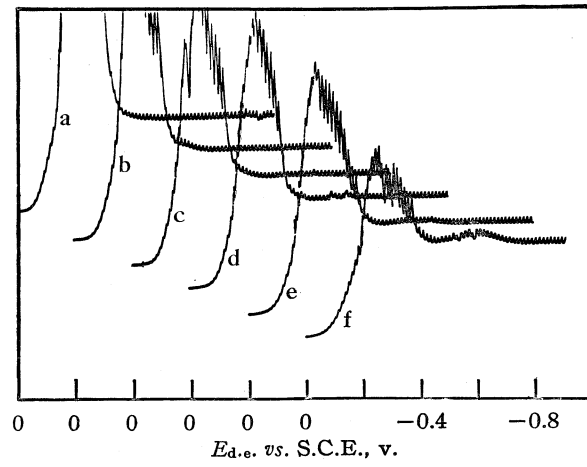

Fig. 11.—Polarograms of 3.23 millimolar copper (II) in 0.100 *M* ammonium tartrate at *p*H (a) 6.07, (b) 6.49, (c) 6.89, (d) 7.21, (e) 7.60, and (f) 7.95.

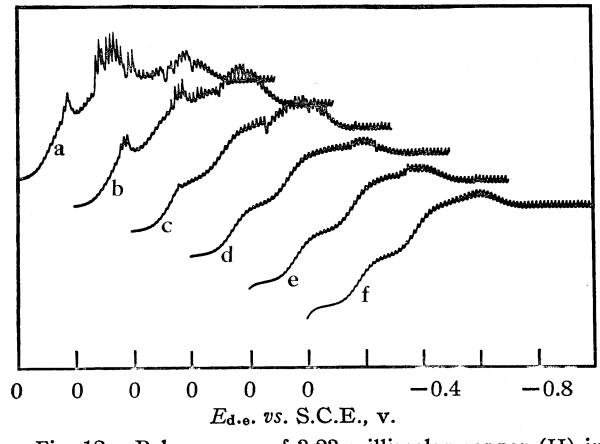

Fig. 12.—Polarograms of 3.23 millimolar copper (II) in 0.100 *M* ammonium tartrate at *p*H (a) 8.25, (b) 8.58, (c) 8.82, (d) 9.11, (e) 9.41, and (f) 9.72.

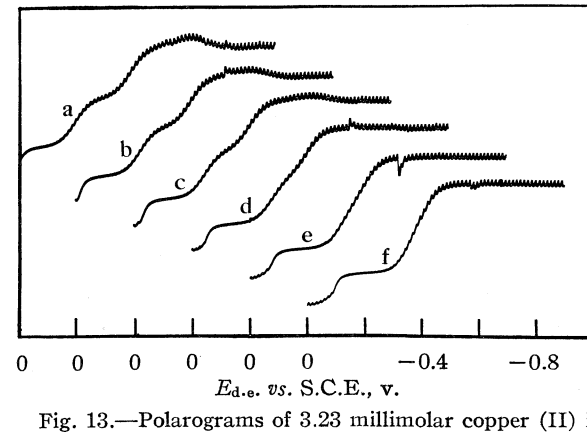

Fig. 13.—Polarograms of 3.23 millimolar copper (II) in 0.100 *M* ammonium tartrate at *p*H (a) 10.03, (b) 10.50, (c) 10.90, (d) 11.38, (e) 11.90, and (f) 12.22.

7.9 in 0.1 *M* ammonium tartrate, and at *p*H 8.2 in 0.25 *M* ammonium tartrate, is accompanied by the development of a very peculiar hump in the

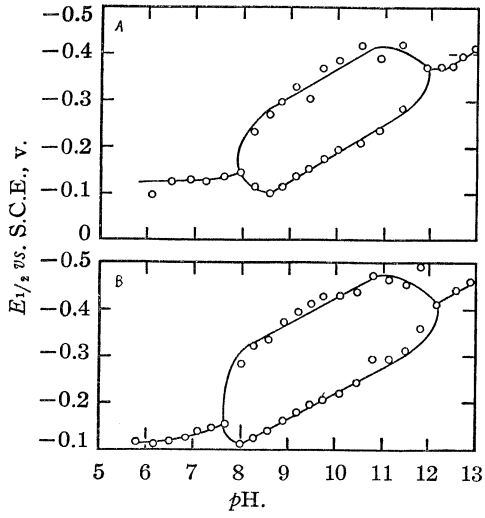

Fig. 14.—Effects of *p*H on the half-wave potentials of the copper (II) waves in (A) 0.10 *M* and (B) 0.25 *M* ammonium tartrate.

plateau of the second wave about 0.2 v. after this plateau is reached. This hump is observed at all *p*H values at which a double wave is found. These two waves are, within the limits of accuracy of the measurements, equal in height throughout this *p*H range, which indicates that reduction to the metal proceeds through the +1 state. For each of the waves $E_{3/4} - E_{1/4}$ is found to be -66 ± 4 mv., in approximate agreement with the expected value for a reversible one-electron reduction.

In 0.1 *M* ammonium tartrate, the half-wave potentials are given by the equations $E_{1/2}^{1} = 0.458 - 0.065$ (*p*H) (± 4 mv.) and $E_{1/2}^{2} = 0.273 - 0.065$ (*p*H) (± 14 mv.). The corresponding equations for 0.25 *M* ammonium tartrate solutions are $E_{1/2}^{1} = 0.359 - 0.0583$ (*p*H) (± 5 mv.) and $E_{1/2}^{2} = 0.156 - 0.0583$ (*p*H) (± 11 mv.). In each case the better agreement with the equation for the first wave is due to the considerably poorer definition of the second.

Now this effect of *p*H is exactly that to be expected if one molecule of ammonia is liberated in each one-electron reduction, so that the copper(II) complex must be formulated as $Cu(NH_3)_2(Tart)_x^{2-2x}$ and the copper(I) complex must be $Cu(NH_3)(Tart)_y^{1-2y}$. On making a correction of 0.40 *p*H unit to compensate for the different concentrations of ammonium ion, the half-wave potentials of the first waves (reduction to +1 copper) at the different concentrations of tartrate are found to be essentially equal (± 10 mv.) at equal concentrations of ammonia. Therefore we must conclude that tartrate ions are not involved in the first step of the reduction, and, in equations 4 and 5

$$Cu(NH_3)_2(Tart)_x^{2-2x} + e \longrightarrow Cu(NH_3)(Tart)_y^{1-2y} + NH_3 + (x - y)Tart^{=} \quad (4)$$

$$Cu(NH_3)(Tart)_y^{1-y} + e \longrightarrow Cu(Hg) + NH_3 + yTart^{=} \quad (5)$$

$x = y$. The same correction to the data for the second waves reveals that, at a constant concentration of ammonia, a 2.5-fold increase in the tartrate concentration shifts the half-wave potential corresponding to equation (5) to a value more negative by about 30 mv. This corresponds to 75 mv. for a tenfold increase in tartrate concentrations, in approximate agreement with the theoretical effect if $y = 1$ in equation 5. Correcting the observed data to solutions containing *M* ammonia and tartrate, we then have

$$Cu(NH_3)(Tart)^{-} + NH_3 \longrightarrow Cu(NH_3)_2(Tart) + e; \; E^0 = -0.04 \text{ v.}$$

and

$$Cu(Hg) + NH_3 + Tart^{=} \longrightarrow Cu(NH_3)(Tart)^{-} + e; \; E^0 = +0.20 \text{ v.}$$

At *p*H values above about 11, when the concentration of hydroxyl ion becomes of the same order of magnitude as the concentration of copper, the two waves coalesce into one which, because of the equality of the $E_1/_2$ values, must be attributed to the reduction of the $Cu(OH)_2(Tart)_2^{-4}$ complex present in the ammonia-free tartrate solutions of the same pH.

Figure 15 illustrates the effect of gelatin on the waves in ammoniacal ammonium tartrate, and re-emphasizes the caution that must be observed in the use of gelatin.

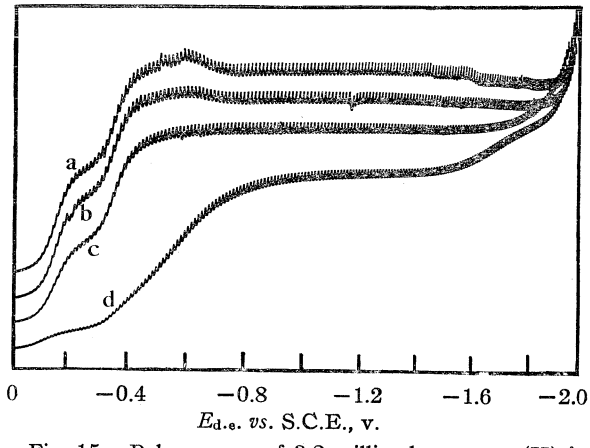

Fig. 15.—Polarograms of 3.2 millimolar copper (II) in 0.10 *M* ammonium tartrate, *p*H 9.55, with (a) 0, (b) 0.001, (c) 0.010, and (d) 0.050 % gelatin.

Summary

Acidic tartrate solutions of +2 copper contain the $Cu(H\ Tart)_4^{=}$ ion which is reduced directly to the metal at about -0.1 v. (*vs.* S.C.E.). At *p*H values between about 7 and 11, the copper is present mainly as a tartrate complex whose formula cannot be determined from polarographic measurements, and in still more alkaline solutions the $Cu(OH)_2(Tart)_2^{-4}$ ion is formed. The dissociation constant of this ion is 1.4×10^{-10}.

The same phenomena are found in ammonium tartrate solutions of *p*H below 7 or above 12, but

in the intermediate range an amminocupric tartrate ion is formed. This is reduced to the metal *via* the +1 state, the reactions being

$$Cu(NH_3)(Tart)^- + NH_3 \longrightarrow Cu(NH_3)_2(Tart) + e;\ E^0 = -0.04 \text{ v.}$$

and

$$Cu(Hg) = NH_3 + Tart''' \longrightarrow Cu(NH_3)(Tart)^- + e;\ E^0 = +0.20 \text{ v.}$$

The solubility of +2 copper in M hydroxide is 2.18×10^{-3} M.

Gelatin severely distorts the waves of all these species, especially at concentrations above 0.001%. Great stress is laid on the caution that should be observed in its use if polarographic data are to be considered to represent the true electrochemical behavior of substances in solution.

NEW HAVEN, CONNECTICUT RECEIVED MARCH 30, 1949

[CONTRIBUTION FROM THE INSTITUTE FOR THE STUDY OF METALS, THE UNIVERSITY OF CHICAGO]

A Thermodynamic Study of Liquid Metallic Solutions. I. The System Lead–Gold

BY O. J. KLEPPA

Introduction

In a detailed experimental study of the thermodynamic properties of binary liquid alloy systems, there are two general ways of approach. One method is to evaluate the activity of a volatile component (Hg, Zn, Cd, Mg) from vapor pressure measurements. The other method depends on measuring the electromotive force in reversible galvanic cells of the type

$$A(l)/A^{n+}/(A + B)(l)$$

where A denotes the baser (more electropositive) metal, B the other metal.

If carried out over a sufficiently large composition and temperature range, both methods will give us, in principle, all the data required for a complete evaluation of the thermodynamic properties (*i. e.*, free energy, entropy and heat of mixing) for the mixture, using the pure components as reference states. Both methods have also found extensive application at moderately high temperatures during the past twenty to twenty-five years.[1]

It has not, however, so far been possible to tie the results of these researches in with any existing theory of solutions.[2] This paper is the first report on a series of investigations started in order, if possible, to arrive at a clearer understanding of the factors governing the properties of such liquid metallic solutions.

Experimental Method.—The system lead–gold is well suited for application of the electromotive force method.

Measurements of the electromotive force, E, of various liquid alloy compositions *versus* pure liquid lead immediately give us the relative chemical potential μ_{Pb} in the mixture through the relationship $\mu_{Pb} - \mu_{Pb}^0 = -2FyE$ where Fy is the faraday constant. The superscript^0 in this paper refers to the pure component.

The temperature gradient of the electromotive force, dE/dT, will give the relative partial molar entropy $\Delta\bar{S}$ in the mixture in a similar way, through the relationship

$$\Delta\bar{S} = \bar{S} - S^0 = 2Fy(dE/dT)$$

These quantities are thus directly available from measurements. Through the equation

$$\mu - \mu^0 = \bar{L} - T\Delta\bar{S}$$

we can also immediately calculate the relative partial molar heat content, $\bar{L}_{Pb}$, for lead in the mixture.

A knowledge of the partial molar properties for one of the components over the whole concentration range makes possible a calculation of the same properties for the other component by (graphical) integration of the Gibbs–Duhem–Margules equation

$$x_1 d\bar{Y}_1 + x_2 d\bar{Y}_2 = 0$$

where $\bar{Y}_1$ is any partial molar quantity for component 1, x_1 is the corresponding mole fraction (or here atomic fraction).

It should, however, be noted that in the case of lead–gold, where it was not possible to extend the measurements into the gold-rich region beyond an atomic fraction of gold of 0.79, the calculation of the partial molar properties for gold in the mixtures is associated with some uncertainty. This uncertainty is carried through in any calculation of the integral thermodynamic properties Y through the equation

$$Y = x_1\bar{Y}_1 + x_2\bar{Y}_2$$

Experimental Procedure

The type of cell used in this investigation was similar to the H-shaped cell extensively applied by H. Seltz and co-workers.[3] However, as the study of the lead–gold system required measurements up to 800–850°, temperatures at which Pyrex will no longer stand up, the cells were made from fused silica. Although extended heating at the highest temperatures caused some devitrification of the cell walls, it was found that these silica cells in general stood up quite well to the attack of the electrolyte used. This consisted of a eutectic mixture (m. p. 360°) of lithium

(1) A fairly complete bibliography is recently given by John Chipman, *Discussions Faraday Soc.*, **4**, 23 (1948).

(2) J. H. Hildebrand, "Solubility," Reinhold Publishing Corp., New York, N. Y., 1936.

(3) H. Seltz, *Trans. Electrochem. Soc.*, **77**, 233 (1940).

chloride and potassium chloride with some 5 wt. per cent. of lead chloride added.

The electrolyte was first melted down in the cell and degassed by heating to 700–800° for a short period of time. Weighed amounts (totaling 3–4 g.) of gold and lead, and of pure lead only, were then melted down in their separate halves of the cell, before the cell was placed in a larger silica tube heated in an electric tube furnace. To prevent temperature fluctuations, the silica tube contained a lead "bath" protected by a chloride melt, into which the cell was immersed.

Tungsten leads, protected from the electrolyte in the cell by close fitting alundum thermocouple tubes, were then inserted, the system closed off and evacuated. The assembled system is shown in Fig. 1.

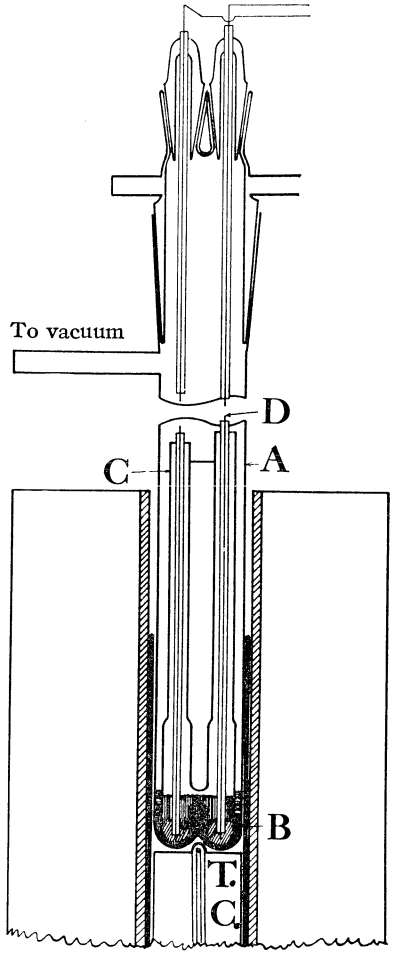

Fig. 1.—Experimental arrangement: A, outer silica tube; B, lead bath; C, silica cell; D, tungsten leads; T. C. thermocouple.

By using a constant voltage transformer for control of the power input it was possible to maintain constant temperature in the system to ±1° over a period of many hours.

The temperature was measured by a chromel–alumel thermocouple in contact with the outside bottom of the silica tube (see Fig. 1, T.C.). It was found in separate experiments that this thermocouple showed a practically constant amount of 2° less than the actual temperature of the lead-bath (in the temperature range used); the reported temperatures are corrected for this difference. The Chromel–Alumel thermocouples were checked at the melting points of lead, antimony and silver.

The electromotive forces, both for cell and thermocouple, were measured by a Rubicon (type B) potentiometer which could be read easily to 0.005 mv.

In a period of two to three days some 100–200 independent measurements of both temperature and electromotive force were carried out at 8–15 different temperatures. When the required data for one alloy composition had been obtained in this way, nitrogen was admitted into the system and additional weighed amounts of gold or lead were added to the alloy electrode. The experiment was then continued for another two to three days until the required data for the new composition had been recorded. After 2 or 3 such consecutive runs, the cell was removed from the system, and the alloy and reference electrodes removed from the cooled off cell for analysis.

It was found that the electromotive force measurements at moderately high temperatures (< 700°) could be reproduced to ±0.02–0.03 mv. At temperatures above 700°, however, scattering increased and the precision dropped to ±0.1–0.2 mv. When measurements were carried out above 850°, it was no longer found possible to get consistent results over any prolonged period of time. This prevented extension of the measurements to alloys richer in gold than about 80 atomic per cent.

The possible presence of gold in the reference electrodes was checked after completion of the runs by spectrographic methods. In all cases, except one, it was found that the gold content was less than 0.02%. This amount is quite negligible compared with other sources of error. In one case, however, 0.31% gold was found in the reference electrode, indicating accidental contamination of the reference electrode by transfer of metal from the alloy side to the pure metal side of the cell. The results of these runs are not reported.

Analysis by conventional analytical methods of the alloy electrodes showed, within the analytical error, no change in composition. The compositions reported are based on weighed-in amounts.

The lead used in this investigation was "Baker's Analysed" with a total of foreign non-volatile matter of 0.02%. The gold was "fine gold" (99.9% Au) supplied by Baker and Company.

Experimental Results

The measured electromotive forces for each alloy composition were plotted *vs.* temperature. Over a range of 200–300°, there was never a detectable change in the slope of any of these curves, and a graphical determination of the temperature gradient of the electromotive force was, therefore, simple. From the same set of curves the electromotive forces for the various compositions at one reference temperature, 600°, were obtained. As most of the experiments were performed at 450–700°, it was decided to use 600° as a reference temperature also for alloys which would not be liquid at this temperature (alloys with less than 32 atomic per cent. lead). This involved an extrapolation of the data for these alloys from higher temperatures, making use of the simultaneously determined temperature gradient of the electromotive force. The reference state for gold in all data reported below is the hypothetical undercooled liquid gold.

The experimental results for the various runs and the corresponding activities a_{Pb} and "entropy fractions"[4] x'_{Pb} are recorded in Table I.

Based on this set of experimental data, the electromotive forces and their temperature gradients for round figure atomic fractions were de-

(4) For an explanation of the term "entropy fraction," see below.

TABLE I

Run	Atomic fraction of lead	E. m. f., mv., at 600°	700°	800°	a_{Pb} 600°	$\Delta E/\Delta T$ mv./100°	x'_{Pb}	Temp. range, °C.
2	0.9665	1.40			0.9623	0.12	0.973	450–700
3	.9345	2.75			.9294	.27	.940	450–700
4	.9008	4.25			.8932	.35	.922	450–700
5	.8205	8.81			.7911	.83	.825	450–700
6	.7393	14.14			.6866	1.26	.746	450–700
7	.6715	18.86			.6056	1.66	.680	450–700
8	.6311	22.91			.5438	2.10	.614	450–700
9	.6054	25.19			.5118	2.32	.583	450–700
10	.5935	25.84			.5030	2.35	.579	450–700
11	.5687	28.70			.4661	2.60	.547	450–700
12	.5078	35.15			.3927	3.49	.445	500–700
13	.4247	45.80			.2959	4.68	.337	500–700
14	.3336	60.25	66.50		.2015	6.25	.234	600–700
15	.2702	74.25	82.45		.1389	8.20	.149	600–780
19	.2135	91.2	101.3	111.4	.0885	10.1	.096	750–830
21	.3697	53.20			.2431	5.56	.275	550–650
22	.3031	65.00	72.10		.1771	7.10	.192	620–700
23	.2502	78.0	86.4	94.8	.1254	8.4	.142	700–800

TABLE II[a]

1	2	3	4	5	6	7	8	9	10
	600° C.		600° C.						
x_{Pb}	$\mu_{Pb} - \mu^0_{Pb}$ cal.	$\Delta\bar{S}_{Pb}$, cal. deg.$^{-1}$	a_{Pb}	a_{Au}	x'_{Pb}	x'_{Au}	$\bar{L}_{Pb}$, cal.	$\bar{L}_{Au}$, cal.	ΔH, cal.
1.000	0	0	1.000	0.000	1.000	0.000	0	(?)	0
0.900	− 205	0.18	0.889	.036	0.913	.045	− 48	−400	− 84
.800	− 460	.42	.767	.087	.809	.093	− 93	−123	− 99
.700	− 780	.71	.638	.150	.699	.144	− 160	75	− 90
.600	−1170	1.08	.509	.229	.581	.204	− 227	198	− 57
.500	−1655	1.60	.385	.322	.447	.280	− 258	243	− 8
.400	−2250	2.32	.273	.429	.311	.375	− 225	234	+ 50
.300	−3065	3.28	.171	.553	.192	.484	− 198	232	+103
.200	−4450	5.0	.077	.716	.081	.637	− 85	203	+145
.100	(−6500)	(8.5)	.023	.879	.014	.860	+1000	38	+134
.000	....	..	.000	1.000	.000	1.000	(?)	0	0

[a] The values in parentheses are based on extrapolation. The reference state for gold is the hypothetical undercooled liquid gold.

termined by graphical interpolation of the smooth curve drawn through the experimental points. The corresponding chemical potentials and partial molar entropies are recorded in columns 2 and 3, Table II.

In column 4 of this table are given the activities of lead at 600°, while column 5 gives the corresponding activities of gold, calculated by graphical integration of the atomic ratios *versus* activity coefficients. Columns 6 and 7 give, in a similar way, the "entropy fractions" for lead and gold, respectively.

The author, in another communication,[5] has suggested the use of the "entropy fraction" to indicate the deviations of the partial molar entropies from those of an ideal solution.

The entropy fraction x_i' is defined by the relationship

$$\Delta\bar{S}_i = -R \ln x_i'$$

It will be seen that this quantity is related to the partial molar entropy in the same manner as the activity is related to the chemical potential. If x' is different from x, the ratio of the two (x'/x) gives a numerical measure for deviations from the ideal partial molar entropy. The quantity (x'/x) might be termed "entropy fraction coefficient" and is particularly useful in graphical integrations involving the partial molar entropy. Like the chemical potential, the partial molar entropy goes numerically to infinity when x goes to zero, while the activity coefficient and (x'/x) of course remain finite. This has been made use of in the computation of the data of column 7.

Plots of activities and "entropy fractions" for both components are given in Fig. 2.

Columns 8, 9 and 10 finally give the calculated values for relative partial heat contents $\bar{L}$ and for the integral heats of mixing ΔH. These quantities are plotted in Fig. 3.

Limits of Error in Computed Data.—The limits of error in the basic data of Table II (columns 2 and 3) are estimated to generally less than ±1% for the chemical potentials and to ±2–3% for the partial molar entropies. This estimation

(5) O. J. Kleppa, *Discussions Faraday Soc.*, **4**, 109 (1948).

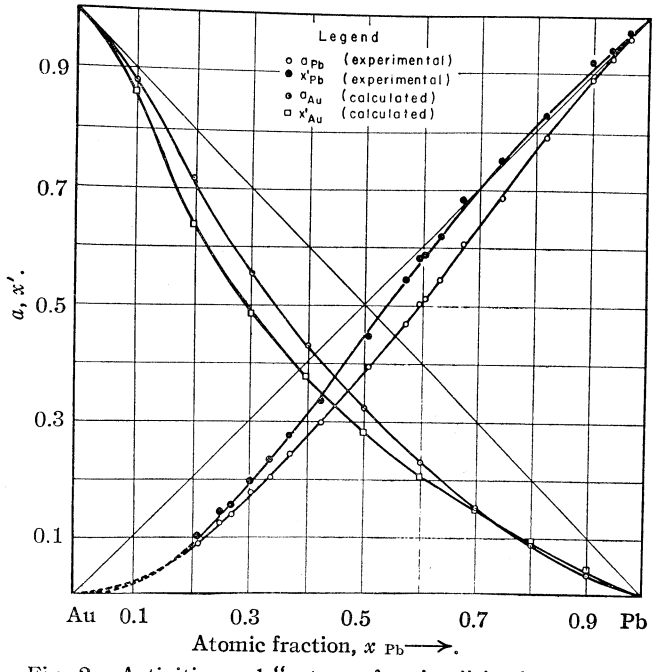

Fig. 2.—Activities and "entropy fractions" in the system Au (l)–Pb (l).

is based primarily on the reproducibility of the measurements, the temperature fluctuations during the experiments and on the possible error involved in the graphical interpolations.

These errors cannot seriously affect the calculated values for the activity and "entropy fraction" for lead. However, the relative partial molar heat content, $\bar{L}_{Pb}$, is derived as a difference between two large numbers, and may accordingly be associated with a considerably greater uncertainty.

In the subsequent calculations of the activities and "entropy fractions" for gold more serious error may also be involved, because of the required extrapolation of the data for lead into the most gold-rich region (bracketed values in columns 2 and 3) and the uncertainty associated with the graphical integration. What is said above about the uncertainty in the partial molar heat content, is even more the case for $\bar{L}_{Au}$ than for $\bar{L}_{Pb}$.

Comparison with Other Data.—Unfortunately, there are no calorimetric data available for the system lead–gold. These would have represented a very desirable check on the thermal data. However, by comparison with the equilibrium phase diagram, we have an independent method for determination of the chemical potential of gold in the liquid alloys rich in gold.

The phase diagram in this system was worked out by Vogel.[6] From his data we find that the liquid in equilibrium with the solid solution of lead in gold at 600° has an atomic fraction of lead of 0.314. As the solid solubility of lead in gold is probably of the order of 0.05% or less at 600°[7] we can neglect it in our calculations without introducing any appreciable error.

The equilibrium condition is then simply

$$\mu'_{Au}\ (\text{solid}) = \mu_{Au}\ (\text{in solution})$$

We must accordingly calculate the chemical potential of pure solid gold at 600°, referred to pure liquid undercooled gold of the same temperature. This immediately also gives the chemical potential of gold in the solution.

For the process Au(l) = Au(s) K. K. Kelley[8] gives $\Delta H = -3030$ cal. at the melting point of gold (1336°K.). In the lack of data for the specific heat of undercooled liquid gold, we make the reasonable assumption that $\Delta C_P = 0$ and find for the considered process

$$\mu'_{Au(s)} - \mu^0_{Au(l)} = 2.268T - 3030$$

whence

$$\log a_{Au} = 0.4957 - (662.3/T)$$

At 600° we calculate $a_{Au} = 0.546$ while this investigation gives $a_{Au} = 0.538$ for $x_{Pb} = 0.314$. In view of the assumptions made and the possible error involved in our computations of the activities of gold in the solutions, this agreement must be considered quite satisfactory.

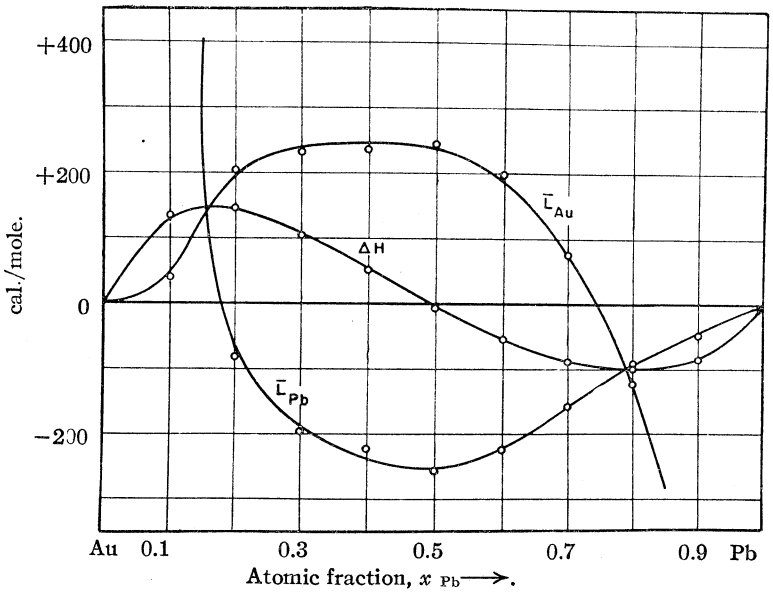

Fig. 3.—Relative partial molar and integral heats of mixing in the system Au (l)–Pb (l).

(6) R. Vogel, *Z. anorg. allgem. Chem.*, **45**, 11 (1905).
(7) M. Hansen, "Aufbau der Zweistofflegierungen," Berlin, 1936.
(8) K. K. Kelley, U. S. Bureau of Mines Bull. **393** (1936).

Thermodynamic Properties of Au_2Pb.—By further study of the phase diagram for lead–gold, it will be seen that between the temperatures 420 and 254°, various liquid mixtures are in equilibrium with solid Au_2Pb, and that between 254 and 215° other mixtures are in equilibrium with solid $AuPb_2$.

We shall use our thermodynamic data for the liquid extrapolated to the appropriate temperatures to calculate the free energy of formation ΔF for Au_2Pb(s), with reference to the pure liquid metals of the same temperatures. In these calculations it is assumed that there is no change in the partial molar entropies in the liquid with temperature. At equilibrium conditions

$$\mu'_{Pb} \text{ (in } Au_2Pb) = \mu_{Pb} \text{ (in solution)}$$
$$\mu'_{Au} \text{ (in } Au_2Pb) = \mu_{Au} \text{ (in solution)}$$

For the process

$$2Au(l, \text{undercooled}) + Pb(l) = Au_2Pb(s)$$

we then have

$$\Delta F = 2\,\mu_{Au} + \mu_{Pb}$$

The results of these calculations are recorded in Table III.

TABLE III

Atomic fraction, x_{Pb}	Equil. temp., °K.	$-\Delta F$ (Au_2Pb)	$-\Delta F/T$	$10^3 \times 1/T$
0.4382	696	4223	6.067	1.437
.4880	681	4268	6.267	1.468
.5381	656	4327	6.615	1.524
.5885	628	4407	7.017	1.592
.6390	593	4495	7.580	1.686
.6694	565	4526	8.010	1.769
.6899	548	4541	8.226	1.824

The data in the first two columns are taken from Vogel,[6] ΔF is calculated from the equation above after the appropriate extrapolation of our experimental data has been carried out. In Fig. 4, $\Delta F/T$ is plotted *versus* $1/T$ in the usual way, and from the slope we find

$$\Delta H = -6000 \pm 300 \text{ cal.}$$

Hence, for the entropy of formation at 692°K.

$$\Delta S = (\Delta H - \Delta F)/T = -2.6 \pm 0.5$$

In the lack of data for the specific heat of undercooled liquid gold and Au_2Pb, we shall not try to evaluate the standard heat of formation of Au_2Pb at room temperature.

Discussion

The thermodynamic properties of the liquid mixture of gold and lead can be summarized as follows. The heat of mixing is small (±100 cal.). The considerable deviation of the solution from Raoult's law can be attributed largely to an anomalously high entropy of mixing.

Any discussion trying to explain the properties of this mixture should perhaps be focused on the entropy of mixing rather than on the heat (energy) of mixing.[9] Unfortunately, the factors contributing to entropy deviations in metallic mixtures are even less understood than those deciding energetic deviations. Although theories exist which try to account for entropy deviations due to one single factor only, no attempt has been made so far to get a more complete understanding of their concerted effect. Among the single factors which, although not mutually independent, undoubtedly may play a role in the determination of the entropy of mixing are the following:

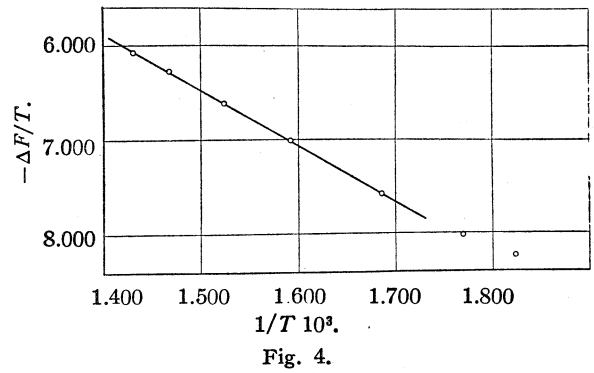

Fig. 4.

Factor	Effect on ΔS	Reference
Short range order	Neg.	Fowler and Guggenheim[10]
Net volume change on mixing $\Delta V > 0$	Pos.	Scatchard[11]
Net volume change on mixing $\Delta V < 0$	Neg.	
Diff. in space req. of each component	Pos.	Hildebrand[12]
Change in sp. heats on mixing	Pos. or neg.	...
Change in coördination no. on mixing	Pos. (?) or neg.	...

The only one of these factors on which we have any decisive information in the case of the gold–lead system, is the difference in space requirement of the gold atom and lead atom, respectively.

At the melting point the atomic volume of liquid lead is 19.4 cm.^{3} per g. atom, while the corresponding figure for gold is 11.5 cm.^{3} If a correction is introduced for the thermal expansion between the melting points and our reference temperature 600°, the difference between the two would be still greater.

It is found, however, that the formulas derived to correct the entropy of mixing for a difference in volume of the two components are quite unable to account for a positive deviation of our order of magnitude.[12]

If data had been available for the net volume change on mixing, the formulas derived by Scatchard[11] might perhaps have explained the excess entropy of mixing. However, without density measurements on liquid lead–gold mixtures, we

(9) A more complete discussion of the factors causing anomalous entropies of mixing in liquid metallic mixtures will be given in a later communication in this series.

(10) R. Fowler and E. A. Guggenheim, "Statistical Thermodynamics," Cambridge University Press, 1939.

(11) G. Scatchard, *Trans. Faraday Soc.*, **33**, 160 (1937).

(12) J. H. Hildebrand, *J. Chem. Phys.*, **15**, 225 (1947).

shall not be able to bring the discussion to a conclusion on this point.

Acknowledgments.—The author is indebted to Mr. R. Fryxell and Mr. L. Howell for carrying out the analytical work involved in this investigation, and to Dr. N. H. Nachtrieb and Dr. T. Rosenqvist for frequent and stimulating discussions during the progress of the research. This work was supported by grants from Union Carbide and Carbon Corp. and from Norges Teknisk-Naturvitenskaplige Forskningsråd.

Summary

The chemical potentials and partial molar entropies of mixing for lead in liquid lead–gold mixtures have been determined by the electromotive force method for compositions up to 79 atomic per cent. gold.

From these data have been calculated for both components activities at 600°, "entropy fractions," and relative partial and integral molar heats of mixing. It was found that the deviation of this mixture from Raoult's law can be largely attributed to a non-ideal entropy of mixing.

The heat and free energies of formation for $Au_2Pb(s)$ from liquid lead and undercooled liquid gold at about 400° were calculated using information from the established equilibrium phase diagram of Au–Pb and from this investigation.

CHICAGO, ILLINOIS RECEIVED APRIL 6, 1949

[CONTRIBUTION FROM GOESSMANN CHEMISTRY LABORATORY, UNIVERSITY OF MASSACHUSETTS]

Composition of Ferric Thiocyanate at High Concentrations

BY STANLEY E. POLCHLOPEK[1] AND J. HAROLD SMITH

Several recent investigations[2–5] have established by a variety of methods that in dilute solution the composition of the ferric thiocyanate complex is $FeSCN^{++}$. Møller[6] used conductivity measurements to identify complexes such as $Fe(SCN)_2^+$ and $Fe(SCN)_4^-$, in more concentrated solutions. In an earlier study Schlesinger and VanValkenburg[7] had concluded that $Fe(SCN)_6^{\equiv}$ was responsible for the red color of ferric thiocyanate solutions on the basis of boiling point elevation and freezing point depression data and absorption spectra.

It has been the purpose of this investigation to study the formation of higher ferric thiocyanate complexes at high concentrations by means of the spectrophotometer, using the method developed by Job[8] and modified by Vosburgh and Cooper.[9] Gould and Vosburgh[5] used this method of continuous variations and found the 1:1 complex at low concentrations, but the method has never been applied to high concentrations of ferric thiocyanate probably because of the very intense color of a concentrated solution. This intense color made necessary the use of very thin absorption cells and the development of a technique for handling these cells.

(1) From a thesis submitted in June, 1948, by Stanley E. Polchlopek to the Graduate School of the University of Massachusetts in partial fulfilment of the requirements for the degree of Master of Science.

(2) Bent and French, THIS JOURNAL, **63**, 568 (1941).

(3) Edmonds and Birnbaum, *ibid.*, **63**, 1471 (1941).

(4) Frank and Oswalt, *ibid.*, **69**, 1321 (1947).

(5) Gould and Vosburgh, *ibid.*, **64**, 1630 (1942).

(6) Max Møller, "Studies on Aqueous Solutions of Ferric Thiocyanate," Dana Bogtrykerri, Copenhagen, 1937.

(7) Schlesinger and Van Valkenburg, THIS JOURNAL, **53**, 1212 (1931).

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(9) Vosburgh and Cooper, THIS JOURNAL, **63**, 437 (1941).

Experimental

Ferric nitrate and potassium thiocyanate were selected as reactants to avoid the formation of other complexes. The ferric nitrate solutions were standardized against sulfato-ceric acid; the potassium thiocyanate solutions were standardized against silver nitrate. Potassium nitrate solutions were used to maintain constant ionic strength whenever possible. The determinations on 0.1 and 0.25 *M* solutions were made with the potassium thiocyanate solutions brought to the ionic strength and *p*H of the ferric nitrate. Check determinations were made without bringing the potassium thiocyanate to the *p*H of the ferric nitrate and it was found that the absorption maxima remained the same as with the *p*H adjusted potassium thiocyanate. In 1.0 *M* solutions it was not possible because of solubility considerations to bring potassium thiocyanate to the same ionic strength as the ferric nitrate and only the *p*H was adjusted. In the 2.0 *M* solutions studied neither the *p*H nor the ionic strength were adjusted. It should be noted that with the high acidity of the thiocyanate solution measurements of optical density had to be made immediately because of the instability of these solutions.

Absorption spectra were determined for solutions in which the ratio of iron(III) to thiocyanate ranged from 1:1 to 1:6 at 0.1 and 0.25 *M* concentrations. These spectra were determined by keeping the volume of the iron(III) solution constant and increasing the volume of thiocyanate. In order that the final volume of ferric thiocyanate be the same for each determination after mixing the components a potassium nitrate solution of the same ionic strength and *p*H was added each time in appropriate volume.

The absorption measurements were taken with a Beckman D. U. Quartz Spectrophotometer. The band widths used in the determinations ranged from 0.8 mμ of spectrum at a wave length of 400 to 4 mμ of spectrum at a wave length of 600 mμ according to data supplied by the manufacturer. The absorption cells used in these measurements were made from "special grade, colorless" microscope slides (A. H. Thomas Co.). Two thin slips of a plastic sheet (or thin cover glasses) were sandwiched between the microscope slides in such a manner that the plastic or glass separators were at both ends of the cell and the center area could be filled with liquid. The cells were clamped at both ends with spring back metal paper clamps. The

plastic separators used were approximately 0.0038 cm. thick and the glass separators were approximately 0.020 cm. Cells of like construction were used with distilled water to adjust the instrument at each wave length.

The slides used were cleaned by immersion in hot sulfuric acid–potassium dichromate cleaning solution, and then rinsed in several detergents and distilled water. If the water drained evenly and readily from the slide, it was accepted as clean. The slide was then polished with lens paper and handled through lens paper throughout the process of assembly. The plastic film and cover glasses used as separators were never touched by hand.

A cell so constructed was filled by capillarity with the ferric thiocyanate introduced into the top of the cell from a pointed medicine dropper. This procedure was found to fill the cell immediately and completely. That the cell was filled uniformly was indicated by the fact that optical density measurements on the same solution and at a specified wave length remained constant regardless of the position of the cell. It was noted that on standing the solution tended to flow slowly out of the cell. It was, therefore, necessary to refill the cell at more or less regular intervals. This was done by introducing the solution at the top of the cell slowly enough so that it completely replaced the original solution which was thus caused to drain out. These flushings had to be carried out very carefully in order not to soil the optical surface of the cell, for the cells could not be cleaned except by complete dismantling. Measurements on solutions of a given series were carried out in the same cell in order to better control the variables in the investigation. For the same reason in order to eliminate any possible effects which might be attributed to fading, all readings of optical density were taken immediately after mixing and, as with Frank and Oswalt's[4] investigation, no evidence of fading was found in freshly prepared solutions.

It must be noted that the absorption cells used in this investigation varied in thickness because the solution placed in the cell often formed a thin film over the separators, causing a very slight displacement. No way to overcome this difficulty was found, and consequently the values for the optical densities of the solution varied very slightly every time a new cell was used. The flushing technique proved so satisfactory, however, that it was possible to use the same cell for getting at least two sets of data for either a continuous variation study or an absorption spectrum without dismantling the cell. So long as the same cell was used, the variations in optical density were no more than those normally encountered when using standard one-cm. cells. The determinations of optical density were repeated several times, and the data presented represent the average of at least three determinations. It was observed that the data for any one study always gave the same shaped curves with the maxima occurring in the same place regardless of any slight variation of the thickness of the cells used.

Results and Discussion

Figure 1 presents the absorption curves for volume ratios of 1:1 to 1:6 of 0.100 *M* iron(III) to 0.100 *M* thiocyanate and indicates that maximum absorption does not occur at the same wave length for each ratio. It was determined that the absorption due to ferric nitrate was negligible at wave lengths higher than 350 mμ with the very thin cells used. This obviated the necessity of corrections for the absorption due to ferric ion at the wave lengths used. Since the total volume for each determination was kept the same by the addition of appropriate volumes of potassium nitrate of equivalent ionic strength, the absorption curves illustrate the mass action effect, and the change in the absorption may be attributed directly to the increase in the thiocyanate concentration. It was anticipated, and found, in view of the low stability of ferric thiocyanate, that absorption would increase as the concentration of thiocyanate increased. The shift in absorption maximum suggests that at high concentrations of thiocyanate higher complexes are being formed.

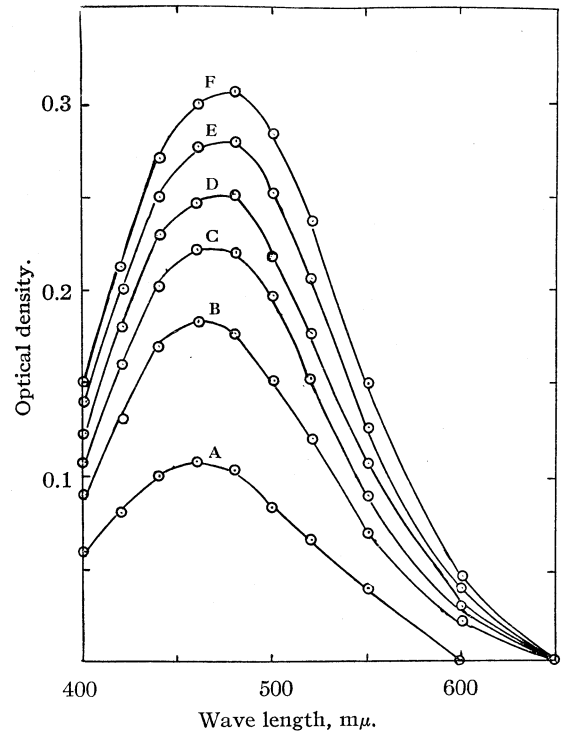

Fig. 1.—Absorption spectra of 0.100 *M* ferric nitrate and 0.100 *M* potassium thiocyanate mixed in ratios of 1:1 (A), 1:2 (B), 1:3 (C), 1:4 (D), 1:5 (E) and 1:6 (F). Iron(III) concentration was constant at 0.0143 *M*. Both solutions were at *p*H 1.7 and ionic strength 0.6. Constant volume was maintained by adding potassium nitrate of like *p*H and ionic strength in approximate amounts. The absorption cell was 0.0038 cm.

Because the absorption spectra show no tendency to intersect, the rules worked out by Vosburgh and Cooper[9] for the selection of wave lengths for a continuous variation study do not apply. The wave lengths used for the continuous variations study were those at which maximum absorption was noted and in addition several wave lengths on both sides of the maximum.

The results of the continuous variations studies for 0.100 *M* solutions are presented in Fig. 2. The fact that the maximum falls at a fraction of approximately 0.4 for iron and 0.6 for thiocyanate indicates presumably that 1.5 thiocyanate ions are associated with each ferric ion. A preferable interpretation is that the ferric thiocyanate solution resulting from mixing solutions of 0.100 *M* ferric nitrate and potassium thiocyanate contains not only the 1:1 complex but other, higher, complexes such as the 1:2.

A study of 0.250 *M* solutions of ferric nitrate

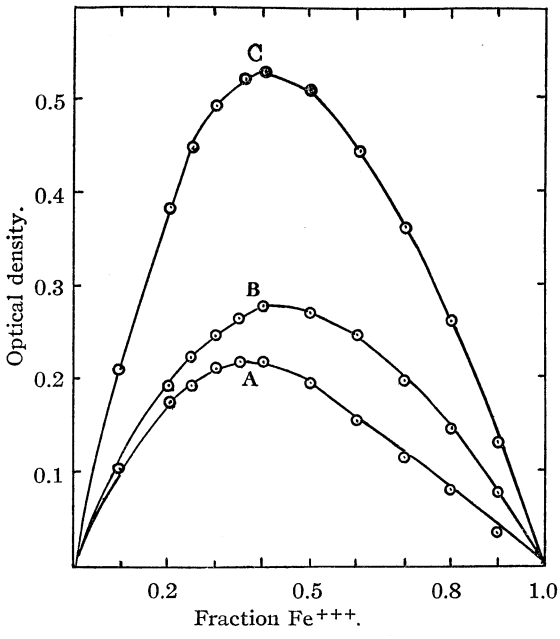

Fig. 2.—Continuous variations studies with 0.100 *M* ferric nitrate and 0.100 *M* potassium thiocyanate, each at *p*H 1.7 and ionic strength 0.6 at wave lengths of 550 mμ (A), 400 mμ (B) and 480 mμ (C). Data for wave lengths of 450 and 500 mμ follow similar plots. The absorption cell was 0.0038 cm.

and potassium thiocyanate showed (Fig. 3) that the absorption increases and the maximum shifts to higher wave lengths as the ratio of thiocyanate to iron(III) increases, thus again illustrating the mass action effect. The continuous variation study on the same solutions (Fig. 4) indicates that the maximum occurs at almost the same point as with the 0.100 *M* solutions, again indicating that the solution contains a mixture of complexes.

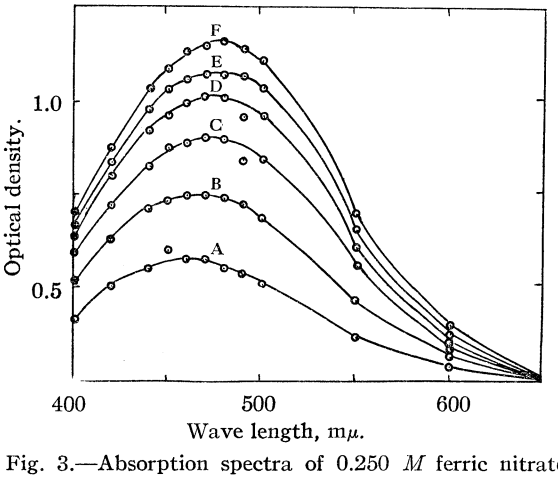

Fig. 3.—Absorption spectra of 0.250 *M* ferric nitrate and 0.250 *M* potassium thiocyanate each at *p*H 1.45 and ionic strength 1.5 mixed in ratios of 1:1 (A), 1:2 (B), 1:3 (C), 1:4 (D), 1:5 (E) and 1:6 (F). Iron(III) concentration was constant at 0.0357 *M*. Constant volume was maintained by adding potassium nitrate of like *p*H and ionic strength in appropriate amounts. The absorption cell was 0.0038 cm.

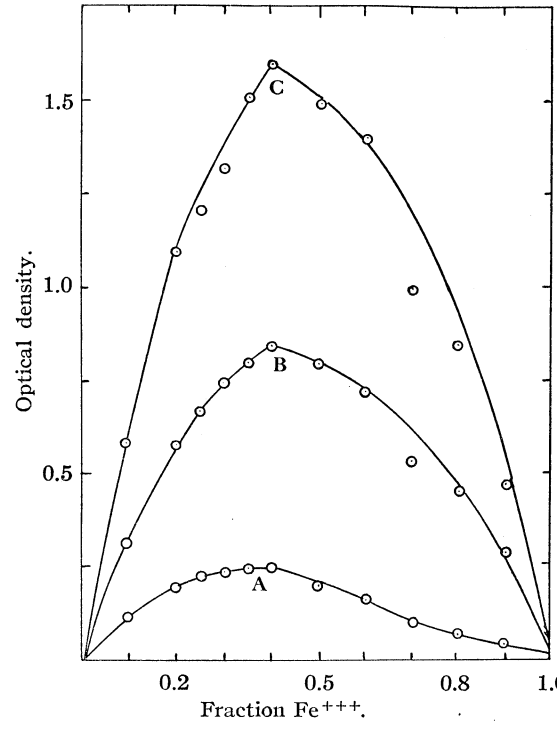

Fig. 4.—Continuous variations studies with 0.250 *M* ferric nitrate and 0.250 *M* potassium thiocyanate each at *p*H 1.45 and ionic strength 1.5 at wave lengths of 600 mμ (A), 400 mμ (B), and 450 mμ (C). Data for wave lengths of 500 and 550 mμ follow similar plots. The absorption cell was 0.0038 cm.

The optical densities of one and two molar solutions were so high that complete absorption data could not be obtained even with the thin cells used. Consequently, in order to study continuous variation, it was necessary to go to the longer wave lengths. Figure 5 shows the maximum for one molar solution at a ratio of thiocyanate to iron (III) of slightly more than 2:1. In other words, while the presence of some $FeSCN^{++}$ cannot be denied, it appears that the solution contains considerable $Fe(SCN)_2^+$ and that even higher complexes are present. A study of two molar solutions showed substantially the same thing, as indicated by Fig. 6. The ratio of thiocyanate to iron(III) at the maxima is slightly higher than for the one molar solutions. In the very concentrated solutions $Fe(SCN)_2^+$ is probably predominant. To check the effect of dilution, samples of the concentrated ferric thiocyanate solutions were occasionally diluted to 0.02 and 0.001 *M* and, as in earlier investigations,[2,3,4,5] only $FeSCN^{++}$ was found. Doubtless this is the predominant complex involved in colorimetric determinations of iron(III) where thiocyanate concentrations are generally very low.

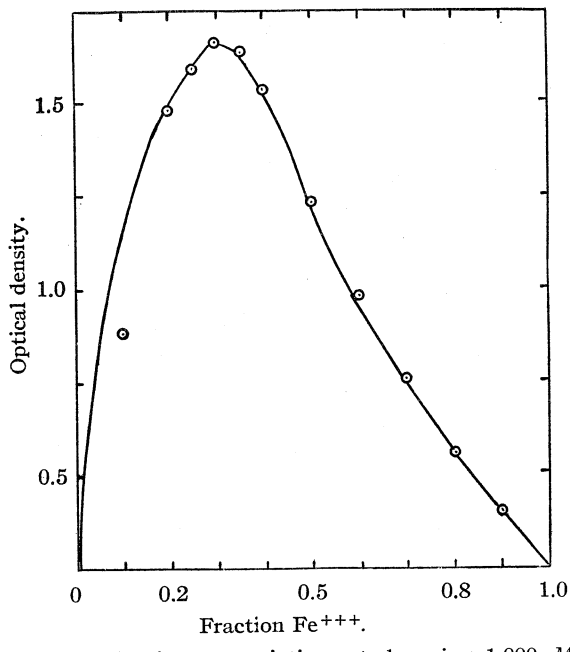

Fig. 5.—Continuous variations study using 1.000 *M* ferric nitrate and 1.000 *M* potassium thiocyanate, each at *p*H 0.75 at 600 mμ. Ionic strength was not controlled. The absorption cell was 0.0038 cm.

Summary

1. Absorption spectra of ferric thiocyanate solutions with ferric ion at 0.0143 and 0.0357 molar and iron(III) to thiocyanate concentration ratios from 1:1 to 1:6 were determined, and are herewith presented. A shift of the absorption maximum toward longer wave lengths as the thiocyanate concentration is increased is noted and interpreted as an indication of higher complexes than $FeSCN^{++}$ which is found in dilute solution.

2. Data obtained by the method of continuous variations are presented which establish the existence of higher complexes. Definite evidence for higher complexes is found even at concentrations no higher than a few hundredths molar. The complex $Fe(SCN)_2^+$ is indicated as predominant in the 0.5 to 1.0 molar concentration range.

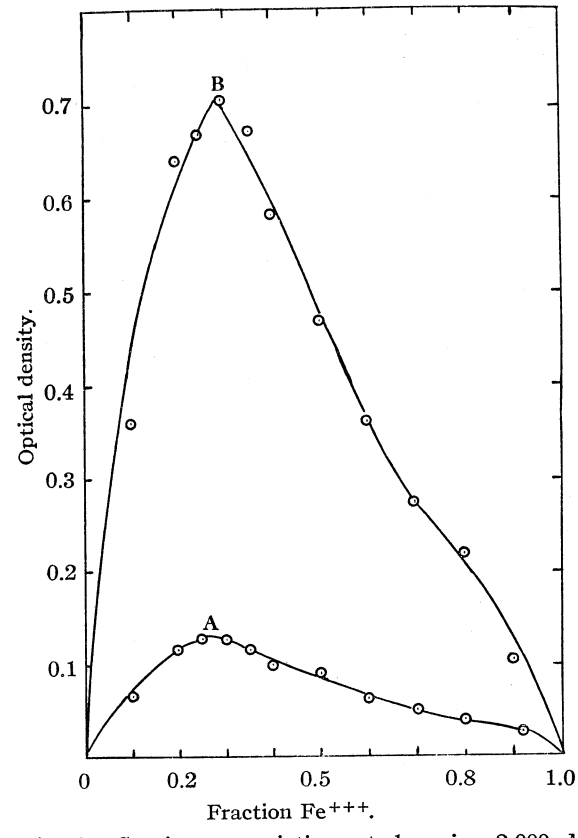

Fig. 6.—Continuous variations study using 2.000 *M* ferric nitrate and 2.000 *M* potassium thiocyanate at 700 mμ (A) and 650 mμ (B). Ionic strength and *p*H were not controlled. The absorption cell was 0.0038 cm.

Evidence for still higher complexes is presented.

3. In view of the complexity of the ferric thiocyanate system at the concentrations studied, no attempt was made to determine equilibrium constants. The several complexes apparently present in any given solution have absorption bands which overlap to such an extent as to make the study of any one particular higher complex extremely difficult, if not impossible, with a spectrophotometric method.

AMHERST, MASSACHUSETTS RECEIVED MARCH 1, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

A Two Dimensional Representation of Quaternary Phase Systems

BY EDWARD V. SAYRE[1]

The solution of many phase separation problems in quaternary systems has been difficult because no single two dimensional diagram has been presented upon which graphical solutions of these problems may be obtained. Several ingenious methods have been described by which the concentration of all four components of a mixture may be represented in one plane. Some of the ways have been through a special use of polar coordinates,[2] or through the representation of a composition by a vector the length of which is determined by the concentration of one component and the position of which is determined by the concentrations of the other three components.[3,4] Blasdale[5] superimposed a Loewenherz and a Jaenecke projection at an arbitrarily convenient position so that the relations between them determined the solvent concentrations. Ricci and Loucks[6] suggested that an orthogonal projection of a three-dimensional Schreinemakers diagram and a Jaenecke projection may be used together in the same way. These methods of representation, however, do not lend themselves to the graphical solution of other than the most simple phase separation problems.

Most graphical methods of solution are performed with less complicated diagrams, which do not individually describe the systems with respect to all four components. Two or more of such separate diagrams are, therefore, required to arrive at a solution. Typical of such methods are the combined use of a vertical and a horizontal projection of a three dimensional Jaenecke isothermal diagram,[7-9] or the use of projections on two different planes through a solid Schreinemakers type diagram.[6,10]

The diagram described in this paper is the result of a double projection of the equilibrium surfaces of a solid Schreinemakers diagram[10] onto its base. These solid figures are, of course, a tetrahedron for additive systems and a pyramid for reciprocal salt pair systems. One projection is an orthogonal projection of the equilibrium points onto the base. The second figure is obtained by projecting the equilibrium points radially onto the base through lines originating at the solvent apex, *i. e.*, a Jaenecke projection. The two projections are superimposed in such a way that the ratio of the distance of an orthogonally projected point from the center of the diagram to the distance of the corresponding Jaenecke point from the center is exactly equal to the mole fraction of solvent present. Thus the diagram permits the indirect determination of solid phases through Schreinemakers' method of residues,[11] the extrapolation of tie lines. Hence by reverse application of this principle the diagram is well adapted for the graphical solution of problems of precipitation from supersaturated solutions. Also any two corresponding points in the double projections together describe a given mixture unambiguously in all four components.

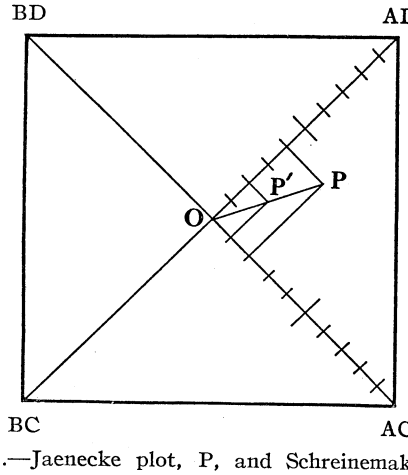

Fig. 1.—Jaenecke plot, P, and Schreinemakers plot, P', for solution of mol fractions 0.2 AD, 0.2 AC, 0.1 BD, and 0.5 solvent.

Construction of the Diagram

The orthogonal projection of a reciprocal salt pair system may be plotted by considering the four half diagonals of the square pyramid base as coördinate axes. As shown in Fig. 1, a point in the diagram quadrant, salt AC—center point O—salt AD, is located by plotting the mole fraction of AC in the total mixture as its abscissa outward along the half diagonal O(AC) and the mole fraction of AD as its ordinate along the half diagonal O(AD). If some of the salt BD, reciprocal to salt AC, is present, the position of the point in the O(AC) direction is plotted equal to mole fraction AC minus mole fraction BD. When the mole

(1) Present address: Eastman Kodak Company, Rochester, New York.

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(3) W. Lodochinkov, *Ann. inst. anal. phys.-chim.* (*USSR*), **2**, 255 (1924); *Z. anorg. allgem. Chem.*, **151**, 185 (1926); **169**, 177 (1928).

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(7) Jaenecke, *Z. anorg. Chem.*, **51**, 132 (1908); **71**, 1 (1911).

(8) H. Buraus, *J. Phys. Chem.*, **45**, 968 (1941).

(9) Findlay and Campbell, "The Phase Rule and Its Applications," 8th edition, Longmans, Green and Co., London, 1938, Chap. XVII.

(10) Schreinemakers, *Z. physik. Chem.*, **69**, 557 (1909).

(11) Schreinemakers, *ibid.*, **11**, 81 (1893); **59**, 641 (1907).

fraction of total salts in the particular mixture plotted is increased by the simple removal of solvent, the mole fraction of each individual salt is increased in the same proportion. In this case, the representing point is extended outward along a straight line originating at the center O, where the mole fraction of total salt is zero. In the full three dimensional diagram, contained in a regular tetrahedral pyramid as illustrated in Fig. 2, the locus of these points representing change of solvent concentration alone is a radial line from the apex terminating on the base. A diagram can be thus radially projected through the Schreinemakers construction of a phase system onto the pyramid base, where total mole fraction of salts equals one. This projection can be plotted in the manner described above by substituting as coördinates the mole fractions of the individual salts in the total dry salts in place of mole fractions in the total salt–aqueous mixture. This figure is the two dimensional Jaenecke diagram of the phase system, and is identical with the figure obtained by the more conventional procedure of plotting mole fractions of ions as coördinates. If the number of moles of a given salt in a mixture is X, the total number of moles of salt Y and the number of moles of solvent Z, then the coördinate of the given salt in the orthogonal projection is $X/(Y+Z)$, and the coördinate in the Jaenecke projection is X/Y. The ratio of the orthogonal coördinate to the Jaenecke coördinate, $X/(Y+Z)/X/Y$, is then equal to the mole fraction of total salts, $Y/(Y+Z)$. Therefore, the ratio of the distance of the orthogonal point from the center origin to the distance of the Jaenecke point from the center is also equal to the mole fraction of total salts. And, since the Jaenecke point alone unambiguously specifies the molar ratios of the salts, the two points together completely define a given mixture. Any finite number of equilibrium data points may be so plotted, and thus a description of an isothermal four-component reciprocal salt pair system may be obtained in a plane.

Figure 3 presents the 25° isothermal diagram of the sodium nitrate–potassium chloride–water system, which is of importance in the manufacture of conversion saltpeter. For simplicity, all equilibrium surfaces have been considered planes and their intersections, therefore, straight lines. This assumption need not be made, since any finite number of data points describing the equilibrium surfaces may be plotted and contour lines drawn between them to represent the true equilibrium surfaces and lines within the accuracy of the available data. Primed figures will designate the orthogonally projected diagram; the unprimed ones the Jaenecke diagram. The data for this system were taken from Findlay and Campbell.[9] Point P completely describes the mixture 0.50 KNO_3, 0.40 $NaNO_3$, 0.10 KCl, 0.00 H_2O. If water is added to the mixture until its mole fraction is 0.8 (0.10 KNO_3, 0.08 $NaNO_3$, 0.02 KCl, 0.80 H_2O) points P and P′ are necessary to describe it. If the mole fraction of water is then halved (0.30 KNO_3, 0.24 $NaNO_3$, 0.06 KCl, 0.40 H_2O) points P and P″ will describe the solution. It is apparent that the distance PP″ is half the distance PP′. Henceforth, points in the Jaenecke diagram will be called base points, and those in the orthogonal diagram called projected points. They will always be designated by unprimed and primed letters, respectively.

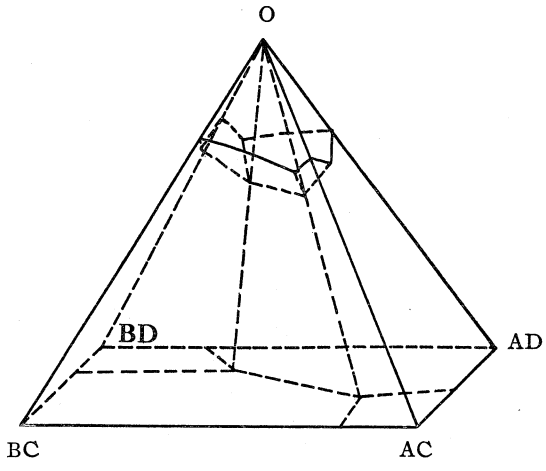

Fig. 2.—Three-dimensional Schreinemakers diagram showing Jaenecke projection on its base.

It is apparent that a solution is not uniquely defined if its base point lies at the center position O. The occurrence of a solution at this position, however, in general simplifies the solution of phase change problems by other methods. The properties of a system in this condition will be discussed later.

Solution of Phase Change Problems

When one determines in what planes a point pair might move through a pyramidal Schreinemakers diagram, the most apparent restriction is that they be planes containing both the base point and the projected point. Therefore, they are planes through the line connecting the base point to the water apex. Considering the point pair P and P′ in Fig. 3, since the position of the base point is in the potassium nitrate section, we know that if any solid phase crystallizes out it will be potassium nitrate. The plane of operation of this phase separation must, therefore, include the base corner point KNO_3. The projection of this plane, determined by points KNO_3, O, and P, is shown in Fig. 3, where it is drawn completely through the figure to point R, its intersection with the base line connecting the $NaNO_3$ and NaCl corners. Then R′, the projection of point R in the orthogonal diagram, is readily determined by the intersection of lines OR and $(NaNO_3')B'$. Similarly, Q′, the intersection of the plane with the equilibrium line F′A′, is determined by the intersection of F′A′ with the line OQ, where Q is the intersection of the base lines FA and $(KNO_3)R$.

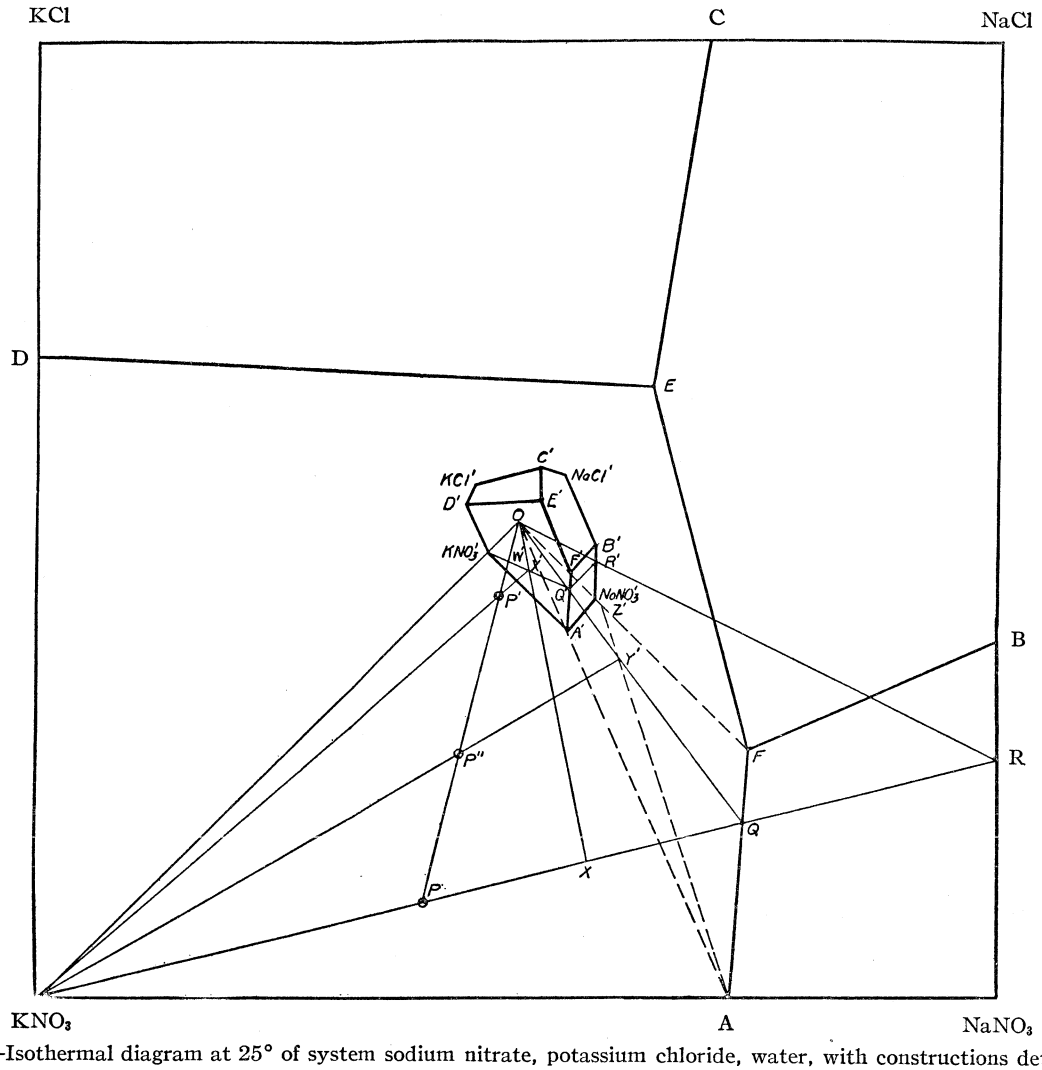

Fig. 3.—Isothermal diagram at 25° of system sodium nitrate, potassium chloride, water, with constructions determining precipitation from supersaturated solutions PP′ and PP″.

The lines $(KNO_3')Q'$ and $Q'R'$ then are the vertical projections of the intersection of plane $(KNO_3)RO$ with the equilibrium surfaces of the phase diagram. The intersection of line OP with line $(KNO_3')Q'$ then is the projection of the point at which OP pierces the equilibrium surface $(KNO_3')A'F'E'D'$. If the projected point along OP is closer to the origin O than this intersection, W′, the mixture represented is an unsaturated solution of salt mixture P; if the projected point is at W′, the solution is saturated with these salts; and if the projected point is below W′, as is P′, solid potassium nitrate will crystallize out.

Since all points along the base line $(KNO_3)R$ express a constant ratio of NaCl to $NaNO_3$, all points in the $(KNO_3)RO$ plane obviously must do likewise. (It has already been shown that a line in this plane originating at the water apex O represents mixtures of constant salt ratios differing only in their water contents.) Similarly, a line in this plane originating at base point KNO_3 fixes a constant ratio of water to mixture R, and motion along such a line correctly describes the addition or removal of pure potassium nitrate to the system. As one crystallizes potassium nitrate from the supersaturated solution of pair PP′, the projected point P′ moves along the line $(KNO_3)P'$ until it reaches the equilibrium surface at X′, the intersection of the operating line with $(KNO_3')Q'$. The base point will at the same time move along $(KNO_3)P$ until it reaches X, the point of intersection with a straight line through O and X′. Evaporation of water from the equilibrium mixture XX′ would move the projected point along the line segment X′Q′ while the base point would move to corresponding positions along XQ.

When potassium nitrate is separated from the supersaturated solution PP″, the base point reaches an equilibrium line on the Jaenecke diagram, *i. e.*, point Q on line AF, before the corresponding projected point Y′ has reached an equilibrium position on the orthogonal diagram. This

indicates that solution PP″ was supersaturated with respect to more than one salt. The crystallization path that such a solution would follow may be decided unambiguously by asking what would occur if water were added to it until the solution was in equilibrium, then this extra water evaporated away, the solution being allowed to follow an equilibrium course. In this particular problem this path would first involve the conversion of PP″ to PW′. Evaporation of water from PW′ would result in precipitation of potassium nitrate until composition QQ′ was reached. At this point a salt mixture of composition A would start crystallizing out, and the saturated solution proceed down path Q′F′. One may theoretically stop this process at any point, however, and remove the remaining added water in a non-equilibrium manner, leaving a supersaturated solution. If one did this upon reaching QQ′, the resulting supersaturated solution would be QY′, exactly the same point at which one arrives by the direct path P″Y′. Since the system is conservative, the simple direct path is as good for calculation as the one detouring over the equilibrium surface.

Similarly, therefore, one may assume upon reaching QY′ the supersaturated solution will separate only salt of composition A. The diagram points may be assumed then to move in the new plane OFA, which is determined by line OQ and base point A (see Fig. 3). The orthogonal projection of the intersection of this plane with the equilibrium surface is obviously A′F′. Again in this case the base point, moving inward along the extended line AQ, reaches a new position of equilibrium, the quintuple base point F, before its projected point, moving inward along line AY′, intersects the equilibrium surface. It is, of course, completely fortuitous that FF′ lies along the diagonal KCl–$NaNO_3$.

The new supersaturated solution FZ′ will crystallize out the triple component mixture of composition F. The position of the base point, F, may be assumed not to change during this process, while the projected point will move inward along line OF until it reaches the equilibrium position F′. Following the usual proportional balance the ratio of number of moles of solid crystallized out to number of moles of saturated solution remaining is given by the ratio of F′Z′ to Z′F.

An interesting special problem arises when the precipitating salt is hydrated. One would have then separate projected and base points representing the solid salt. In the problem of describing the separation of this salt from its supersaturated solution, the course of the projected point of the solution would be along the straight line originally connecting it to the projected point of the solid, while the course of the base point would be along the straight line connecting it to the base point of the solid.

In the solution to the problems presented above, two simplifying assumptions were made. One of them was that the equilibrium surfaces were planes and their intersections straight lines. This assumption may be easily avoided and in no way affects the fundamentals of the method presented above. For example, in Fig. 3 one might have plotted a number of experimental points of the surface A′(KNO_3′)D′E′F′ and drawn contour lines between these experimental points both in the orthogonal and Jaenecke projections. Then the intersections of line (KNO_3)Q with the contour lines on the base would determine the intersections of plane (KNO_3)OQ with the corresponding orthogonally projected contour lines. Hence the path of crystallization, (KNO_3′)Q′, would have been determined in its true curved form.

The second simplifying assumption was that the proportion of two salts precipitating along a line of two-fold saturation is constant. This is the same as assuming that, for example, Jaenecke line AF in Fig. 3 is straight. This assumption is fundamental to the procedure of solutions described, for without it one would have to move by trial and error in the curved surface OAF. The assumption is a very good approximation, however, since the degree to which line AF would vary from straightness would be no greater than the degree to which the activity coefficients of potassium nitrate and sodium nitrate would change at different rates along the path A′F′.

Limitations of the Method.—It is apparent that occasionally one would operate in a plane vertically intersecting a three dimensional Schreinemakers diagram. The projection of such a plane in the two dimensional diagram would be a straight line, on which it would be impossible to perform many of the geometric constructions described above. However, because all motion in this case is restricted to a straight line in the diagram, it is usually apparent where at least one of the composition points will come to rest, as it was in the case of motion along the line OF in Fig. 3. Phase separations from the special type of solution described above for which the base point lies directly beneath the center origin will always take place in such vertically placed planes. Therefore, if the original concentration is known, it is usually easy to calculate changes from it with the help of the diagram even though it is impossible to plot the original concentration in an unambiguous manner.

If the phase system is one of very insoluble salts, the orthogonal projection will be inconveniently close in toward the origin, and an extremely large diagram might be required for exact construction. This difficulty can be avoided by enlarging the center portion of the diagram containing all of the orthogonal projection into a second diagram. The intersection of lines in the normal diagram with the periphery of the center section in it chosen for enlargement, together with the equilibrium points concerned, give sufficient information for transfer-

ing lines from the normal to the enlarged partial diagram and vice versa.

Application to other Four-Component Systems.—The methods described above can be applied to systems composed of water and three salts with a common ion if the following method of plotting is followed. The figure appears in an equilateral triangular graph with vertices A, B and C and point of intersection of perpendiculars from these vertices to their opposite bases, O. Then a point is determined by plotting the mole fractions of salts A and B as coördinates along the axes OA and OB originating at the center O. The point is then moved parallel to the third axis OC, a distance equal to mole fraction of salt C.

Acknowledgment.—The author wishes to thank Professor J. J. Beaver for his constructive criticism of this paper.

Summary

A two-dimensional, quaternary phase diagram is presented in which compositions are described in all four constituents and in which graphical solutions to general phase separation problems may be made. The diagram is constructed by superimposing an orthogonal projection of a three dimensional Schreinemakers diagram upon a Jaenecke projection in such a way that the method of wet residues may be applied.

NEW YORK, N. Y. RECEIVED NOVEMBER 7, 1947

[CONTRIBUTION FROM THE METCALF RESEARCH LABORATORY, BROWN UNIVERSITY]

Properties of Electrolytic Solutions. XLIV. Conductance of Some Long Chain Salts in Ethylene Chloride, Pyridine and Nitrobenzene at 25°[1]

BY HAROLD L. PICKERING[2] AND CHARLES A. KRAUS

I. Introduction

Weaver[3] has measured the conductance of several long chain salts in ethylene chloride and nitrobenzene. In these solvents the salts behaved like normal electrolytes. It seemed worth while, therefore, to measure the conductance of a larger number of long chain salts. It was of particular interest to determine the limiting conductance of long chain ions and to find how the conductance of such ions depends on the number of carbon atoms that they contain, on the one hand, and their arrangement about the central nitrogen atom, on the other.

To this end, the conductance of a number of long chain salts was measured in ethylene chloride, pyridine and nitrobenzene. In addition, the conductance of several ordinary quaternary ammonium salts was determined in order to fill gaps in the list of ion conductances.

II. Experimental

1. **Salts.**—These were prepared according to conventional methods. It is important to use only well purified starting materials. Nitrates and picrates were prepared by metathesis of iodides with silver salts in methanol or ethanol. The following salts were prepared: (1) *n*-octadecylpyridonium nitrate (m. p., 79–80°), (2) di-*n*-octadecyldimethylammonium picrate (m. p., 75.5–76.2°), (3) di-*n*-octadecyldi-*n*-butylammonium picrate (m. p. 50.5–51.5°), (4) *n*-octadecyltri-*n*-butylammonium nitrate (m. p., 90.5–91.5°), (5) *n*-octadecyltri-*n*-butylammonium picrate (m. p., 42–43°), (6) *n*-octadecyltrimethylammonium iodide (m. p., 237–238.5°), (7) *n*-octadecyltrimethylammonium picrate (m. p., 134–135°), (8) *n*-propylpyridonium picrate (61–62°), (9) tetra-*n*-butylammonium picrate (m. p., 73.5–74.5°), (10) tetra-*n*-propylammonium picrate (m. p., 115–116°). Earlier preparations of tetra-*n*-butylammonium triphenylborofluoride (11) and formate (12) were measured after several recrystallizations.

The salts were recrystallized as follows: (1) hexane plus few drops of ethanol, (2) hot absolute ethanol, (3), (5) methanol plus few drops of ethanol, (4) dioxane–water followed by hexane–ethanol, (6), (7) absolute ethanol, (8) 99% ethanol, (9), (10), (12) 95% ethanol, (11) ethanol plus 10% hexane.

2. **Solvents.**—Solvents were prepared as described in earlier papers.[4] Solvent resistances were measured with a special parallel arm bridge permitting of precise measurements up to 10^7 ohms.

3. **Apparatus and Procedure.**—These were the same as those described in earlier papers of this series.[4]

III. Results

In Table I are given equivalent conductances at different concentrations (expressed in moles per liter of solution) for several salts in ethylene chloride. Similar data are given for solutions in pyridine in Table II and for solutions in nitrobenzene in Table III. All measurements were carried out at 25 ± 0.01°. In computations, the following values were employed for physical constants.

	Density	Viscosity	Diel. const.
Ethylene chloride	1.2455	0.00787	10.23
Pyridine	0.97792	.008824	12.01
Nitrobenzene	1.1986	.01811	34.5

IV. Discussion

1. **Ethylene Chloride and Pyridine.**—The data of Table I for ethylene chloride and those of Table III, for pyridine, have been analyzed

(1) This paper is based on a portion of a thesis presented by Harold L. Pickering in partial fulfilment o f the requirements for the Degree of Doctor of Philosophy in the Graduate School of Brown University, August, 1947.

(2) National Research Council Fellow, Brown University, 1946–1947. Present address: Research Laboratory, Stanolind Oil and Gas Company, Tulsa, Oklahoma.

(3) Weaver and Kraus, THIS JOURNAL, **70**, 1707 (1948).

(4) (a) Mead, Fuoss and Kraus, *Trans. Faraday Soc.*, **33**, 594 (1936), ethylene chloride; (b) Witschonke and Kraus, THIS JOURNAL, **65**, 2472 (1947), nitrobenzene; (c) Carignan and Kraus, *ibid.*, **71**, 2983 (1949), pyridine.

TABLE I

CONDUCTANCE OF SOME QUATERNARY AMMONIUM SALTS IN ETHYLENE CHLORIDE

$C \times 10^4$	Λ	$C \times 10^4$	Λ
A. N-Octadecylpyridonium nitrate		B. Di-*n*-octadecyldimethylammonium picrate	
29.25	6.728	12.79	12.92
3.359	15.53	3.059	20.75
1.804	19.70	2.034	23.50
0.7853	26.49	1.250	26.95
.4071	32.70	0.8192	30.01
.2027	39.78	.4463	34.25
.1070	45.88	.2192	38.60
		.1227	41.40
C. Di-*n*-octadecyldi-*n*-butylammonium picrate		D. N-Octadecyltri-*n*-butylammonium nitrate	
14.64	19.35	22.96	16.83
3.218	28.23	3.649	28.95
2.109	30.87	2.440	32.24
1.488	32.99	1.529	36.17
0.9060	35.78	0.7387	42.05
.5696	38.08	.4271	46.03
.2881	40.79	.2328	49.65
.1436	42.75	.09721	53.42
E. N-Octadecyltrimethylammonium formate		F. N-Octadecyltrimethylammonium iodide	
22.99	3.323	13.915	8.893
4.044	6.962	3.871	14.54
2.271	8.930	2.436	17.19
1.669	10.20	1.643	19.73
1.165	11.89	1.118	22.45
0.7884	14.00	0.8038	24.91
.4940	16.93	.4420	29.88
.2293	22.80	.1769	37.91
.1655	25.62		
G. N-Octadecyltrimethylammonium picrate		H. N-Propylpyridonium picrate	
17.34	10.96	37.63	11.13
3.840	18.70	4.471	23.37
2.193	22.59	2.805	27.42
1.597	25.00	1.806	31.67
1.200	27.29	1.017	37.74
0.8274	30.37	0.6386	42.88
.5738	34.15	.3482	49.51
		.2101	54.63
		.1350	58.49

TABLE II

CONDUCTANCE OF SOME QUATERNARY AMMONIUM SALTS IN NITROBENZENE

$C \times 10^4$	Λ	$C \times 10^4$	Λ
A. N-Octadecyltrimethylammonium picrate		B. N-Octadecyltri-*n*-butylammonium picrate	
23.59	22.80	18.43	21.83
10.42	24.05	9.397	22.59
4.459	24.92	4.472	23.23
2.402	25.36	2.264	23.63
1.669	25.57	1.156	23.91
0.8075	25.87	0.5718	24.11
.3536	26.09	.3041	24.30
.2060	26.16	.1411	24.43
C. Di-*n*-octadecyldimethylammonium picrate		D. Di-*n*-octadecyldi-*n*-butylammonium picrate	
20.78	20.65	30.54	19.85
9.645	21.66	10.24	21.20
4.909	22.29	5.767	21.70
2.355	22.78	3.710	22.00
1.194	23.07	2.309	22.26
0.6244	23.30	1.452	22.46
.3219	23.45	0.9777	22.60
.1530	23.56	.6178	22.74
		.3129	22.84
		.1601	22.94
E. Tetra-*n*-butylammonium triphenylborofluoride		F. N-Octadecylpyridonium nitrate	
21.91	20.79	53.21	23.04
10.59	21.70	26.10	26.07
5.795	22.23	12.79	28.40
2.848	22.71	6.618	29.97
1.291	23.07	3.255	31.16
0.7723	23.24	2.119	31.64
.3428	23.42	1.021	32.31
.1518	23.63	0.5094	32.73
		.2037	33.10

TABLE III

CONDUCTANCE OF SOME QUATERNARY AMMONIUM SALTS IN PYRIDINE

$C \times 10^4$	Λ	$C \times 10^4$	Λ
A. N-Octadecyltri-*n*-butylammonium picrate		B. Tetra-*n*-amylammonium picrate	
4.474	38.18	4.243	41.78
2.278	41.66	2.355	45.07
1.444	43.62	1.232	48.09
0.8643	45.46	0.6791	50.27
.4114	47.47	.3348	52.08
.1768	48.92	.2150	52.97
C. Tetra-*n*-propylammonium picrate		D. Tetraethylammonium picrate[a]	
2.913	49.76	5.6119	53.66
1.884	52.21	2.6677	59.17
1.104	54.72	1.6327	62.34
0.6816	56.55	0.77968	66.09
.5040	57.48	0.43674	68.27
.1912	59.56	0.21450	70.35

[a] Measurements by Dr. C. J. Carignan.

by the method of Fuoss[5] and values of the limiting conductance, Λ_0, and the dissociation constant, K, have been obtained. These values are collected in Table IV, where limiting conductances are given in column 2, cation conductances as determined by the method of Fowler[5] in column 3 and dissociation constants in column 4. In Figs. 1 and 2 are shown Fuoss plots for several salts in ethylene chloride and pyridine, respectively.

As may be seen from the figures, the salts measured in ethylene chloride and pyridine conform to the Fuoss relation within the limit of experimental error, and successive series are in good agreement.

(5) (a) Burgess and Kraus, THIS JOURNAL, **70**, 706 (1948); (b) Fowler and Kraus, *ibid.*, **62**, 2237 (1940).

TABLE IV

CONSTANTS FOR SALTS IN ETHYLENE CHLORIDE AND PYRIDINE

Salt	Λ_0	Λ_0^+	$K \times 10^4$
A. Ethylene Chloride			
$OctdMe_3NPi$	54.91	23.7	0.49
$Octd_2Me_2NPi$	47.73	16.5	0.78
$OctdBu_3NNO_3$	57.90	17.8	1.12
$Octd_2Bu_2NPi$	46.13	14.9	2.61
$OctdPydNO_3$	62.77	22.7	0.21
PrPydPi	71.84	40.6	.49
$OctdMe_3NI$	53.6	29.9[a]	.28
$OctdMe_3OCHO$	60.24	36.5[a]	.049
B. Pyridine			
$OctdBu_3NPi$	50.79	17.1	12.0
$Octd_2Bu_2NPi$[a]	47.03	13.3	10.1
Am_4NPi	55.28	21.6	11.3
Pr_4NPi	62.11	28.4	11.2
Et_4NPi	73.31	39.6	10.4

[a] Iodide and formate ions

[a] Privately communicated by Mr. E. J. Bair, of This Laboratory.

In ethylene chloride, the iodide and formate ions have rather low conductances; this is particularly true of the iodide. It is a striking fact that, in this solvent, the conductances of the chloride, bromide and iodide ions differ widely, being, respectively, 39.1, 33.8 and 29.9. The conductance of the iodide is 23% less than that of the chloride ion.

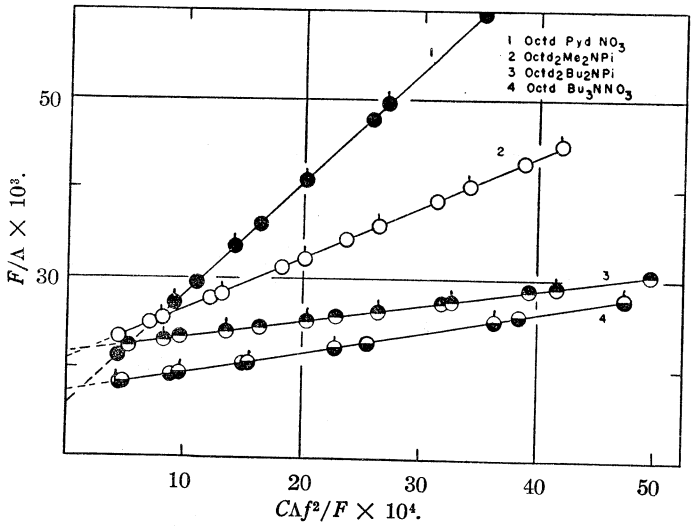

Fig. 1.—Fuoss plots for long chain salts in ethylene chloride.

The dissociation constant for octadecylpyridonium nitrate is about one half that of propylpyridonium picrate. The same is true of octadecyltributylammonium nitrate as compared with dioctadecyldi-*n*-butylammonium picrate. Octadecyltrimethylammonium formate is an especially weak salt, its constant being one-fifth that of the iodide.

The dissociation constants of the homologous series of quaternary ammonium picrates in ethylene chloride increase regularly with increasing numbers of carbon atoms in the substituent groups as Tucker has shown.[6] In this connection, it is of interest to note that the constant for dioctadecyldibutylammonium picrate is 2.61×10^{-4} as against 2.38×10^{-4} for tetra-*n*-amylammonium picrate. The constant for tetraethylammonium picrate is 1.59×10^{-4}.

In contrast to the regular change of the dissociation constant of the quaternary ammonium picrates in ethylene chloride, in pyridine the constant changes but little and, seemingly, irregularly. As may be seen from Table II, b, the constant for tetraethylammonium picrate is 10.4×10^{-4} while that for tetrabutylammonium picrate is 12.8×10^{-4}. But the constant for tetra-*n*-amylammonium picrate is only 11.3×10^{-4}, and that for dioctadecyldibutylammonium picrate is 12.0×10^{-4}. It is of interest to note that while in ethylene chloride the constant for tetra-amylammonium picrate is 7.4 times that of the corresponding tetramethylammonium salt, in pyridine the constants for the same two salts have a ratio of only 1.7. It is evident that the effect of chain length on the interaction of quaternary ions with the picrate ion in pyridine differs greatly from that in ethylene chloride. Whether the inversions found for the constants in pyridine are real or a result of experimental error remains uncertain as yet. Luder's conductance values for tetrabutylammonium picrate have subsequently been twice checked and confirmed independently. The symmetrical quaternary ammonium salts used in this investigation were the same as those used earlier by Tucker[1] except for their recrystallization.

2. Nitrobenzene.—Strong salts (*i. e.*, salts of large ions) are so highly dissociated in nitrobenzene that their dissociation constants cannot be evaluated. Values of Λ_0 may be determined by extrapolation of Λ–$\sqrt{C}$ plots. In Table V are given values of Λ_0 for the different salts measured; for the stronger salts, Λ_0 was obtained by extrapolation of the Λ–$\sqrt{C}$ plots. The weak salts were analyzed by the Fuoss method and values of the Λ_0 so obtained are given in column 2 and values of the dissociation constant, K, in the last column. Cation conductances are given in column 3. These are based on the conductance of the tetrabutylammonium triphenylborofluoride, it being assumed in accordance with Fowler[5b] that the two ions of this salt have the same conductance. Percentage deviations for the theoretical Onsager slope, Δ, are given in column 4.

Taylor and Kraus[7] measured the conductance of

(6) Tucker and Kraus, THIS JOURNAL, **69**, 454 (1947).
(7) Taylor and Kraus, *ibid.*, **69**, 1731 (1947).

TABLE V

CONSTANTS OF SOME QUATERNARY AMMONIUM SALTS IN NITROBENZENE

Salt	Λ_0	Λ_0^+	Δ%	$K \times 10^4$
Bu_4NPh_3BF	23.78	11.9	0.6	...
$Octd_2Bu_2NPi$	23.23	7.2	3.2	...
$OctdBu_3NPi$	24.64	8.6	4.1	...
$Octd_2Me_2NPi$	23.82	7.8	10.0	860
$OctdMe_3NPi$	26.50	10.5	19.4	430
$OctdPydNO_3$	33.39	10.8	146.	79

tetrabutylammonium triphenylborofluoride and found the slope of the Λ–$\sqrt{C}$ plot to be 4% less than the theoretical. It seemed worth while to measure this salt using another preparation.[8] The results of two series of measurements are shown graphically in Fig. 3. The slope of the plot is 0.6% below the theoretical. In other words, this salt conforms to the theoretical slope within the experimental error.

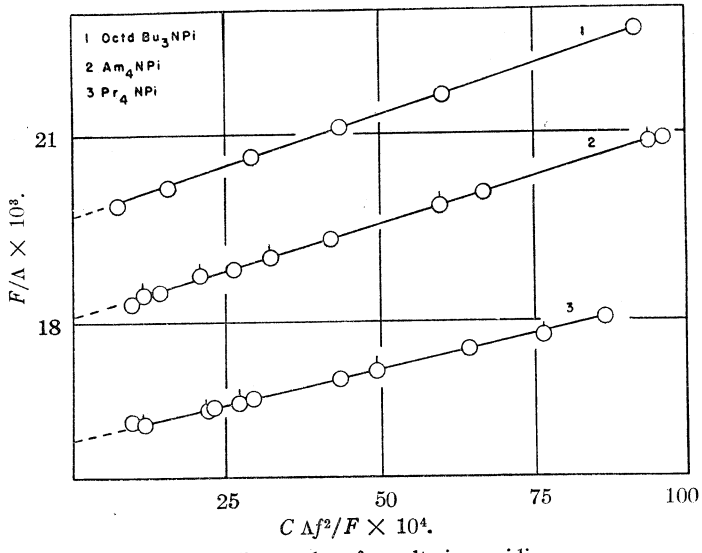

Fig. 2.—Fuoss plots for salts in pyridine.

The picrate ion in the ion pairs is smaller than the triphenylborofluoride ion. Dioctadecyldibutylammonium and octadecyltributylammonium picrate show slopes 3.2 and 4.1% greater than the theoretical. The picrates of the two methyl derivatives show markedly greater slopes. The slope of octadecylpyridonium nitrate is much greater than the theoretical. It may be pointed out that in ethylene chloride the dissociation constant of dioctadecyldimethylammonium picrate is approximately four times that of octadecylpyridonium nitrate; in nitrobenzene, the ratio of constants for the same two salts is approximately ten.

(8) Reynolds and Kraus, THIS JOURNAL, 70, 1704 (1948).

3. Conductance of Long Chain Cations.—Thompson[9] has suggested that in comparing the conductance of the symmetrical quaternary ammonium ions as a function of the number of carbon atoms in the substituent alkyl groups, it is better to compare the reciprocal of ion conductances rather than the ion conductances themselves. In other words, it is best to compare equivalent ion resistances. He has shown that with the symmetrical quaternary ammonium ions in ethylene chloride, the reciprocal ion conductances vary approximately as a linear function of the number of carbon atoms from tetraethyl- to tetra-amylammonium, inclusive.

In comparing ion conductances as a function of carbon atom content in different solvents it is helpful to take the viscosities of the solvents into account. Accordingly, in Fig. 4, we have plotted the reciprocals of the product of ion conductance and viscosity for a number of quaternary ammonium ions as a function of the number of carbon atoms that they contain, for ethylene chloride, nitrobenzene and pyridine. To avoid confusion in the plots, the origin for each succeeding solvent has been displaced 8 carbon atoms to the right as indicated in the figure.

As may be seen from Fig. 4, the tetramethylammonium ion meets with much greater resistance in proportion to the number of carbon atoms that it contains than do the larger ions. The resistance of this ion, when adjusted for the viscosity of the solvent, is very nearly the same in ethylene chloride and nitrobenzene but it is much smaller in pyridine. The resistance with which an ion meets in its motion through a solvent medium is made up of two parts: first, a normal Stokes

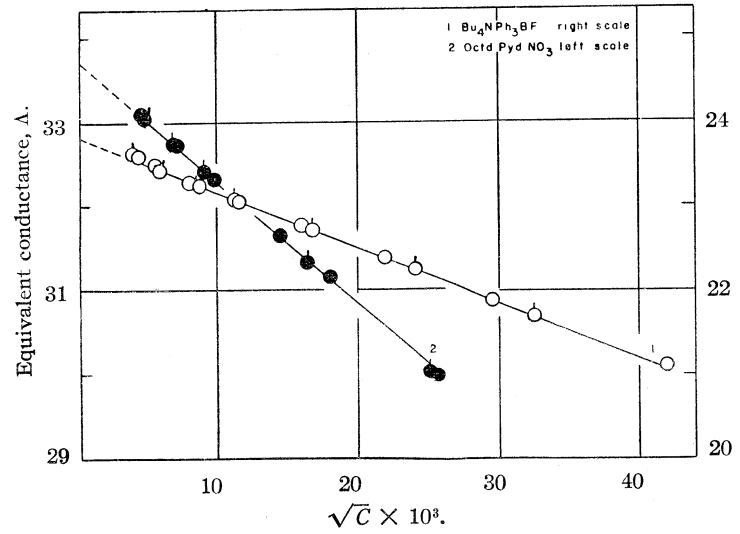

Fig. 3.—Λ-$\sqrt{C}$ plots for salts in nitrobenzene.

(9) W. E. Thompson, Thesis, Brown University, May, 1941.

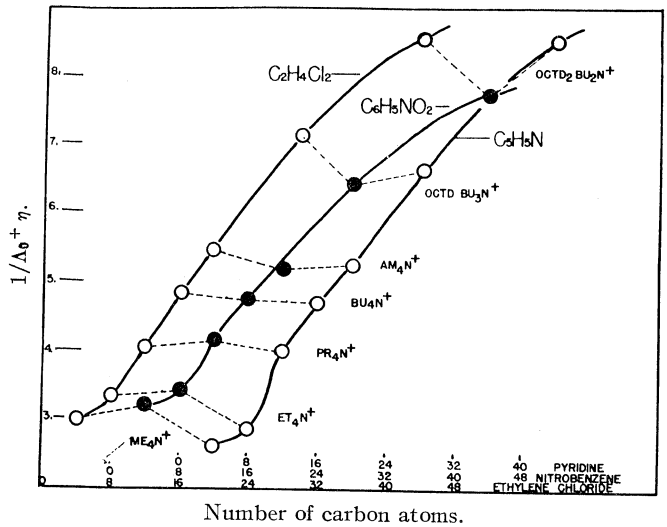

Fig. 4.—Plots of reciprocals of ion conductance–viscosity products for cations in ethylene chloride, nitrobenzene and pyridine as function of number of carbon atoms. (Note displacement of horizontal scales.)

frictional resistance and, second, a resistance due to the interaction of the charge on the ion with the dipole molecules of the solvent. The latter will depend on the size and shape of the ion and of the solvent molecules and the strength of the dipoles. It is to such factors that the tetramethylammonium ion owes its higher resistance in ethylene chloride and nitrobenzene as compared to that in pyridine.

In ethylene chloride, ion resistance varies as a linear function of the number of carbon atoms from the tetraethyl- to the tetra-amylammonium ion, inclusive. In other words, the introduction of a carbon atom causes the same increase in resistance, irrespective of the number of atoms already in the substituent groups. Even the octadecyltributylammonium ion deviates but little from the linear relation. With the dioctadecyldibutylammonium ion, the deviation is greater but not large.

For the smaller ions, the resistance curve in nitrobenzene parallels that in ethylene chloride. However, beginning with the tetrabutylammonium ion, the curve deviates from linearity and for the largest ion the deviation is very large. In contrast, the curve in pyridine deviates widely from that in ethylene chloride for smaller ions but parallels it for large ions. In going from the tetraethyl- to the tetrapropylammonium ion, the resistance change in pyridine is large in comparison with that in the other two solvents. The change in going from the tetramethyl- to the tetraethylammonium ion is exceptionally small. It would seem that the difference in ion resistance of smaller ions as between pyridine and the other two solvents must be ascribed to specific interaction of ions and solvent molecules. The difference in ion resistance for large ions as between nitrobenzene and the other two solvents may be ascribed to the compacting of the carbon atoms in the chains in the case of nitrobenzene. Indeed, the fact that the resistance of ions in ethylene chloride is proportional to the number of carbon atoms would seem to indicate that in this solvent the chains are extended. The same is true in pyridine but here we have differences in the case of smaller ions that must be attributed to other factors. In nitrobenzene, possibly due to weaker van der Waals interaction, the chains may no longer be extended and ion resistances would, accordingly, be smaller.

According to Walden's rule, the product of ion conductance and viscosity is a constant for large ions in solvents of different viscosities. From Fig. 4, it is evident that Walden's rule holds only as an approximation. Thus, for the seven quaternary ammonium ions, from tetramethyl- to dioctadecyldibutylammonium, inclusive, the maximum percentage differences for the $\Lambda_0\eta$ product in the three solvents is 19 (Me_4N^+), 16, 4, 3, 5, 10 and 9% ($Octd_2Bu_2N^+$). The product for the tetrabutyl- and the tetraamylammonium ions has the same value in pyridine and nitrobenzene while, for the dioctadecyldibutylammonium ion, it has the same value in ethylene chloride and pyridine. If Walden's rule is to be employed for the purpose of evaluating ion conductances in solvents where transport numbers cannot be determined experimentally, it would seem to be preferable to employ the tetrabutylammonium ion the $\Lambda_0{}^+\eta$ product of which is more nearly constant than is that of other ions. The tetraethylammonium ion yields unreliable results. The same can be said of the picrate ion as one of us has pointed out elsewhere.[10]

V. Summary

1. The conductances of seven long chain salts have been measured in ethylene chloride; five have been measured in nitrobenzene and one has been measured in pyridine. Cation conductances have been evaluated from the results of these measurements.

2. Several other salts have been measured in one or more of these solvents. Ion conductances have been derived from these measurements.

3. The conductance of tetrabutylammonium triphenylborofluoride in nitrobenzene has been remeasured. The slope of the Λ_0–$\sqrt{C}$ plot corresponds to the theoretical value within the limit of experimental error.

4. Plots are shown for the reciprocals of ion conductance viscosity products for the five symmetrical quaternary ammonium ions from tetramethyl- to tetraamyl, inclusive, and for octadecyltributyl- and dioctadecyldibutylammonium ions in ethylene chloride, nitrobenzene and pyridine.

(10) Kraus, *Ann. N. Y. Acad. of Sci.*, **51**, 789 (1949).

In ethylene chloride the equivalent resistance is a linear function of the number of carbon atoms from the tetraethyl- to the tetra-amylammonium ions, inclusive. Thereafter, resistance deviates slightly toward lower resistances as the number of carbon atoms increases. The resistance curve in nitrobenzene parallels that in ethylene chloride for smaller ions but deviates widely for large ions. The resistance curve for pyridine parallels that for ethylene chloride for large ions but deviates widely for small ions.

PROVIDENCE, R. I. RECEIVED APRIL 6, 1949

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Amino Acid Composition of α-Casein and β-Casein[2]

BY WILLIAM G. GORDON, WILLIAM F. SEMMETT, ROBERT S. CABLE AND MYRON MORRIS

The heterogeneity of cow's milk casein has been established by solubility studies and electrophoretic analysis. Warner[3] reviewed earlier work on this problem and described the chemical separation of casein into two mutually distinct components,[4] α-casein and β-casein, which occur in unfractionated casein in the approximate ratio of 4:1. The fractions isolated by Warner, although not electrophoretically homogeneous over the entire *p*H range, were purified, so that neither fraction contained any of the other. Comparison of the nitrogen and phosphorus contents of the isolated fractions with those of whole casein showed some significant differences; the values for β-casein, the minor component, differed from the values for whole casein more markedly than did those for α-casein.

The present paper deals with the amino acid analysis of α-casein and β-casein. Whole casein was also analyzed by the same methods for purposes of comparison. It has been possible to account for essentially all the nitrogen of each protein in terms of known amino acid residues and amide nitrogen.

Experimental

Proteins Used.—The samples of whole casein, α-casein and β-casein were prepared by Dr. Warner according to his published directions.[3] Electrophoretic analysis showed that each fraction was free of the other. In preliminary experiments, two preparations of each protein were analyzed for total nitrogen, phosphorus, lysine, tryptophan, tyrosine and amino nitrogen. The results indicated that there was no significant difference in composition between the two preparations. Therefore, in all subsequent experiments no distinction was made between different preparations of the same protein.

Methods of Analysis.—All analyses were carried out on air-dried protein samples; moisture determinations were made as suggested by Chibnall, *et al.*[5] True ash was determined according to Warner,[3] total nitrogen by the Kjeldahl method as used by Miller and Houghton[6] and phosphorus by the method of Fiske and SubbaRow[7] after digestion with sulfuric and nitric acids. Amino nitrogen values were obtained by the Van Slyke method as modified by Doherty and Ogg,[8] and amide nitrogen was estimated in Conway micro-diffusion cells according to the procedure suggested by Warner and Cannan.[9] In the latter procedure, a series of Conway vessels, each containing 10 mg. protein in 1 ml. 1.5 *N* sodium hydroxide in the outer compartment and 1.5 ml. 2% boric acid in the inner chamber, was set up at 35°. At intervals which ranged from thirty-five to sixty-five hours, vessels were removed from the oven, and the distilled ammonia was titrated with 0.01 *N* hydrochloric acid. The value at each reaction time was determined in triplicate. A progressive increase in ammonia liberated with time was observed, so that a linear extrapolation of the values to zero time was made to obtain the amide nitrogen figures.

Unless otherwise noted, hydrolysis of the proteins was carried out in 6 *N* hydrochloric acid in an oil-bath at 120° for twenty hours.

Lysine was determined by means of a specific decarboxylase both on total hydrolyzates and on catholytes obtained by ionophoresis of aliquots of the same hydrolyzates. Hanke's adaptation[10] of Gale's method[11] to the Van Slyke–Neill manometric apparatus was used. Ionophoresis was employed for the primary purpose of securing catholytes suitable for photometric determinations of arginine and histidine. A three-compartment cell patterned after that of Albanese[12] was constructed, and the general procedure of Gordon, Martin and Synge[13] was followed, with hydrolyzates prepared from 0.5 g. of protein. Arginine and histidine were then determined by Macpherson's modifications[14] of the Sakaguchi–Weber and Pauly reactions on the catholytes obtained after repeated (4 times) ionophoresis.[15] The values obtained for lysine in these catholytes were consistently lower (6 to 9%) than those found in the original hydrolyzates. On the

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Preliminary reports of this work have been presented at meetings of the American Society of Biological Chemists, by title at the Chicago Meeting [*Federation Proc.*, **6**, 255 (1947)]; and orally at the Detroit Meeting [*ibid.*, **8**, 202 (1949)].

(3) Warner, THIS JOURNAL, **66**, 1725 (1944).

(4) A third component, γ-casein, may be present to the extent of a few per cent.; this point is discussed by McMeekin and Polis in "Advances in Protein Chemistry," Vol. V, Academic Press, Inc., New York, in press.

(5) Chibnall, Rees and Williams, *Biochem. J.*, **37**, 354 (1943).

(6) Miller and Houghton, *J. Biol. Chem.*, **159**, 373 (1945).

(7) Fiske and SubbaRow, *ibid.*, **66**, 375 (1925).

(8) Doherty and Ogg, *Ind. Eng. Chem., Anal. Ed.*, **15**, 751 (1943).

(9) Warner and Cannan, *J. Biol. Chem.*, **142**, 725 (1942).

(10) We are indebted to Prof. M. E. Hanke for details of his procedure [*Federation Proc.*, **5**, 137 (1946)], for a preparation of the enzyme and for a culture of *Bacterium cadaveris*.

(11) Gale, *Biochem. J.*, **39**, 46 (1945).

(12) Albanese, *J. Biol. Chem.*, **134**, 467 (1940).

(13) Gordon, Martin and Synge, *Biochem. J.*, **35**, 1369 (1941).

(14) Macpherson, *ibid.*, **36**, 59 (1942).

(15) After our analyses for the basic amino acids had been completed, the comprehensive paper on this scheme of analysis by Macpherson appeared.[51] Our experience confirms (a) the need for repeated ionophoresis of the catholyte to effect complete purification of the basic amino acid fraction, and, (b) the increased precision of the colorimetric methods when standards are used instead of calibration curves. In our hands, however, determination of lysine by difference on the basis of nitrogen analyses on the catholyte was not entirely trustworthy.

TABLE I

MICROBIOLOGICAL ASSAY CONDITIONS

Amino acid	Organism[a]	Basal medium	Standard amino acid[b]	Range[c] of standard curve used	Hours of incubation at 37°
Glycine	*L. mesenteroides* P-60	Shankman[29]		25–100[d]	48
Valine	*L. arabinosus* 17-5	Stokes[28]	DL	15–80	48–96
Leucine	*S. faecalis R*	Stokes[28,e]	L	15–80	40–48
Isoleucine	*S. faecalis R*	Stokes[28,e]	DL	10–70	40–48
Proline	*L. mesenteroides* P-60	Henderson[30]	L	25–50	120
Phenylalanine	*L. arabinosus* 17-5	Henderson[30]	DL	10–60	48
Aspartic acid	*L. mesenteroides* P-60	Henderson[30]	L	20–70	96
Glutamic acid	*L. arabinosus* 17-5	Stokes[28,f]	L	10–60	48

[a] Obtained from the American Type Culture Collection. [b] Special samples of L-leucine and DL-isoleucine were obtained from Merck and Company through the courtesy of Dr. E. E. Howe; stated purity of the L-leucine was at least 99% and of the DL-isoleucine at least 96%, as determined by solubility tests. Other standard amino acids were of the "Analytically or Chemically Pure Grade" of Amino Acid Manufactures, University of California, Los Angeles. [c] In micrograms of L-amino acid per tube containing a final volume of 10 ml. [d] Range shown does not include glycine added to basal medium to overcome induction period.[29] [e] Modified by the addition of 250 mg. sodium citrate per tube containing a final volume of 10 ml. in order to enhance growth and acid production.[31,32] [f] Modified by the substitution of L-asparagine for aspartic acid.[33]

assumption that mechanical losses involved in repeated ionophoresis accounted for this discrepancy, the lysine determinations on original hydrolyzates were accepted as more nearly correct, and a correction based on lysine recovery was applied to all arginine and histidine values.

Tyrosine and tryptophan were determined on alkaline stannite hydrolyzates according to the Brand and Kassell adaptation[16] of the Millon-Lugg procedure. The corrections recommended by Brand and Kassell were applied to the results. Also, tryptophan analyses were made on the unhydrolyzed proteins by the glyoxylic acid reaction as applied by Shaw and McFarlane.[17] The tryptophan values obtained by the two methods were in good agreement.

Cystine determinations were made, by Kassell and Brand's modification[18] of the phosphotungstic acid reaction, on hydrochloric acid and hydrochloric acid–formic acid hydrolyzates, and by Vassel's adaptation[19] of the Fleming reaction, on hydrochloric acid–formic acid hydrolyzates, with concordant results. The occurrence of cysteine in casein in unlikely.[20]

Methionine was determined both as volatile iodide and as homocysteine after hydrolysis with hydriodic acid according to the Kassell and Brand modification[21] of Baernstein's method. The correction factors of Kassell and Brand were applied.

Serine was determined by oxidation with periodate and distillation of formaldehyde by the technique of Boyd and Logan[22] and estimation of formaldehyde photometrically with chromotropic acid according to MacFadyen.[23] Threonine was estimated by periodate oxidation and diffusion of acetaldehyde in Conway vessels by the method of Winnick.[24] Correction factors for decomposition of serine and threonine during acid hydrolysis have been worked out by Rees[25] for mixtures of amino acids. We have assumed that the factors (100/89.5 for serine and 100/94.7 for threonine) were applicable to hydrolyzates of casein and its fractions, and the serine and threonine values have been so corrected. The corrected figures for serine may still be low, in view of the greater lability to acid hydrolysis of serine combined as phosphoserine in phosphoproteins, as compared with that of free serine. Thus, Nicolet, *et al.*, give 7.38% as the probable serine content of casein, compared with 5.5% found on direct acid hydrolysis.[26] A correction factor based on these figures would be 100/74.5.

Glycine, valine, leucine, isoleucine, proline, phenylalanine, aspartic acid and glutamic acid were determined by microbiological assay. Our technique in general was patterned after that of Stokes and co-workers,[27,28] but differed with respect to the following minor variations. Cells for inoculum were suspended in a small volume of physiological saline and added to the basal medium previously sterilized by filtration through a Seitz filter. Five-ml. portions of the mixture were then pipetted into tubes containing 5-ml. aliquots of either standard amino acid or unknown, previously sterilized by autoclaving. Standards were run in quadruplicate at 10 levels of amino acid concentration and unknowns in quadruplicate at 5 levels. Lactic acid production was determined by titration (glass electrode). Conditions used in the assays are summarized in Table I; further deviations from published procedures are noted there.

Attempts to work out a microbiological assay method for alanine from suggestions in the literature[34–36] were unsuccessful. Likewise, attempts to determine alanine by the Alexander and Seligman method in its original form[37] or as applied to protein hydrolyzates by Michel and Michel[38] were unsatisfactory. Our values for alanine were obtained by the method of Aqvist,[39] which involves deamination to lactic acid, conversion of the lat-

(16) Brand and Kassell, *J. Biol. Chem.*, **131**, 489 (1939).
(17) Shaw and McFarlane, *Can. J. Research*, **16B**, 361 (1938).
(18) Kassell and Brand, *J. Biol. Chem.*, **125**, 115 (1938).
(19) Vassell, *ibid.*, **140**, 323 (1941).
(20) Kassell and Brand, *ibid.*, **125**, 435 (1938).
(21) Kassell and Brand, *ibid.*, **125**, 145 (1938).
(22) Boyd and Logan, *ibid.*, **146**, 279 (1942).
(23) MacFadyen, *J. Biol. Chem.*, **158**, 107 (1945).
(24) Winnick, *ibid.*, **142**, 461 (1942).
(25) Rees, *Biochem. J.*, **40**, 632 (1946).
(26) Nicolet, Shinn and Saidel, Buffalo Meeting, Am. Chem. Soc., Sept., 1942, Abstracts, p. 22B.
(27) Stokes and Gunness, *J. Biol. Chem.*, **157**, 651 (1945).
(28) Stokes, Gunness, Dwyer and Caswell, *ibid.*, **160**, 35 (1945).
(29) Shankman, Camien and Dunn, *J. Biol. Chem.*, **168**, 51 (1947).
(30) Henderson and Snell, *ibid.*, **172**, 15 (1948).
(31) Teply and Elvehjem, *ibid.*, **157**, 303 (1945).
(32) Rabinowitz and Snell, *ibid.*, **169**, 631 (1947).
(33) Baumgarten, Mather and Stone, *Cereal Chem.*, **22**, 514 (1945).
(34) Brand, Saidel, Goldwater, Kassell and Ryan, THIS JOURNAL, **67**, 1524 (1945).
(35) Buehler, Schantz and Lamanna, *J. Biol. Chem.*, **169**, 295 (1947).
(36) Knight, *J. Exptl. Med.*, **86**, 125 (1947); *J. Biol. Chem.*, **171**, 297 (1947); we wish to thank Dr. Knight for a culture of the strain of *Streptococcus faecalis R* used in his alanine determinations.
(37) Alexander and Seligman, *J. Biol. Chem.*, **159**, 9 (1945).
(38) Michel and Michel, *Bull. soc. chim. biol.*, **29**, 886 (1947).
(39) Aqvist, *Acta Physiol. Scand.*, **13**, 297 (1947).

ter to acetaldehyde and determination of the aldehyde with *p*-hydroxybiphenyl. The figures should be regarded only as approximations.

Comments on Methods.—Vickery[40] has stressed the need for maintaining certain specialized standards of accuracy in amino acid analysis of proteins. In conforming to these standards insofar as possible, we have made liberal use of the "standard proteins," β-lactoglobulin and bovine serum albumin, and of mixtures of amino acids, for control analyses. Each method of analysis was tested on a "standard protein" before it was adopted for use. In the microbiological assays, an analysis of lactoglobulin was made simultaneously with every run on unknown protein. With few exceptions, our results on lactoglobulin and serum albumin agreed closely with the analyses listed by Brand.[41]

Table II shows the divergent values for lactoglobulin, together with other figures from the recent literature. Alanine analyses of lactoglobulin by the Aqvist method, although they average 7.8%, a not unreasonable value, are not included in the table because the results were erratic.

TABLE II

AMINO ACID ANALYSES OF LACTOGLOBULIN, G./100 G. OF PROTEIN

	Brand[41]	Values from present work	Other values
Glycine	1.4	1.8	1.56 (Keston, *et al.*[42])
Isoleucine	8.4	7.1	5.86 (Stein and Moore[43])
Proline	4.1	4.8	4.84 (Keston, *et al.*[42])
Serine	5.0	4.3	4.07 (Rees[25])
Threonine	5.85	5.3	5.11 (Rees[25])

It will be obvious, especially to protein analysts, that to obtain results in agreement with reliable values in the literature within a few per cent., although reassuring, is no proof of accuracy. This is particularly true of the serine, threonine and other determinations which involve correction for destruction during hydrolysis, of the amide nitrogen determination, and of some of the microbiological procedures. Therefore analyses of casein, α-casein and β-casein were carried out under identical conditions and simultaneously whenever possible, so that observed differences in composition could be accepted as real, at least in a comparative sense.

Discussion

Averaged analytical results are listed in Table III. All have been corrected for moisture. Since true ash amounted to less than 0.4% in each protein, it was disregarded in the calculations. Corrections previously mentioned have been applied to the figures for methionine, tryptophan, arginine, histidine, serine, threonine and tyrosine.

α-Casein and β-casein differ in their content of most of the amino acids. Most striking, perhaps, are the observed differences in proline, tryptophan and tyrosine content, and the presence of less than 0.1% cystine in β-casein. Histidine, glutamic acid, threonine and, obviously, amide nitrogen are considered to be present in equal concentration within experimental error. The differences in glycine, isoleucine and serine content, although not large, are considered as probably significant, especially since any differences in composition relative to casein would be accentuated in β-casein, the minor component. Definite conclusions regarding alanine cannot be drawn from the available data; the figures for this amino acid are included only to show its approximate concentration.

There have been previous reports that casein fractions differ in phosphorus, tyrosine and tryptophan content but, as Warner[3] has pointed out, it is unlikely that the fractions analyzed were homogeneous. However, the alcohol-soluble casein containing little phosphorus, which was isolated by Osborne and Wakeman[44] and by Linderstrøm-Lang[45] may well be a distinct component of casein, with its own characteristic amino acid composition.[4]

In more recent studies, Mellander[46] has reported that α-casein, prepared by Warner's method, contained 6.8% serine, whereas his original casein contained 3.5%. And in an abstract by Hagberg and Swanson[47] it is stated that "α-casein contained a higher percentage of total phosphorus, aspartic acid, glutamic acid and tyrosine" (than β-casein, being implied). Our data, except for glutamic acid, are in accord with the latter statement. The comparison of Mellander regarding serine, however, seems questionable because of the low value of 3.5% for casein (*cf.* Rees[25]) and because of the following considerations.

If it is assumed that casein is composed of only α-casein and β-casein, and if the analyses for any common constituent differ significantly in the three proteins, then the relative amounts of α-casein and β-casein in casein may be calculated. Thus, using the figures for tyrosine in Table III, 6.3, 8.1 and 3.2%, one obtains a ratio of 63:37 for the proportion of α-casein to β-casein in casein. This calculation has been made for 14 of the constituents listed in Table III; the resulting ratios range from 58:42 to 78:22 and average 69:31. The ratio deduced by Warner from electrophoretic patterns was 80:20. Mellander's values do not fit any reasonable ratio of this kind, but if the value of 3.5% serine in casein is indeed low, the figure of 6.8% in α-casein is possible.

The completeness of the analyses as shown by the summations of nitrogen in Table III might

(40) Vickery, *Ann. N. Y. Acad. Sci.*, **47**, 63 (1946).
(41) Brand, *ibid.*, **47**, 187 (1946).
(42) Keston, Udenfriend and Cannan, THIS JOURNAL, **71**, 249 (1949).
(43) Stein and Moore, *J. Biol. Chem.*, **176**, 337 (1948).
(44) Osborne and Wakeman *J. Biol. Chem.*, **33**, 243 (1918).
(45) Linderstrøm-Lang, *Compt. rend. trav. lab. Carlsberg*, **17**, No. 9, 116 pp. (1929).
(46) Mellander, *Upsala Läkarefören. Förh.*, **52**, 107 (1947).
(47) Hagberg and Swanson, *J. Dairy Sci.*, **31**, 718 (1948).

TABLE III

COMPOSITION OF WHOLE CASEIN, α-CASEIN AND β-CASEIN

Constituent	Whole casein	α-Casein, g./100 g. protein	β-Casein	Whole casein, g. amino acid	α-Casein N/100 g. protein N	β-Casein N/100 g. protein N
Total N	15.63	15.53	15.33			
Total P	0.86[a]	0.99[a]	0.61[a]			
Amino N	0.93 (0.92–0.94) [4,1][b]	0.99 (0.97–1.00) [4,1]	0.72 (0.71–0.73) [4,1]			
Glycine	2.7 (2.59–2.85) [3,5]	2.8 (2.66–2.85) [3,5]	2.4 (2.28–2.41) [2,5]	3.2	3.4	2.9
Alanine	3.0[c] (2.0–4.0) [4,3]	3.7[c] (2.2–4.1) [4,3]	1.7[c] (0.5–3.1) [4,3]	3.0[c]	3.7[c]	1.7[c]
Valine	7.2 (7.02–7.48) [3,5]	6.3 (6.18–6.37) [3,5]	10.2 (9.89–10.40) [2,5]	5.5	4.9	8.0
Leucine	9.2 (8.86–9.46) [2,5]	7.9 (7.79–8.07) [2,5]	11.6 (11.57–11.71) [2,5]	6.3	5.4	8.1
Isoleucine	6.1 (6.06–6.23) [3,5]	6.4 (6.27–6.56) [3,5]	5.5 (5.23–5.68) [3,5]	4.2	4.4	3.8
Proline	11.3 (10.89–11.53) [4,5]	8.2 (8.04–8.31) [4,5]	16.0 (15.60–16.40) [2,5]	8.8	6.4	12.7
Phenylalanine	5.0 (4.88–5.07) [2,5]	4.6 (4.47–4.67) [3,5]	5.8 (5.62–6.05) [3,5]	2.7	2.5	3.2
Cystine	0.34[d]	0.43[d]	0.0–0.1[d]	0.3	0.3	...
Methionine	2.8[e]	2.5[e]	3.4[e]	1.7	1.5	2.1
Tryptophan	1.2[f]	1.6[f]	0.65[f]	1.1	1.4	0.6
Arginine	4.1 (3.98–4.19) [2,3]	4.3 (4.24–4.37) [2,3]	3.4 (3.24–3.48) [2,3]	8.4	8.9	7.1
Histidine	3.1 (2.94–3.18) [2,3]	2.9 (2.80–3.03) [2,3]	3.1 (3.11–3.14) [2,3]	5.4	5.1	5.5
Lysine	8.2 (8.11–8.18) [3,2]	8.9 (8.85–8.95) [3,2]	6.5 (6.47–6.57) [3,2]	10.1	11.0	8.1
Aspartic acid	7.1 (6.78–7.46) [3,5]	8.4 (8.10–8.65) [3,5]	4.9 (4.70–5.09) [3,5]	4.8	5.7	3.4
Glutamic acid	22.4 (21.10–24.40) [4,5]	22.5 (21.10–25.20) [5,5]	23.2 (22.40–23.90) [2,5]	13.6	13.8	14.4
Amide N	1.6 (1.60–1.61) [2,1]	1.6 (1.59–1.64) [3,1]	1.6 (1.60–1.66) [3,1]	10.2	10.3	10.4
Serine	6.3 (6.15–6.41) [4,3]	6.3 (6.20–6.38) [5,3]	6.8 (6.76–6.89) [2,3]	5.4	5.4	5.9
Threonine	4.9 (4.68–5.05) [6,3]	4.9 (4.69–5.11) [7,3]	5.1 (4.98–5.17) [3,3]	3.7	3.7	3.9
Tyrosine	6.3 (6.00–6.84) [17,2]	8.1 (7.82–8.28) [13,2]	3.2 (3.09–3.30) [7,2]	3.1	4.0	1.6
Total	115.8[g]	115.7[g]	117.4[g]	101.5	101.8	103.4

[a] These values are identical with those reported by Warner.[3] [b] Figures in brackets show the number of determinations, followed by the number of duplicative analyses in each determination; figures in parentheses are averages of the duplicative analyses and show the range of the individual determinations from which the final average value was calculated; in the microbioassays, analyses at 5 levels of unknown concentration are considered as duplicative analyses. [c] These values are provisional. [d] The figures listed are averaged results of two methods; found for casein by Brand–Kassell method, 0.35(0.30–0.39)[6,2]; and by Vassel method, 0.33(0.30–0.34)[6,2]; found for α-casein, by Brand–Kassell method 0.42(0.40–0.49)[7,2] and by Vassel method 0.43(0.41–0.45)[5,2]; less than 0.1% cystine was found in β-casein by either method. [e] Averaged results of 2 methods; found for casein by volatile iodide, 2.85(2.63–3.05)[5,2], and as homocysteine, 2.73(2.65–2.80)[5,1]; found for α-casein, 2.55(2.49–2.62)[4,2] and 2.53(2.47–2.66)[4,1]; found for β-casein, 3.42(3.38–3.46)[2,2] and 3.45(3.44–3.46)[2,1]. [f] Averaged results of 2 methods; found for casein by Brand–Kassell method, 1.23(1.06–1.37)[17,2] and by Shaw-McFarlane, 1.26(1.18–1.32)[12,2]; found for α-casein, 1.46(1.32–1.53)[13,2] and 1.65(1.56–1.75)[11,2]; found for β-casein, 0.74(0.72–0.77)[7,2] and 0.55(0.46–0.65)[5,2]. [g] Total includes amino acids, amide N calculated as ammonia (1.9%), and phosphorus calculated as phosphoric acid (2.7, 3.1 and 1.9%, respectively, for casein, α-casein and β-casein).

conceivably be the result of numerous compensating errors. The presence of other amino acids or other groups must be considered possible, although it is reasonably certain that they could not be present in large concentration. Additional evidence for the essential completeness of the analyses may be found in the summations by McMeekin, *et al.*,[48] of amino acid residue weights, 98.13, 98.12 and 99.15, for whole casein, α-casein and β-casein, respectively.

The values herein reported for the amino acid composition of whole casein are compared with figures from the literature (Table IV) in order to demonstrate that casein is fairly well characterized in spite of its heterogeneity. The selection of data from the great number of published values is admittedly arbitrary, as is also the omission of hydroxyproline and citrulline.

To show correlations between physical properties and amino acid composition, the data in Table III have been recalculated in terms of side chain groups (Table V). The treatment follows that of Brand, *et al.*,[34] with respect to grouping of side chain residues and calculating free α-amino, free α-carboxyl, free glutamic acid carboxyl and glutamine groups. It has been assumed that all the phosphorus is present as phosphoserine, the excess of serine being listed as free serine groups. The phosphoserine side chains are considered dibasic anionic groups. Incidentally, if they are considered monobasic anionic groups, and if the free α-amino and free α-carboxyl groups are not included in the summations, the figures for total groups become 845, 837 and 873 moles of amino acids per 10^5 g. of whole casein, α-casein and β-casein, respectively; the reciprocals of these totals, 118.3, 119.5 and 114.5, are

(48) McMeekin, Groves and Hipp, THIS JOURNAL, **71**, 3298 (1949).

TABLE IV

AMINO ACID COMPOSITION OF WHOLE CASEIN, G./100 G. OF PROTEIN

	Values from present work	Values from literature
Glycine	2.7	1.9[29]
Alanine	3.0	3.5[49]
Valine	7.2	7.2[30]
Leucine	9.2	10.3[30]
Isoleucine	6.1	7.6[30]
Proline	11.3	11.6[30]
Phenylalanine	5.0	5.5[30]
Cystine	0.34	0.34[20]
Methionine	2.8	3.1[20]
Tryptophan	1.2	1.2[50]
Arginine	4.1	4.0[51]
Histidine	3.1	3.2[51]
Lysine	8.2	8.3[51]
Aspartic acid	7.1	7.2[52]
Glutamic acid	22.4	22.0[53]
Amide N	1.6	1.4[25]
Serine	6.3	5.9[25]
Threonine	4.9	4.6[25]
Tyrosine	6.3	6.2[30]
Total	112.8	115.0

then the respective approximate average residue weights.

An important difference in the properties of α-casein and β-casein, which has been utilized in this Laboratory in their separation, is the greater solubility of β-casein in ethanol–water mixtures. The larger proportion of non-polar groups in β-casein (Table V) may well account for this.

Differences in the electrophoretic mobilities of α-casein and β-casein observed by Warner[3] may be explained also on the basis of amino acid composition. In solutions, both acid and alkaline to the isoelectric points of the proteins, α-casein had the higher mobility. The higher proportions of cationic and anionic groups in α-casein fit in with this observation. The greater concentration of phosphoric ester residues in α-casein is also noteworthy because of the particular contribution of these groups to the higher mobility of α-casein in alkaline solution.

A correlation between amino acid composition and specific volume for each of these proteins is demonstrated by McMeekin, *et al.*[48]

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(49) Tristram, *Biochem. J.*, **40**, 721 (1946).
(50) Sullivan and Hess, *J. Biol. Chem.*, **155**, 441 (1944).
(51) Macpherson, *Biochem. J.*, **40**, 470 (1946).
(52) Hac and Snell, *J. Biol. Chem.*, **159**, 291 (1945).
(53) Bailey, Chibnall, Rees and Williams, *Biochem. J.*, **37**, 360 (1943).

TABLE V

SIDE CHAIN GROUPS IN WHOLE CASEIN, α-CASEIN AND β-CASEIN

Group	Equiv./10⁵ g. protein: Whole casein	α-Casein	β-Casein
Cationic groups			
Arginine	24	25	20
Histidine	20	19	20
Lysine	56	61	44
Free α-amino	10	10	7
Total cationic groups	110	115	91
Anionic groups			
Aspartic	53	63	37
Free glutamic	38	39	44
Free α-carboxyl	10	10	7
Phosphoserine	56	64	40
Total anionic groups	157	176	128
Total ionic groups	267	291	219
Non-ionic polar groups			
½ Cystine	3	4	0
Methionine	19	17	23
Tryptophan	6	8	3
Tyrosine	35	45	18
Free serine	32	28	45
Threonine	41	41	43
Glutamine	114	114	114
Total non-ionic polar groups	250	257	246
Total polar groups	517	548	465
Non-polar groups			
Glycine	36	37	32
Alanine	34	42	19
Valine	61	54	87
Leucine	70	60	88
Isoleucine	47	49	42
Phenylalanine	30	28	35
Proline	98	71	139
Total non-polar groups	376	341	442
Total groups	893	889	907

Summary

A comparative analysis of the amino acid composition of whole casein and its two major components, α-casein and β-casein, has been made. Within the experimental error of the analytical methods, all the nitrogen of each protein has been accounted for in terms of known amino acids and amide nitrogen.

α-Casein and β-casein differ considerably in their content of many amino acids, and these differences are reflected in such physical properties as solubility and electrophoretic mobility.

Although heterogeneous, whole casein is a fairly well characterized protein with respect to amino acid composition.

PHILADELPHIA 18, PENNA. RECEIVED APRIL 4, 1949

[Contribution from the Eastern Regional Research Laboratory[1]]

Apparent Specific Volume of α-Casein and β-Casein and the Relationship of Specific Volume to Amino Acid Composition

By T. L. McMeekin, M. L. Groves and N. J. Hipp

The partial specific volumes of proteins are of great importance in determining their molecular weights by sedimentation and diffusion. The apparent specific volumes are calculated from the densities of the protein solutions and are identical with the partial specific volumes in dilute solutions. A value of about 0.750 has been reported for the partial specific volume of many proteins.[2] It has been suggested,[3,4] however, that the apparent specific volume of a protein is largely determined by the volume increments of the amino acid residues of which it is composed. The recent complete amino acid analyses of α-casein and β-casein by Gordon, *et al.*,[5] which show considerable differences in the composition of these proteins, offer the opportunity of comparing the specific volume calculated from the amino acid content with the experimentally determined specific volume.

Experimental

Casein Preparations.—The preparations were the same as those used by Gordon, *et al.*,[5] and described by Warner,[6] with the exception of β-casein, which was prepared by Hipp, *et al.*,[7] by a modification of the method devised by Warner. The β-casein was free from α-casein, as shown by electrophoresis, and contained 0.60% phosphorus and 15.3% nitrogen. The amino acid analysis of β-casein by Gordon, *et al.*, however, was made on the sample prepared by Warner. Consequently, our calculated specific volume of β-casein is based on one preparation, whereas our experimentally determined specific volume is based on another, a sample which has not been analyzed for amino acids. It is believed, however, that the electrophoretic analyses and the nitrogen and phosphorus content characterized β-casein well enough to make a valid comparison of the measurements of the two preparations.

Density Measurements.—The casein samples were dissolved in the minimum amount of dilute sodium hydroxide to give a *p*H of 6.4 to 6.9—approximately 4.6 cc. of 0.1 *N* sodium hydroxide for each gram of casein. Densities were determined at 25° in pycnometers of about 20-ml. capacity. The protein concentration was determined on aliquots of the solution by dry weight at 105°. The calculated amount of sodium present was subtracted in calculating the dry weight. The dry weight value agreed with the weight of casein used in making the solutions. Densities of solutions of whole casein were also determined in 6.66 molar urea solutions and in acid solutions of *p*H 3.1. Urea was purified by dissolving it in 70% alcohol at 40° and precipitated by chilling to −5°. The recrystallized urea was dried *in vacuo* at 50°. Casein solutions with a *p*H of 3.1 were prepared by dissolving casein in dilute sodium hydroxide and adding lactic acid rapidly with stirring until the desired *p*H was reached. In each case the density of a solution containing all the added ingredients, with the exception of the casein, was determined and used as the solvent density in calculating the apparent specific volumes.

Densities and Apparent Specific Volumes of Casein Solutions.—Table I gives the data on the densities and calculated apparent specific volumes of α-casein, β-casein and whole casein solutions. The equation of Svedberg and Chirnoaga[8] was used in calculating the apparent specific volumes: $V = [w - (1 - h)]/\rho h$, where w is weight of solvent in pycnometer, l is weight of solution, h is weight of protein, and ρ is density of solvent. No correction was made for ash because these preparations contained only small amounts of true ash.[6]

Table I

Densities and Apparent Specific Volumes of Casein Solutions

Concn. of casein g. per 100 cc.	*p*H of solution	Density of solution at 25°	Density of solvent	Apparent specific volume of solution
		Whole Casein in Alkali		
1.82	6.4	1.00247	0.99757	0.732
2.73	6.4	1.00522	.99777	.729
5.44	6.4	1.01313	.99847	.732
			Av.	0.731
		Whole Casein in Acid		
0.0[a]	3.1	.....	.....	0.730
2.07	3.1	1.00546	.99978	.725
3.31	3.1	1.01060	1.00140	.721
4.14	3.1	1.01417	1.00248	.716
		Whole Casein in 6.66 *M* Urea		
4.07	5.2	1.10557	1.0973	0.726
5.47	5.2	1.10803	1.0972	.731
6.46	5.2	1.10988	1.0972	.732
			Av.	0.730
		α-Casein		
2.67[b]	6.4	1.00507	0.99777	0.728
5.33[b]	6.4	1.01320	.99847	.725
1.81[c]	6.4	1.00248	.99757	.730
2.74[c]	6.4	1.00528	.99782	.729
4.39[c]	6.4	1.01010	.99819	.730
5.48[c]	6.4	1.01345	.99847	.728
			Av.	0.728
		β-Casein		
1.38[d]	6.9	1.00099	0.99742	0.743
2.76[d]	6.9	1.00491	.99777	.743
5.54[d]	6.9	1.01288	.99847	.741
3.51[e]	6.9	1.00723	.99797	.738
			Av.	0.741

[a] Extrapolated value. [b,c] Different preparations of α-casein. [d,e] Different preparations of β-casein.

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Svedberg and Pedersen, "The Ultracentrifuge," Oxford Press England, 1940.

(3) Cohn, McMeekin, Edsall and Blanchard, *J. Biol. Chem.*, **100**, Proc. xxviii (1933); This Journal, **56**, 784 (1934).

(4) Cohn and Edsall, "Proteins, Amino Acids and Peptides as Ions and Dipolar Ions," Reinhold Publ. Co., New York, N. Y., 1943.

(5) Gordon, Semmett, Cable and Morris, This Journal, **71**, 3293 (1949).

(6) Warner, *ibid.*, **66**, 1725 (1944).

(7) Hipp, unpublished results.

(8) Svedberg and Chirnoaga, This Journal, **50**, 1399 (1928).

Calculation of the Specific Volumes of Caseins from the Volumes of the Amino Acid Residues.—The method of Cohn and Edsall[4] for calculating the apparent specific volume of proteins was followed in detail. The specific volume was calculated by the equation $V_p = \Sigma V_i W_i / \Sigma W_i$, where W_i is the per cent. by weight of the i'th amino acid residue in the protein as found by analysis, and V_i is the specific volume of this residue. The molecular weights and corresponding specific volumes of the amino acid residues were the ones given by Cohn and Edsall, with the exception of cystine. The cystine residue was considered to be cystine minus two molecules of water, resulting in a molecular weight for the residue of 204.18 instead of 222.18. Consequently, a value of 6.6 cc. was subtracted for the volume of the second molecule of water removed from cystine, giving a calculated molal volume for its residue of 128.8 cc. instead of 135.4 cc. When the molal volume of the residue is divided by the weight of the residue, a value of 0.63 is obtained for the specific volume of the cystine residue.

Phosphorus is present in casein in the form of a phosphoric acid ester of serine.[9] Values for the atomic volume of phosphorus and the oxygen atoms of phosphoric acid are not available for calculating the specific volume of serine phosphoric acid. Consequently, the molal volume of serine phosphoric acid was determined, and its residue volume in casein calculated. Serine phosphoric acid was made by the method of Levene and Schormuller,[10] as modified by Plimmer.[11] The product melted at 171.5° and contained 7.69% nitrogen and 17.1% phosphorus. Theoretical values for serine phosphate are 7.57% nitrogen and 16.76% phosphorus. Table II gives the values for the density and molal volume of aqueous solutions of serine phosphate.

TABLE II

MOLAL VOLUME OF SERINE PHOSPHATE

Concentration g. per 100 cc.	Density at 25°	Molal volume
2.002	1.00745	89.4
3.203	1.01359	89.9
4.004 (0.22 *M*)	1.01764	90.3

The value of 90.3 cc. for the molal volume of serine phosphate is used in calculating its residue volume, because the concentration of 0.22 *M* is close to the concentration of 0.25 *M*, used by Cohn and Edsall in their data on the molal volume of amino acids. In calculating the specific volume of serine phosphoric acid residue, 7.4 cc. was subtracted from 90.3 cc., and the result was divided by the molecular weight of the residue (167.07), giving a value of 0.50. The value of 7.4 cc. per mole change in volume caused by the formation of an amino acid from an amino acid residue in the protein was derived by Cohn and Edsall by adding the value of the atomic volumes of 2 hydrogen and 1 oxygen (6.6 cc.) to the calculated difference between the electrostriction and covolume effects (0.8 cc.).

Table III gives calculated values for the per cent. by volume of amino acid residues based on the amino acid analyses of Gordon, *et al.*,[5] for whole casein, α-casein and β-casein, as well as calculated values for their specific volumes.

Discussion

Several values have been reported for the partial specific volume of casein solutions. Chick and Martin[12] calculated the apparent density of the casein molecule in solution to be 1.39, or 0.720 for the apparent specific volume. Svedberg, Carpenter and Carpenter[13] gave the value of 0.750 for the partial specific volume of casein in solution. Our values for whole casein, as well as α-casein and β-casein, are between these two reported values. The accuracy of the value for the specific volume of a protein in solution is dependent on the accuracy of the method for determining the protein concentration. The concentrations of casein reported in Table I were determined in most cases by two methods—(1) by weighing the casein accurately before dissolving it and subtracting the moisture content, and (2) by determining the solids in the solution and subtracting the value for the dry weight of the material added to dissolve the casein. In all cases the values obtained by the two methods were in good agreement. The values for concentration reported in urea solutions were obtained from the weight of casein used.

The apparent specific volume of whole casein was 0.731 when it was dissolved in dilute alkali or in 6.66 *M* urea. When the whole casein was dissolved in lactic acid, the apparent specific volume varied considerably with the concentration of casein used. However, the extrapolated value of 0.730 for zero concentration is in agreement with the values obtained in alkali and urea solutions. The value of 0.728 for the apparent specific volume of α-casein is only slightly less than that for whole casein and is in fact within the experimental variation in determining the specific volume. This value, however, is in agreement with the expected value; Warner[6] has estimated that whole casein contains 80% α-casein and 20% β-casein and the value of the apparent specific volume of β-casein is 0.741.

The calculated specific volumes of the caseins based on the amino acid analyses of Gordon, *et al.*,[5] and the specific volumes of the amino acid residues are in good agreement with the experimentally determined specific volume in each case. These results confirm the hypothesis that the apparent specific volume of a protein is essentially determined by the volume of amino acid residues. These results indicate that if the value for the ap-

(9) Lipmann, *Biochem. Z.*, **262**, 3 (1933).
(10) Levene and Schormuller, *J. Biol. Chem.*, **105**, 547 (1934).
(11) Plimmer, *Biochem. J.*, **35**, 461 (1941).
(12) Chick and Martin, *Biochem. J.*, **7**, 92 (1913).
(13) Svedberg, Carpenter and Carpenter, THIS JOURNAL, **52**, 241 (1930).

Table III

Specific Volumes of Caseins Calculated from the Volumes of the Amino Acid Residues

	Amino acid residues, %			Specific volume of amino acid residue, V	Per cent. by volume of amino acid residue: VW		
	Whole casein	α-Casein	β-Casein		Whole casein	α-Casein	β-Casein
Glycine	2.05	2.13	1.82	0.64	1.31	1.36	1.17
Alanine	(2.39)	(2.95)	(1.36)	.74	1.77	2.19	1.00
Serine	2.82	2.40	3.90	.63	1.78	1.52	2.45
Phosphoserine	4.61	5.33	3.25	.50	2.30	2.66	1.63
Threonine	4.16	4.16	4.33	.70	2.91	2.91	3.03
Valine	6.09	5.33	8.63	.86	5.24	4.58	7.42
Leucine	7.93	6.81	10.00	.90	7.14	6.13	9.00
Isoleucine	5.26	5.52	4.74	.90	4.73	4.97	4.27
Proline	9.54	6.92	13.50	.76	7.25	5.26	10.26
Phenylalanine	4.46	4.10	5.17	.77	3.43	3.16	3.98
Methionine	2.46	2.20	2.99	.75	1.85	1.65	2.24
Cystine	0.29	0.37	....	.63	0.18	0.23	....
Tryptophan	1.09	1.46	0.59	.74	0.81	1.08	0.44
Tyrosine	5.68	7.30	2.88	.71	4.03	5.18	2.05
Histidine	2.74	2.56	2.74	.67	1.84	1.72	1.84
Arginine	3.67	3.85	3.05	.70	2.57	2.70	2.13
Lysine	7.18	7.80	5.69	.82	5.89	6.39	4.67
Aspartic acid	6.14	7.27	4.24	.60	3.69	4.36	2.54
Glutamic acid	4.92	5.01	5.62	.66	3.25	3.30	3.71
Glutamine	14.65	14.65	14.65	.67	9.81	9.81	9.81
Total	98.13	98.12	99.15		71.78	71.16	73.64
Per cent. by volume of amino acid residues.....$\Sigma V_i W_i$					71.78	71.16	73.64
Per cent. by weight of amino acid residues.....ΣW_i					98.13	98.12	99.15
Specific volume, calculated.....$\Sigma V_i W_i / \Sigma W_i$					0.731	0.725	0.743
Specific volume, observed (Table I).....					.731	.728	.741

parent specific volume of a protein as determined does not agree reasonably well with the value calculated from the specific volumes of the amino acid residues a redetermination should be made of either the apparent specific volume or the amino acid content. Thus Putnam, Lamanna and Sharp[14] have calculated from the volumes of the amino acid residue that the apparent specific volume of botulinus antitoxin is 0.738, while Kegeles[15] found 0.755 for this protein. Here the variation between the calculated value and the observed value appears to be greater than might be expected. A value of 0.746 for the apparent specific volume of β-lactoglobulin may be calculated from the amino acid analysis of Brand, *et al.*[16] This value is in good agreement with the determined value of 0.751 reported by Pedersen[17] and confirmed by Brand and Kassell.[18] (The value of 6.1% for the isoleucine content of β-lactoglobulin reported by Smith and Greene[19] was used instead of Brand's value of 8.4%.)

(14) Putnam, Lamanna and Sharp, *J. Biol. Chem.*, **176**, 401 (1948).
(15) Kegeles, This Journal, **68**, 1670 (1946).
(16) Brand, Saidel, Goldwater, Kassell and Ryan, *ibid.*, **67**, 1524 (1945).
(17) Pedersen, *Biochem. J.*, **30**, 961 (1936).
(18) Brand and Kassell, *J. Biol. Chem.*, **145**, 365 (1942).
(19) Smith and Greene, *ibid.*, **172**, 111 (1948).

Summary

Values for the apparent specific volume of whole casein, α-casein and β-casein have been calculated from density determinations and from the volumes of the amino acid residues. The values calculated by the two methods are in good agreement, indicating that the apparent specific volume of a protein is largely determined by the volume of its amino acid residues.

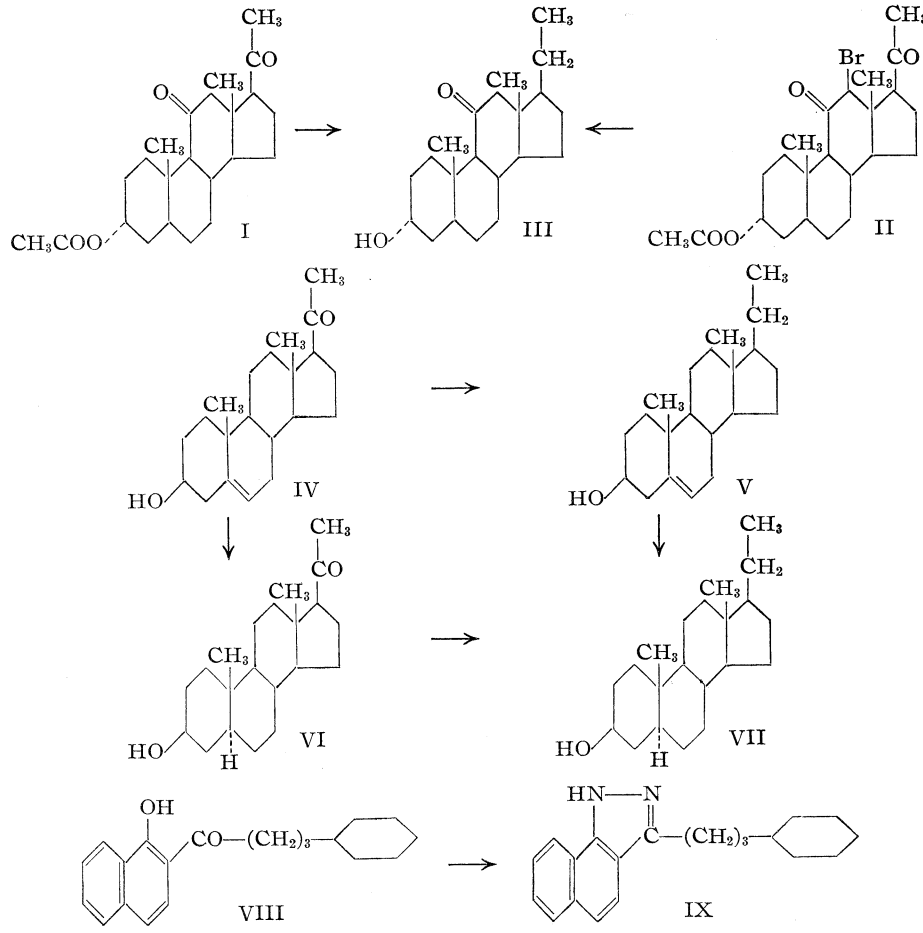
Philadelphia 18, Pa. Received April 5, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

Reduction of Steroid Ketones and other Carbonyl Compounds by Modified Wolff–Kishner Method

BY HUANG-MINLON[1]

According to Dutcher and Wintersteiner[2] the reduction of C_3-steroid ketones by the Wolff–Kishner method under usual conditions gives mainly the corresponding C_3-epimeric carbinols with small amounts of the expected C_3-methylenic products. In the case of the α,β-unsaturated ketone, cholestenone, the reduction follows a still more complex course. In addition to the epimeric unsaturated carbinols and a small amount of the normal product, Δ^4-cholestene, the saturated carbinols, α-coprosterol and β-cholestanol have also been isolated. The authors stated that the abnormal reduction can be explained by the assumption that the hydrazone or semicarbazone is partially hydrolyzed to free ketone, which is then reduced by sodium alcoholate to give the secondary alcohol. These possibilities are, however, eliminated by the modified Wolff–Kishner reduction,[3,4] in which the water is evaporated during the heating period. Moreover, the excess of hydrazine hydrate used in this reaction should keep the concentration of the regenerated ketone at a low level.[2] In fact all the C_3-steroid ketones so far investigated gave the normal C_3-methylenic compounds by the modified Wolff–Kishner reduction. The formation of carbinols has never been observed. This reaction proceeds also normally on keto groups at other positions, C_7, C_{12}, C_{17} and C_{20}, except at C_{11}, which remains unattacked. Thus, 3-hydroxy-11-ketoetiocholanic acid is unreduced. 3,α-Acetoxy-11,20-diketopregnane (I) gave a reduced product melting at 152–153° in which one of the two keto groups is unattacked. In view of the fact that the 20-keto compounds, such as Δ^5-pregnen-3(β)-ol-20-one (IV) and its hydrogenation product, allopregnan-3(β)-ol-20-one (VI) can be transferred to Δ^5-pregnan-3(β)-ol (V) and 3,β-hydroxyallo-pregnane (VII), respectively, the reduced product from I may be formulated as 3,α-hydroxy-11-ketopregnane (III). Δ^5-Pregnen-3(β)-ol (V), which has not previously been reported, is transferred to the known compound, allopregnan-3(β)-ol (VII) by catalytic hydrogenation. From the reaction products of 3,α-acetoxy-11,20-diketo-12-bromopregnane (II) two isomeric compounds could be isolated, one of which melts at 152–153° and is identical with III and the other melts at 109°. Both give the same analytical result, but the latter is more dextrorotatory and its structure is under investigation.



(1) On leave of absence from the National Research Institute of Chemistry, Academia Sinica.

(2) Dutcher and Wintersteiner, THIS JOURNAL, **61**, 1992 (1939).

(3) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(4) Huang-Minlon, *ibid.*, **70**, 2802 (1948).

TABLE I

Compound	Product	M. p., °C.	Recryst. from	Yield, %	$[\alpha]^{25}D$	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Estrone	3-Hydroxy-1,3,5-estratriene[a]	134–134.5	Dil. alc.	79.2	+89 (in alc.)	$C_{18}H_{24}O$	84.31	84.50	9.46	9.44
Dehydroepiandrosterone	Δ^5-Androsten-3(β)-ol[b]	132–133	Ethyl acetate	71.5	−47° (alc.)	$C_{19}H_{30}O$	83.13	83.28	11.01	11.07
Δ^5-Pregnen-3(β)-ol-20-one	Δ^5-Pregnen-3(β)-ol	133–134	Methanol	79.5	−46° (alc.)	$C_{21}H_{34}O$	83.39	83.52	11.33	11.02
	Acetyl derivative	147–148	Methanol			$C_{23}H_{36}O_2$	80.18	80.28	10.53	10.45
Allopregnan-3(β)-ol-20-one[c]	Allopregnan-3(β)-ol[d]	136–137	Methanol	84.7	+18 ($CHCl_3$)	$C_{21}H_{36}O$	82.83	82.82	11.92	11.79
	Acetyl derivative	115–116	Acetone		−61° ($CHCl_3$)					
Androstandione	Androstane[e]	48–49	Dil. acetone	83.3	+1° ($CHCl_3$)	$C_{19}H_{32}$	87.75	87.83	12.25	12.28
Testosterone	Δ^4-Androsten-17-ol (Desoxytestosterone)[f]	152–153	Petroleum ether	55.2	+47° (alc.)	$C_{19}H_{30}O$	83.13	83.16	11.01	11.03
	Acetyl derivative	98–100	Dil. methanol							
Cholestanone	Cholestane[g]	79–80	Ether–alc.	83.4	+24.8° ($CHCl_3$)					
Cholestenone	4-Cholestene	77–78	Acetone–alc.	61.4	+64.0° ($CHCl_3$)	$C_{27}H_{46}$	87.47	87.28	12.53	12.69
3α-Acetoxy-11,20-diketopregnane	3α-Hydroxy-11-ketopregnane	153–153.5	Dil. CH_3OH	70.5	+79.6° ($CHCl_3$)	$C_{21}H_{34}O_2$	79.20	79.53	10.73	10.95
3α-Acetoxy-11,20-diketo-12-bromopregnane	3α-Hydroxy-11-ketopregnane And its isomer	152–153 109[h]	Dil. CH_3OH Ether–methanol	40.0 2.4	+79.9° ($CHCl_3$) +107.5° ($CHCl_3$)	$C_{21}H_{35}O_2$ $C_{21}H_{34}O_2$	79.20 79.20	79.48 79.66	10.73 10.73	10.41 10.44
Dehydrocholic acid	Cholanic acid	165–166[g]	Acetone	91.6						
Methyl 3-benzoxy-12-ketocholanate	Lithocholic acid[i]	188–189[g]	Acetone	99.3	+34° (alc.)					
Ethyl 3,12-dihydroxy-7-ketocholanate	Acetic cholelic acid[j]	138–141[g]		62.3						
Vanillin	3,4-Dimethoxy-1-methylbenzene[k]	B. p. 133–135 (50 mm.)		77.3	$n^{25}D$ 1.5257					
Veratraldehyde	3,4-Dimethoxy-1-methylbenzene	B. p. 122–124 (27 mm.)		81	$n^{25}D$ 1.5259					
9-Anthraaldehyde[l]	9-Methylanthracene[m]	80–81	CH_3OH	88		$C_{15}H_{12}$	93.74	93.81	6.25	6.16
α-Naphthaldehyde semicarbazone	1-Methylnaphthalene	B. p. 125 (24 mm.)		71	($n^{25}D$ 1.6153) (picrate m. p. 141–142)					
Cinnamic aldehyde	Propenylbenzene	B. p. 176–178 (755 mm.)		70	($n^{25}D$ 1.5464)					
Friedeline[n]	Friedelane[n]	244–245	$CHCl_3$ (alc.)	83	+42.5 ($CHCl_3$)	$C_{30}H_{52}$	87.30	87.25	12.70	12.80
Cerine[o]	Friedelane	243–244	$CHCl_3$ (alc.)	75.4	+42.0 ($CHCl_3$)	$C_{30}H_{52}$				
2-(γ-Cyclohexylbutyro)-α-naphthol	3-(γ-cyclohexylpropyl)-6,7-benzoindazole)	129–130	Alcohol	75		$C_{20}H_{24}N_2$	82.13	82.35	8.27	8.19

[a] Butenandt and Westphal, *Z. physiol. Chem.*, **223**, 147 (1934). [b] Butenandt and Suranyi, *Ber.*, **75**, 591 (1942). [c] Prepared from Δ^5-pregnenolone according to Plattner, Heusser and Angliker, *Helv. Chim. Acta*, **29**, 468 (1946). [d] Ruzicka, Meister and Prelog, prepared from dehydroepiandrosterone, *ibid.*, **30**, 867 (1947). [e] Butenandt and Tschering, *Z. physiol. Chem.*, **229**, 185 (1934); Prelog, Ruzicka and Wieland, *Helv. Chim. Acta*, **27**, 66 (1944). [f] Marker, Wittle and Tullar prepared from Δ^5-cholestene, THIS JOURNAL, **62**, 223 (1940). [g] Not depressed by admixture with authentic sample. [h] The residue of the methanolic mother liquor of (a) was dissolved in a mixture of benzine (30–60°) and benzene (4-1) and eluted with the same mixed solvents (3:1, 2:1, 1:1) and finally with pure benzene. This low melting isomer is isolated from the first crystalline fractions. [i] After acidifying with dil. HCl the crude product was washed with hot water to remove benzoic acid liberated from the starting material. [j] One sample is transferred to desoxycholic acid m. p. 170–171° not depressed by mixture with authentic sample. [k] On methylation of the crude reduced product with dimethyl sulfate. [l] Prepared according to "Org. Syntheses," **20**, 11 (1940). [m] Fieser and Hartwell obtained this product melting at 77–78° in lower yield from the same starting material by usual Wolff–Kishner reduction, THIS JOURNAL, **60**, 2555 (1938). [n] Ruzicka, Jeger and Ringnes [*Helv. Chim. Acta*, **27**, 932 (1944)] reduced this compound by usual Wolff–Kishner procedure, but the yield of friedelane is not given. [o] Drake and Jacobsen [THIS JOURNAL, **57**, 1570 (1935)] also obtained same reduced product, friedelane, from friedeline and cerine by Clemmensen reduction.

Similar smooth reduction of the carbonyl group in other compounds apart from the steroids, was also noted (see Experimental). One case, however, needs to be specially mentioned for its abnormal behavior. Thus the carbonyl compound (VIII) did not give the corresponding methylene compound by the modified Wolff–Kishner reduction but gave the indazole derivative (IX) in good yield. This, however, is not surprising since α-aceto-β-naphthol is known to react with hydrazine yielding indazole derivative.[5]

Acknowledgment.—I am indebted to Prof. L. F. Fieser for his encouragement in the pursuance of this investigation.

(5) Witt and Braun, *Ber.*, **47**, 3216 (1914); Fries and Schimmelschmidt, *Ber.*, **58**, 2835 (1925).

Experimental[6]

The reduction has been carried out by procedures similar to those described in previous papers.[3,4] Thus a mixture of the starting material, diethylene or triethylene glycol (Note 1), alkali hydroxide and 85% hydrazine hydrate (Notes 2 and 3) was refluxed for about half an hour and the condenser was then removed to allow the aqueous liquor to evaporate and the temperature of the reaction mixture to rise to about 200°. In cases where either the starting material or the reduced product is volatile a take-off adapter was used instead of removing the condenser to evaporate aqueous liquor. After refluxing at this temperature for about two hours the reaction mixture was cooled, diluted with water (Note 4) and the separated reaction product was filtered or extracted with ether (Note 5). The results are summarized in Table I (Notes 6 and 7).

Catalytic reduction of Δ^5-pregnen-3(β)-ol (V) to allopregnan-3(β)-ol (VII): 0.2 g. of Δ^5-pregnen-3(β)-ol in 30 cc. of alcohol containing 3 drops of hydrobromic acid (48%) was shaken with hydrogen in the presence of 0.05 g. of Adams catalyst until the calculated amount of hydrogen was absorbed. The reaction mixture was filtered and the filtrate was concentrated in vacuum to a small volume. On dilution with water allopregnan-3(β)-ol (VII) separated in plates. It was recrystallized from methanol, m. p. 136–137, not depressed by admixture with the Wolff–Kishner reduction product from VI; yield 0.18 g.

NOTE 1.—The amount of diethylene glycol or triethylene glycol used can be varied according to the solubility of the carbonyl compound or its hydrazone formed during the reaction so that a clear or nearly clear reaction mixture is obtained during the heating period. Sometimes it is advisable to dissolve the carbonyl compound in alcohol before addition of glycol and other reagents, *e.g.*, in the case of cholestanone and cholestenone.

NOTE 2.—The amount of alkali hydroxide used is about 10% to the volume of the glycol used and the amount of 85% hydrazine hydrate used is always in excess (3 moles or more).

NOTE 3.—In reduction of alkali-sensitive compounds such as aldehydes, α,β-unsaturated ketones and those carbonyl compounds in which the carbonyl group is adjacent to an asymmetric center it is advisable to reflux the glycol solution of starting material with hydrazine hydrate for about half an hour and then add a concentrated aqueous solution of alkali hydroxide slowly as described previously.[4]

NOTE 4.—If the reduced product is acidic, it is obtained by acidifying the cooled reaction mixture with dilute hydrochloric acid.

NOTE 5.—In cases where the starting material contains methoxy group the crude reduced product was remethylated with dimethyl sulfate.

NOTE 6.—Most of the technical steroid ketones[7] were recrystallized before reduction, since otherwise the yield is sometimes unsatisfactory. The yields of reduced products given in Table I are on the basis of pure products for which the melting points are given.

NOTE 7.—In cases where the carbonyl compound is unstable and difficult to purify such as α-naphthaldehyde the hydrazone or semicarbazone can be taken as starting material for reduction.

(6) The microanalyses were carried out by Shirley Katz of this Laboratory.

Summary

1. The modified Wolff–Kishner method has been applied to the reduction of a number of steroid ketones and a few other carbonyl compounds giving excellent or comparatively good yields.

2. In the case of the steroids the reduction proceeds normally on the keto groups at positions C_3, C_7, C_{12}, C_{17} and C_{20}, but the C_{11} keto group remains unattacked.

(7) Steroid samples furnished through the courtesy of Merck & Co. and the Schering Corporation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Drugs Effecting Muscular Paralysis. Some Substituted Dioxolanes and Related Compounds[1]

BY V. BOEKELHEIDE, L. LIBERMAN, J. FIGUERAS,[2a] C. KRESPAN,[2b] F. C. PENNINGTON AND D. S. TARBELL

The drugs which effect muscular paralysis may be divided into two classes, depending on whether the predominant action is peripheral or central in nature.[3] The usual curariform agents, including most natural alkaloids and certain quaternary ammonium salts, belong to the former class. The first important compounds to be discovered having a central action were *o*-toloxy-1,2-propanediol (myanesin) and certain related α-glyceryl ethers.[4] Recently,[5] it was found that another class of compounds, the 2-substituted-4-hydroxymethyl-1,3-dioxolanes, possessed an action similar to that of the α-glyceryl ethers. In fact, the results of testing in mice indicate that the best compounds of the dioxolane series exceed those of the α-glyceryl ether series both in degree of activity and in margin of safety. In an attempt to find the scope of activity and the effect of changes of structure on activity in the dioxolane series, a number of substituted dioxolanes have been prepared. In the present paper the synthesis of these dioxolanes is described and evidence is presented establishing the structures of several of the most active members of this series.[6]

The synthesis of the substituted dioxolanes was accomplished, in general, by heating the appropriate carbonyl compound with glycerol or ethylene glycol and an acid catalyst in the presence of a hydrocarbon solvent and with continuous removal

(1) Aided by a Grant from the National Foundation for Infantile Paralysis, Inc.

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(3) Craig, *Chem. Rev.*, **42**, 285 (1948).

(4) Berger and Bradley, *Brit. J. Pharmacol.*, **1**, 265 (1946).

(5) Berger, Boekelheide and Tarbell, *Science*, **108**, 561 (1948).

(6) The results of the physiological testing of these compounds will be reported separately by F. M. Berger, M.D., School of Medicine and Dentistry, University of Rochester, Rochester, New York.

TABLE I

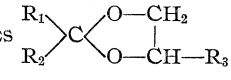
2,2-DIALKYL-4-HYDROXYMETHYL-1,3-DIOXOLANES (See Structure I)

Cpd.	R_1	R_2	B. p., °C.	Mm.	$n^{21}D$	d^{21}	M Calcd.	M Obsd.	Yield, %	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
III	$-CH_3$	$-CH_2CH_2CH_3$	100	5	1.4427	1.024	41.66	41.46	65	$C_8H_{16}O_3$	59.97	59.74	10.07	10.01
IV	$-CH_3$	$-(CH_2)_3CH_3$	105	5	1.4450	1.006	46.28	46.25	75	$C_9H_{18}O_3$	62.03	61.08	10.41	10.30
V	$-CH_3$	$-C(CH_3)_3$	76	1	1.4493	1.021	46.28	45.82	70	$C_9H_{18}O_3$	62.03	61.49	10.41	9.90
VI	$-CH_3$	$-(CH_2)_4CH_3$	80	1	1.4464[b]	0.983	50.91	51.09	80	$C_{10}H_{20}O_3$	63.79	63.66	10.71	10.78
VII	$-CH_3$	$-CH(CH_3)(CH_2)_2CH_3$	95–100	2	1.4487				23	$C_{10}H_{20}O_3$	63.79	63.30	10.71	10.64
VIII	$-CH_3$	$-(CH_2)_5CH_3$	135	5	1.4486	.985	55.52	55.45	62	$C_{11}H_{22}O_3$	65.31	65.01	10.96	10.71
IX	$-CH_3$	$-(CH_2)_6CH_3$	113	1	1.4498	.967	60.14	60.11	66	$C_{12}H_{24}O_3$	66.63	66.30	11.18	11.19
X	$-CH_2CH_3$	$-CH_2CH_3$	95	4	1.4457	1.033	41.66	41.33	84	$C_8H_{16}O_3$	59.97	59.29	10.07	9.63
XI	$-CH_2CH_3$	$-(CH_2)_3CH_3$	106	2	1.4481	0.999	50.91	50.46	78	$C_{10}H_{20}O_3$	63.79	63.52	10.71	10.52
XII	$-CH_2CH_3$	$-(CH_2)_4CH_3$	121	4	1.4499	.990	55.52	54.82	68	$C_{11}H_{22}O_3$	65.31	65.04	10.96	10.60
XIII	$-CH(CH_3)_2$	$-CH(CH_3)_2$	115	9	1.4502	.995	50.91	50.75	24	$C_{10}H_{20}O_3$	63.79	63.50	10.71	10.52
XIV	$-CH_2CH(CH_3)_2$	$-CH_2CH(CH_3)_2$	103	2	1.4494	.980	60.14	59.86	47	$C_{12}H_{24}O_3$	66.63	66.67	11.18	11.09

[a] The value of 1.60 was used for ether oxygen; see Newman and Renoll, THIS JOURNAL, **67**, 1621 (1945). [b] Dupire, *Compt. rend.*, **214**, 359 (1942), reported the values: $n^{19}D$ 1.5132; d^{19} 1.100.

TABLE II

SUBSTITUTED 1,3-DIOXOLANES



Cpd.	R_1	R_2	R_3	B. p., °C.	Mm.	$n^{21}D$	d^{21}	M Calcd.	M Obsd.	Yield, %	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
XV	$-H$	$-(CH_2)_5CH_3$	$-CH_2OH$	106	4	1.4508	1.002	50.92	50.57	79	$C_{10}H_{20}O_3$	63.79	63.31	10.71	10.53
XVI	$-CH_3$	$-CH_2Cl$	$-CH_2OH$	112	10	1.4692	1.252	37.32	37.08	79	$C_6H_{11}O_3Cl$	43.25	42.99	6.66	6.62
XVII	$-CH_2Cl$	$-CH_2Cl$	$-CH_2OH$	110	3	1.4069	1.4919	42.16	41.63	65	$C_6H_{10}O_3Cl_2$	35.84	35.14	5.01	5.09
XVIII	$-CH_3$	$-CH(CO_2Et)(CH_2)_3CH_3$	$-CH_2OH$	131	2	1.4527	1.057	66.44	66.53	61	$C_{13}H_{24}O_5$	59.98	59.83	9.29	9.23
XIX	$-CH_3$	$-CH(CO_2Et)(CH_2)_3CH_3$	$-H$	112	5	1.4398				57	$C_{12}H_{22}O_4$	62.58	62.99	9.63	9.72
XX[a]	$-CH_3$	$-CH(CH_2OH)(CH_2)_3CH_3$	$-H$	106	5	1.4520	1.007	50.92	50.43	48	$C_{10}H_{20}O_3$	63.79	64.13	10.71	10.76
XXI	$-CH_3$	*o*-$CH_3CH_6H_4$–	$-CH_2OH$	118	1	1.5267	1.125	56.55	56.89	15	$C_{12}H_{16}O_3$	69.21	68.62	7.75	7.75

[a] See Experimental.

TABLE III

SUBSTITUTED DIOXASPIRANES AND 1,3-DITHIOLANES

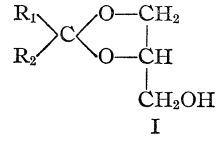
Cpd.	Name	B. p., °C.	Mm.	$n^{21}D$	d^{21}	Yield, %	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
XXII	2-M[a]-1,4-dioxaspiro-(4,4)-nonane	122	12	1.4730[c]	1.130	42	$C_8H_{14}O_3$	60.74	60.82	8.92	8.95
XXIII	2-M-6-methyl-1,4-dioxaspiro-(4,4)-nonane	122	11	1.4702[d]	1.099	25	$C_9H_{16}O_3$	62.74	61.94	9.37	9.13
XXIV	2-M-7-methyl-1,4-dioxaspiro-(4,5)-decane	102	2	1.4733	1.069	58	$C_{10}H_{18}O_3$	64.50	64.62	9.68	10.14
XXV	2-*n*-Amyl-2-methyl-4-M-1,3-dithiolane	93	1	1.5453		66	$C_{10}H_{20}OS_2$	54.04	53.75	9.14	8.70
XXVI	2,2-Dimethyl-4-M-1,3-dithiolanedisulfone[b]					79	$C_6H_{12}O_5S_2$	31.58	31.57	5.29	5.16

[a] M = hydroxymethyl. [b] See Experimental; m. p. 110–112°. [c] M calcd., 39.48; M obsd., 39.27. [d] M calcd., 44.10; M obsd., 43.74.

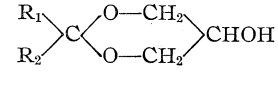
of the water formed. Those dioxolanes which were prepared and have not previously been reported, are listed in Tables I, II and III.

For the preparation of some of the compounds listed in Tables I, II and III, the general method could not be applied. Compound XX, 2-(1′-hydroxymethylamyl)-2-methyl-1,3-dioxolane, was prepared by the sodium and alcohol reduction of the corresponding ester, XIX. It was of interest that XX was the only compound prepared which had high physiological activity but did not have a hydroxymethyl group at the 4-position of the dioxolane ring. Compound XXV, 2-*n*-amyl-2-methyl-4-hydroxymethyl-1,3-dithiolane, was prepared by the condensation of methyl *n*-amyl ketone and 2,3-dimercapto-1-propanol (B. A. L.). Compound XXVI was obtained by the peroxide oxidation of 2,2-dimethyl-4-hydroxymethyl-1,3-dithiolane.

The condensation of a carbonyl compound with glycerol may yield either a dioxolane derivative (I) or a *m*-dioxane derivative (II). Although in



I



II

previous work[7–9] it has been assumed that ketones react with glycerol to give products having the dioxolane structure, this has apparently been established only for the condensation of acetone with glycerol.[10,11] An indication that ketones condense with glycerol to give dioxolane derivatives was obtained when it was found that methyl *n*-amyl ketone condensed readily with ethylene glycol but gave no product at all with trimethylene

(7) Dworzak and Herrmann, *Monatsh.*, **52**, 83 (1929).
(8) Kuhn, *J. prakt. Chem.*, **156**, 103 (1940).
(9) Dupire, *Compt. rend.*, **214**, 359 (1942).
(10) Irvine, Macdonald and Soutar, *J. Chem. Soc.*, **107**, 337 (1915).
(11) Hibbert and Morazain, *Can. J. Research*, **2**, 214 (1930).

glycol. Similar results have been cited by Dworzak and Herrmann[7] as evidence that ketones and glycerol give dioxolane derivatives. However, the work of Hibbert and his collaborators[12,13] has shown that such reasoning, when applied to the condensation of aldehydes with glycerol, is misleading. Therefore, the structures of the condensation products of glycerol with methyl *n*-amyl ketone and with methyl *n*-hexyl ketone were investigated and definitely shown to be of the dioxolane type.

The evidence for the dioxolane structure, I, was established as follows. The condensation product of glycerol and methyl *n*-hexyl ketone, on conversion to the corresponding methyl ether followed by acid hydrolysis, gave only α-methyl glyceryl ether. Thus, the condensation product must be 2-methyl-2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane, since the corresponding *m*-dioxane derivatives would yield a β-methyl glyceryl ether. Likewise the condensation product of glycerol and methyl *n*-hexyl ketone, on treatment with trityl chloride in pyridine under the usual conditions whereby primary but not secondary alcohol groups are etherified,[14] gave an 83% yield of the corresponding trityl ether. The condensation product of glycerol and methyl *n*-hexyl ketone must therefore be almost entirely 2-methyl-2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane.

Finally, a sample of 2-methyl-2-*n*-amyl-4-hydroxymethyl-1,3-dioxolane of known structure was prepared by the alkaline hydrolysis of the condensation product of methyl *n*-amyl ketone and 3-(3′,5′-dinitrobenzoxy)-1,2-propanediol. The infrared absorption spectrum of the 2-methyl-2-*n*-amyl-4-hydroxymethyl-1,3-dioxolane, thus prepared, was found to be identical within experimental error with that of the condensation product of glycerol and methyl *n*-amyl ketone. The absorption spectra are given in Fig. 1.

On the other hand, there is considerable evidence in the literature[15] that aldehydes condense with glycerol to give mixtures of the corresponding 4-hydroxymethyl-1,3-dioxolanes (I) and the corresponding 5-*m*-dioxanols (II). Since the condensation product of glycerol and heptanal possessed a fairly high degree of physiological activity, an investigation of its structure was made.

When the condensation product of glycerol and heptanal was allowed to react with trityl chloride in anhydrous pyridine, as before, there was obtained a 58% yield of the corresponding trityl ether. This rather low yield indicates that, while the product predominantly has structure I, there is also present some material having structure II.

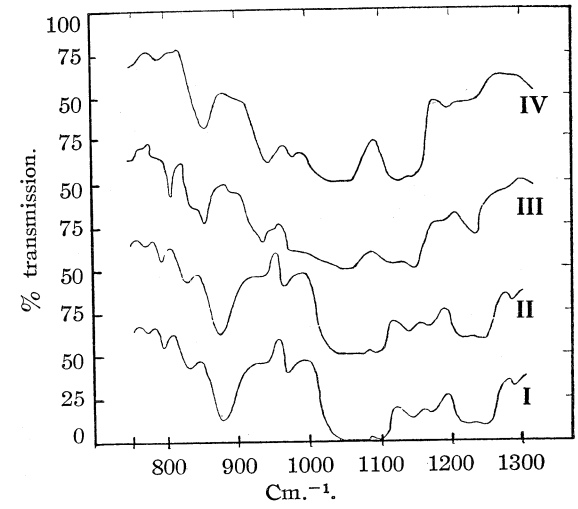


Fig. 1.—Infrared absorption spectra of the condensation product of glycerol and methyl *n*-amyl ketone (I); 2-*n*-amyl-2-methyl-4-hydroxymethyl-1,3-dioxolane (II); condensation product of glycerol and heptanal (III); and 2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane (IV). Spectra were obtained using 0.025 mm. cell.

Further evidence for this conclusion was obtained from infrared absorption spectra studies. A sample of 2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane of known structure was prepared by the alkaline hydrolysis of the condensation product of heptanal and 3-(3′,5′-dinitrobenzoxy)-1,2-propanediol. A comparison of the infrared absorption spectra (see Fig. 1) of this sample with that of the condensation product of glycerol and heptanal showed that, despite a close similarity of the two curves, there were certain real differences. The condensation product of glycerol and heptanal showed absorption peaks at 811 cm.$^{-1}$ and 1240 cm.$^{-1}$, which were not present in the spectra of the pure 2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane. However, until a pure sample of 2-*n*-hexyl-5-*m*-dioxanol is available for comparison, it is not possible to estimate accurately the amount of 2-*n*-hexyl-5-*m*-dioxanol present in the condensation product of glycerol and heptanal.

The infrared absorption spectra studies were initiated in the hope that some characteristic of the spectrum could be related to the dioxolane ring structure and that the infrared absorption spectra of these compounds could be used as a diagnostic test for the presence of the dioxolane ring. However, our knowledge of these spectra is still insufficient to allow such a diagnosis.

Experimental[16]

Formation of the Substituted Dioxolanes, Dioxaspiranes, and Dithiolanes Listed in Tables I, II and III.—With the

(12) Hibbert and Timm, THIS JOURNAL, **46**, 1283 (1924).

(13) Trister and Hibbert, *Can. J. Research*, **14**, 415 (1937).

(14) Helferich and Becker, *Ann.*, **440**, 1 (1924). Although it is realized that secondary alcohols may be etherified by trityl chloride [see Hockett and Hudson, THIS JOURNAL, **53**, 4456 (1931); **56**, 945 (1934)] and therefore this method is not an absolute criterion for the presence or absence of a secondary hydroxyl, it is felt that the method supplies supporting evidence since conditions highly unfavorable to etherification of a secondary hydroxyl were employed.

(15) (a) Van Roon, *Rec. trav. chim.*, **48**, 173 (1929); (b) Trister and Hibbert, *Can. J. Research*, **14**, 415 (1937); Hill, Wheeler and Hibbert, THIS JOURNAL, **50**, 2235 (1928); Hibbert and Sturrock, *ibid.*, **50**, 3376 (1928); and other papers in this same series.

(16) Analyses by Mrs. G. L. Sauvage; all melting points are uncorrected.

exceptions and additions noted below, the compounds listed in Tables I, II and III were prepared by the condensation of the appropriate carbonyl compound with glycerol, ethylene glycol, or 2,3-dimercapto-1-propanol (B. A. L.) according to the following procedure. A mixture of the appropriate carbonyl compound (0.20 mole), double-distilled glycerol (0.25 mole), toluenesulfonic acid (0.5 g.) and toluene (100 ml.) was heated in a three-necked flask with stirring and with provision for continuous removal of water.[17] When the expected amount of water had separated or when no further separation of water occurred, the reaction mixture was cooled, washed successively with a 25-ml. portion of a 5% potassium carbonate solution and three 50-ml. portions of water. The toluene was removed under reduced pressure and the residual oil distilled.

(A) Sodium α-(2-Methyl-4-hydroxymethyl-1,3-dioxolan-2-yl)-caproate.—A mixture of 21.0 g. of 2-(1′-carbethoxyamyl)-2-methyl-4-hydroxymethyl-1,3-dioxolane (XVIII) and 65 ml. of a 5% sodium hydroxide solution was boiled under reflux until the solution became clear (four hours). After evaporation of the solution to dryness, the residue was taken up in a minimum amount of alcohol and reprecipitated by addition of ether. Recrystallization of the crude material from a mixture of alcohol and ether yielded 15.1 g. (75%) of a white powder, m. p. 240–245°.

Anal. Calcd. for $C_{11}H_{19}O_5Na$: Na, 9.05. Found (as Na_2SO_4): Na, 9.09; 9.70.

(B) 2-(1′-Hydroxymethylamyl)-2-methyl-1,3-dioxolane (XX).—To a solution of 26.3 g. of 2-(1′-carbethoxyamyl)-2-methyl-1,3-dioxolane (XIX) in 150 ml. of absolute alcohol, a total of 23.0 g. of sodium and 170 ml. of absolute alcohol, was added alternately in small portions. When the reaction of sodium with alcohol was complete, 75 ml. of water was added and most of the alcohol was removed under reduced pressure. The organic residue was extracted with ether, washed, and the ether was removed. Distillation of the residue yielded 9.9 g. (48%) of a colorless oil, b. p. 106° at 5 mm.

(C) 2-Hydroxymethyl-8-methyl-8-aza-1,4-dioxaspiro-4,5-decane.[18]—A solution of 1.0 g. of 1-methyl-4-piperidone hydrochloride,[19] 0.65 g. of glycerol, and 25 ml. of chloroform was heated in such a manner that as the chloroform slowly distilled, fresh chloroform was added to maintain constant volume. After two hours, the reaction was stopped and the chloroform was removed *in vacuo*. An excess of 45% potassium hydroxide was added to the residue, and the organic layer was extracted with ether, dried, and distilled. There was obtained 0.5 g. of a light yellow oil, b. p. 104–106° at 1 mm.

A **picrate** of the oil was prepared in ether and was obtained as light yellow crystals, m. p. 154–157°.

Anal. Calcd. for $C_{15}H_{20}N_4O_{10}$: C, 43.27; H, 4.84. Found: C, 43.01; H, 4.83.

(D) 2,2-Dimethyl-4-hydroxymethyl-1,3-dithiolanedisulfone (XXVI).—To a solution of 2.3 g. of 2,2-dimethyl-4-hydroxymethyl-1,3-dithiolane[20] in 5 ml. of acetic acid, there was added dropwise 4.5 ml. of a 30% hydrogen peroxide solution. The mixture was allowed to stand overnight and was then poured into 50 ml. of water. On partial evaporation of the solution crystals separated and they were collected on a filter. Recrystallization of the crude material from a mixture of benzene and hexane yielded 2.4 g. (79%) of white crystals, m. p. 110–112°.

Evidence for the Structure of the Condensation Products of Glycerol and Ketones

(A) Preparation and Hydrolysis of 2-*n*-Hexyl-2-methyl-4-methoxymethyl-1,3-dioxolane.—A solution of 2-*n*-hexyl-2-methyl-4-hydroxymethyl-1,3-dioxolane (39.5 g., 0.195 mole) in toluene (20 ml.) was slowly added to an excess of sodium (0.20 mole) in boiling toluene (100 ml.). After the reaction with sodium was complete, the solution was removed from the excess sodium by decantation and methyl iodide (42.6 g., 0.30 mole) was slowly added with stirring. The reaction mixture was then boiled under reflux for one hour. The sodium iodide, which precipitated, was removed by filtration, the solvent was removed *in vacuo*, and the residue was distilled. There was obtained 22.9 g. (54%) of a colorless oil; b. p. 79° at 1 mm.; $n^{20}D$ 1.4350; d^{20} 0.9364.

Anal. Calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.30; H, 11.76.

Hydrolysis of a sample of 2-*n*-hexyl-2-methyl-4-methoxymethyl-1,3-dioxolane (22.9 g., 0.11 mole) was accomplished by heating it for several hours with 25 ml. of a 1% solution of hydrochloric acid containing sufficient alcohol to produce a homogeneous solution. The alcohol was then removed *in vacuo*, and the solution was extracted with ether to remove any methyl *n*-hexyl ketone present. After neutralization of the solution with lead carbonate followed by filtration, the water was removed *in vacuo* and the residue was distilled. There was obtained 5.4 g. (45%) of a viscous oil; b. p. 63° at 0.05 mm.; $n^{20}D$ 1.4463; d^{20} 1.1138. The oil formed a diphenylcarbamate, m. p. 119–120°. These properties agree well with those reported for α-methyl glycerol ether.[21]

The presence of methyl *n*-hexyl ketone in the ethereal extract was established by formation of the 2,4-dinitrophenylhydrazone, m. p. 57–58°.[22]

(B) Formation of 2-*n*-Hexyl-2-methyl-4-triphenylmethoxymethyl-1,3-dioxolane.—A sample of 2-*n*-hexyl-2-methyl-4-hydroxymethyl-1,3-dioxolane (29.9 g., 0.148 mole) was treated with trityl chloride (42.6 g., 0.148 mole) in anhydrous pyridine (30 ml.) according to the procedure of Seikel and Huntress.[23] The product obtained did not crystallize and could not be distilled without decomposition. Purification was finally effected as follows. The oil was treated with pentane (100 ml.) to precipitate any triphenylcarbinol, the pentane was removed, and the resulting oil was recrystallized from ethanol using a dry-ice cooling-bath. There was obtained 53.0 g. (83%) of a viscous, colorless oil, $n^{21}D$ 1.5607.

Anal. Calcd. for $C_{30}H_{36}O_3$: C, 81.03; H, 8.10. Found: C, 80.79; H, 7.86.

(C) Preparation of 2-*n*-Amyl-2-methyl-4-hydroxymethyl-1,3-dioxolane of Known Structure.—A mixture of 3-(3′,5′-dinitrobenzoxy)-1,2-propanediol[24] (20.0 g., 0.07 mole), methyl *n*-amyl ketone (18.0 g., 0.14 mole), and benzene (70 ml.) was treated in the usual manner for preparing dioxolanes. The residual oil, which resulted, was treated with pentane and cooled to effect crystallization. There was obtained 19.3 g. (73%) of light yellow crystals, m. p. 43–48°. Repeated recrystallization of the crude material from a benzene–hexane mixture gave white crystals, m. p. 56–57°, liquid becomes clear at 60°.

Anal. Calcd. for $C_{17}H_{22}N_2O_7$: C, 53.40; H, 5.76. Found: C, 53.72; H, 5.66.

Since there are two diastereoisomeric forms possible for 2-*n*-amyl-2-methyl-4-(3′,5′-dinitrobenzoxymethyl)-1,3-dioxolane, it seemed probable that the crude product represented a mixture of both forms. Evidence for this was obtained from the fact that a sample of the crude product, which had been crystallized once from acetonitrile and melted at 52–54°, gave as good an analysis (Found: C, 53.59; H, 5.87) as did the highest melting product previously obtained.

Hydrolysis of the 2-*n*-amyl-2-methyl-4-(3′,5′-dinitrobenzoxymethyl)-1,3-dioxolane was carried out on the crude mixture obtained above so that separation of diastereoisomers would not be effected by crystallization

(17) See "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 378.

(18) We are indebted to Dr. L. E. Craig for this experiment.

(19) Craig and Tarbell, THIS JOURNAL, **71**, 465 (1949).

(20) Stocken, *J. Chem. Soc.*, 592 (1947).

(21) Hibbert, Whelen and Carter, THIS JOURNAL, **51**, 303 (1929), give $n^{17}D$ 1.4463, d^{17} 1.1197; and a diphenylcarbamate derivative, m. p. 118–119°.

(22) Allen, *ibid.*, **52**, 2955 (1930).

(23) Seikel and Huntress, *ibid.*, **63**, 593 (1941).

(24) Fairbourne and Foster, *J. Chem. Soc.*, **127**, 2763 (1925).

and so that the hydrolysis product would be comparable for an infrared absorption study to that obtained by direct synthesis. A mixture of 2-*n*-amyl-2-methyl-4-(3′,5′-dinitrobenzoxymethyl)-1,3-dioxolane (9.7 g., 0.25 mole), potassium hydroxide (2.8 g.) and water (100 ml.) was boiled gently for one hour. The basic solution was dried, the ether was removed, and the residual oil was distilled yielding 3.0 g. (62.5%) of a colorless oil; b. p. 70–72° at 0.5 mm., $n^{21}D$ 1.4468, d^{21} 0.988. These physical properties and the infrared absorption spectra of this compound (see Fig. 1) are essentially identical with those obtained for the product from the direct reaction of methyl *n*-amyl ketone and glycerol.

Evidence for the Structure of the Condensation Product of Glycerol and Heptanal

(A) Treatment of the Condensation Product with Trityl Chloride in Pyridine.—The condensation product was treated with trityl chloride in anhydrous pyridine according to the procedure of Seikel and Huntress.[23] The reaction mixture was heated on the steam-bath for five minutes. From 18.8 g. of condensation product there was obtained, after one crystallization from alcohol, 26.0 g. (58%) of white crystals, m. p. 56–58°. This crude material apparently represents a mixture of the diastereoisomeric racemates, which are possible for 2-*n*-hexyl-4-(triphenylmethoxymethyl)-1,3-dioxolane. By repeated recrystallization of this material from alcohol a pure sample of white crystals, m. p. 70–71°, was obtained.

Anal. Calcd. for $C_{29}H_{34}O_3$: C, 80.93; H, 7.90. Found: C, 81.03; H, 7.81.

(B) Preparation of a Sample of 2-*n*-Hexyl-4-hydroxymethyl-1,3-dioxolane of Known Structure

2-*n*-Hexyl-4-(3′,5′-dinitrobenzoxymethyl)-1,3-dioxolane.—A mixture of 25.0 g. of 3-(3′,5′-dinitrobenzoxy)-1,2-propanediol,[24] 18.2 g. of heptanal and 80 ml. of benzene was heated in a flask connected to an ordinary water-eliminator. When the expected quantity of water had separated, the benzene was removed and the residue was triturated with hexane. The fluffy, white crystals, m. p. 65–68°, which separated, were collected on a filter and weighed 16.0 g. (48%). Since this crude material probably represents a mixture of the two possible diastereoisomeric racemates, it was employed without further purification in the hydrolysis experiment described below. Repeated recrystallization of the crude material from a mixture of benzene and hexane gave a pure sample of one of the racemates, m. p. 74–75°.

Anal. Calcd. for $C_{17}H_{22}N_2O_8$: C, 53.41; H, 5.76. Found: C, 53.43; H, 5.67.

2-*n*-Hexyl-4-hydroxymethyl-1,3-dioxolane.—A mixture of 14.0 g. of the crude 2-*n*-hexyl-4-(3′,5′-dinitrobenzoxymethyl)-1,3-dioxolane, m. p. 65–68°, and 90 ml. of a 5% potassium hydroxide solution was boiled under reflux for three hours. The organic layer was then extracted with ether, washed, dried, and the ether was removed. Distillation of the residue yielded 4.0 g. (58%) of a colorless oil; b. p. 80° at 0.2 mm.; $n^{21}D$ 1.4492; d^{21} 0.988; *M* calcd. 50.92; $M_{obsd.}$ 51.05.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.83; H, 10.78.

Summary

Some substituted dioxolanes, dioxaspiranes and dithiolanes of possible interest as agents for effecting muscular paralysis have been prepared. On the basis of chemical evidence and infrared absorption spectra data, the condensation products of glycerol with methyl *n*-amyl ketone and methyl *n*-hexyl ketone have been assigned the structures of 2,2-dialkyl-4-hydroxymethyl-1,3-dioxolanes.

On the basis of similar evidence the condensation product of glycerol and heptanal is thought to be a mixture of which the predominant constituent is 2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane.

ROCHESTER, NEW YORK RECEIVED FEBRUARY 21, 1949

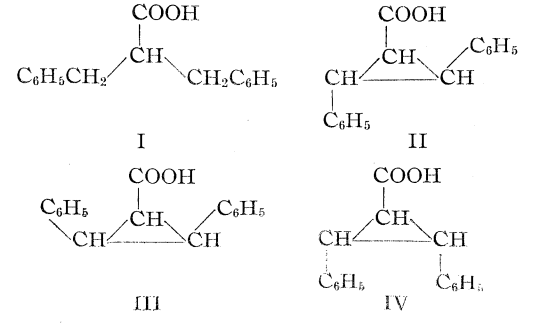
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Analogs of Dibenzylacetic Acid[1]

BY ALFRED BURGER, DIETER G. MARKEES,[2] WILLIAM R. NES[3] AND WILLIAM L. YOST[4]

Certain dialkylaminoalkyl esters of dibenzylacetic acid abolish spasm produced by barium chloride or histamine several times as effectively as papaverine while their atropine-like activity against spasm caused by acetylcholine is generally low.[5] A comparison of analogous compounds in which the benzyl groups have been altered by cyclization or isosteric replacements promised to clarify further this relationship.

The first of our variations of the structure of dibenzylacetic acid (I) was concerned with a steric fixation of the two benzyl carbon atoms by incorporating them in a cyclopropane ring. The required 2,3-diphenylcyclopropanecarboxylic acids were prepared by adding ethyl diazoacetate to *cis*- and *trans*-stilbene, respectively, decomposing the intermediate pyrazoline derivative without isolation, and hydrolyzing the resulting esters. *trans*-Stilbene gave only one racemic acid (II), and only one of the two meso forms (III and IV) expected from *cis*-stilbene could be isolated from the reaction mixture. For further comparison, 2,2-diphenylcyclopropanecarboxylic acid (V) was



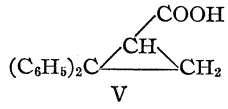
(1) Presented in part before the 114th Meeting of the American Chemical Society, Washington, D. C., August 31, 1948.

(2) Charles C. Haskell Postdoctorate Fellow, 1947.

(3) Du Pont Senior Fellow, 1948.

(4) Smith, Kline and French Fellow, 1947.

(5) Wagner-Jauregg, Arnold and Born, *Ber.*, **72**, 1551 (1939).

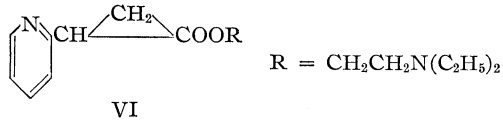


V

prepared from ethyl diazoacetate and 1,1-diphenylethylene.[6] The yields of the cyclopropane derivatives were low in all these cases, perhaps because of the aromatic character of the extracyclic double bond of the starting materials.

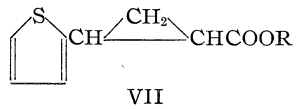
Dialkylaminoalkyl esters of the diphenylcyclopropanecarboxylic acids were prepared where the supply permitted.

We had available in this Laboratory 2-phenylcyclopropanecarbonyl chloride,[7] and converted it to the diethylaminoethyl ester. In an analogous manner, diethylaminoethyl 2-(2-pyridyl)- and 2-(2-thienyl)-cyclopropanecarboxylates were prepared (VI and VII). The acid moieties of these esters were obtained from ethyl diazoacetate and 2-vinylpyridine, and 2-vinylthiophene, respectively, by a series of reactions described for the phenyl prototype.[7]



R = $CH_2CH_2N(C_2H_5)_2$

VI



VII

In order to avoid the formation of stereoisomeric mixtures of these heterocyclic cyclopropanecarboxylic acids, purification through the acid chloride was chosen in each case. Basic esters were prepared from the chlorides and diethylaminoethanol.

This series was not further investigated when a basic ester of 2-phenyl-2-methyl-cyclopropanecarboxylic acid was described recently.[8]

Another approach to analogs of antispasmodics of the dibenzylacetic acid type was sought among basic esters (VIIIa) and amides (VIIIb) of diphenoxyacetic acid.

$(C_6H_5O)_2CHCOR$ VIII

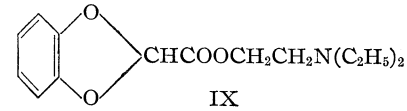
R = (a) $O(CH_2)_nNR_2$
(b) $NH(CH_2)_nNR_2$
(c) Cl

In these compounds, the oxygen atoms replace the isosteric methylene groups of the benzyl radicals. Since diphenoxyacetic acid is the diphenyl acetal of glyoxylic acid and is attacked readily by hydrolytic agents, it was considered possible that esters of the formula VIIIa may exert a short-lived antispasmodic activity which would give place to the antiseptic effect of phenol as the latter is liberated in analogy to Nencki's salol principle.

The preparation of these derivatives offered no difficulty. Diphenoxyacetyl chloride (VIIIc), prepared from the acid and thionyl chloride,[9] reacted smoothly with aminoalcohols and aminoalkyl dialkylamines. The resulting basic esters and amides could not be distilled without decomposition but were isolated as salts or hydrates. They were colorless substances most of which did not crystallize without some effort. Although stable for limited periods of time, they decomposed slowly after several months with a distinct odor of phenol.

It would have been shorter to prepare these basic esters from ethyl diphenoxyacetate by base-catalyzed ester interchange[10] but the materials decomposed at the high temperature of the reaction.

A much lower degree of stability was displayed by diethylaminoethyl *o*-phenylenedioxyacetate (IX) which decomposed in a sealed dark vessel within a few hours and could not be identified by analysis. It shares this instability with phenylenedioxyacetic acid and its simple alkyl esters which are easily hydrolyzed even by dilute alkali.



IX

Pharmacological Observations.—Several of the dialkylaminoalkyl esters described in this paper have been tested by Dr. E. J. Fellows. He reports that none of the phenylacetal-type esters exhibited antispasmodic activity in concentrations of 1×10^{-6} when tested by the isolated intestinal strip method. Only γ-(2-methylpiperidino)-propyl diphenoxyacetate hydrochloride protected guinea pigs from bronchospasm produced by aerosolized histamine in doses devoid of side effects. Several esters of this series (diethylaminoethyl, morpholinoethyl, and γ-(2-methylpiperidinopropyl)), as well as β-morpholinoethyl diphenoxyacetamide caused local anesthesia of a low order for 7.6 to 16.3 minutes when applied topically to rabbits' eyes in a 1% concentration but all of them showed signs of irritation. The same held true for β-diethylaminoethyl 2-phenylcyclopropanecarboxylate.

Acknowledgment.—We are grateful to Smith, Kline and French Laboratories for support of this work, and to Dr. E. J. Fellows of this Company for the pharmacological tests.

Experimental[11]

2-Aryl- and 2-Heteroarylcyclopropane-1-carboxylic Acids and Derivatives. General Procedures.—A mixture of 0.1 mole of the ethylene derivative and 0.1 mole of ethyl diazoacetate, and usually about two volumes of xylene was warmed to 120–130° until evolution of nitrogen began. The reaction proceeded exothermically except in the case of 1,1-diphenylethylene, and was completed by refluxing until no more gas was evolved. The solvent was

(6) Wieland and Probst, *Ann.*, **530**, 274, 289 (1937).
(7) Burger and Yost, THIS JOURNAL, **70**, 2198 (1948).
(8) Tilford, Van Campen and Shelton, *ibid.*, **69**, 2902 (1947).
(9) Scheibler and Baumann, *Ber.*, **62**, 2057 (1929).
(10) Holmes, U. S. Patent 2,399,736 (1946); Hill and Holmes, U. S. Patent 2,394,770 (1946).
(11) All melting points are corrected. Many of the microanalyses have been performed by Clark Microanalytical Laboratory, Urbana, Illinois.

TABLE I

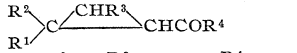
PREPARATION OF SUBSTITUTED CYCLOPROPANECARBOXYLIC ACIDS

Starting ethylene derivative	Ethyl ester of cyclopropane-carboxylic acid formed	Solvent used	Heating, hours	Yield, %, ethyl ester	Hydrolysis, hours	Yield, %, crude acid based on olefin
2-Vinylthiophene	2-(2-Thienyl)	Xylene	1	76	6.5	72
2-Vinylpyridine	2-(2-Pyridyl)	Xylene	0.5	63	10[a]	60
trans-Stilbene	2,3-Diphenyl[b]	....	0.5	..	3	5
cis-Stilbene	2,3-Diphenyl[b]		0.25	..	3	5
1,1-Diphenylethylene	2,2-Diphenyl	Xylene	4	6.7	3	4.5

[a] Hydrolysis in concentrated hydrochloric acid. [b] The ester was not fractionated, the reaction mixture was saponified, and the carboxylic acid separated from non-acidic products.

TABLE II

PHYSICAL PROPERTIES AND ANALYSES OF SUBSTITUTED CYCLOPROPANECARBOXYLIC ACIDS AND DERIVATIVES

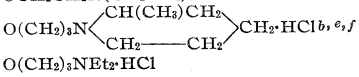


R′	R²	R³	R⁴	Appearance[i]	Crystn. solvent	M. p. or b. p., °C.	Mm.	Formula	Percentage composition Calcd.	Found	Calcd.	Found
C_6H_5	H	H	$OC_2H_4NEt_2$	Oil		161	4.4	$C_{16}H_{23}NO_2$	C, 73.53	73.26	H, 8.87	8.60
						156	3.1					
C_4H_3S[a]	H	H	OC_2H_5	Y. oil[b]		107	3	$C_{10}H_{12}O_2S$	.....	....	.....	..
C_4H_3S[a]	H	H	OH	Nd.	H_2O	124–125		$C_8H_8O_2S$	Mol. wt. 168.2	169.3	.....	..
C_4H_3S[a]	H	H	NH_2	Lf.	H_2O	163–164		C_8H_9NOS	N, 8.38	8.28	.....	..
C_4H_3S[a]	H	H	NHC_6H_5	Nd.	C_6H_6–pet. eth.	119		$C_{14}H_{13}NOS$	N, 5.76	5.67	.....	..
C_4H_3S[a]	H	H	$OC_2H_4NEt_2$	Y. oil		161	2.5	$C_{14}H_{21}NO_2S$	N, 5.24	5.24	.....	..
C_5H_4N[c]	H	H	OC_2H_5	Y. oil		116	3	$C_{11}H_{13}NO_2$	N, 7.33	7.30	.....	..
C_5H_4N[c]	H	H	OC_2H_5 (picrate)	Y. nd.	EtOH	122–124		$C_{17}H_{16}N_4O_9$	N, 13.33	13.28	.....	..
C_5H_4N[c]	H	H	OH	Prisms	C_6H_6–pet. eth.	98–100		$C_9H_9NO_2$	N, 8.58	8.41	.....	..
C_5H_4N[c]	H	H	$OC_2H_4NEt_2$	Y. oil		162–163	2	$C_{15}H_{22}N_2O_2$	N, 10.68	10.38	.....	..
C_6H_5	H	C_6H_5[d]	OH[e]	Nd.	EtOH–H_2O	153–154		$C_{16}H_{14}O_2$	C, 80.65	80.21	5.92	6.00
C_6H_5	H	C_6H_5[d]	NH_2[e]	Nd.	EtOH–H_2O	126.5–127.5		$C_{16}H_{15}NO$	N, 5.90	5.82	.....	..
C_6H_5	H	C_6H_5[d]	NHC_6H_5	Nd.	EtOH–H_2O	191–191.5		$C_{22}H_{19}NO$	N, 4.47	4.71	.....	..
C_6H_5	H	C_6H_5[d]	$OC_2H_4NEt_2$·HCl	Powder	EtOAc	185–188		$C_{22}H_{28}ClNO_2$	N, 3.75	3.82	.....	..
C_6H_5	H	C_6H_5[f]	OH	Oil[g]				$C_{16}H_{14}O_2$	.....	....	.....	..
C_6H_5	H	C_6H_5[f]	NH_2	Nd.	EtOH–H_2O	212–215		$C_{16}H_{15}NO$	N, 5.90	5.68	.....	..
C_6H_5	C_6H_5	H	OC_2H_5	Y. oil[b]					.....	....	.....	..
C_6H_5	C_6H_5	H	OH	Nd.	Ether	166–169[h]		$C_{16}H_{14}O_2$	C, 80.65	80.73	5.92	6.13
C_6H_5	C_6H_5	H	NH_2	Nd.	EtOH–H_2O	178.5–179.5		$C_{16}H_{15}NO$	N, 4.47	4.56		
C_6H_5	C_6H_5	H	NHC_6H_5	Nd.	EtOH	222–223		$C_{22}H_{19}NO$	N, 5.90	5.70		

[a] 2-Thienyl. [b] This ester was not purified for analysis. [c] 2-Pyridyl. [d] *trans*-. [e] First prepared by J. W. Kuck. [f] *cis*-. [g] Neither *cis*-2,3-diphenylcyclopropanecarboxylic acid nor its ethyl ester could be obtained in the pure state. [h] Wieland and Probst[6] reported m. p. 171°. [i] y = yellow; nd = needles; lf = leaflets.

TABLE III

DERIVATIVES OF DIPHENOXYACETIC ACID, $(C_6H_5O)_2CHCOR$

R	Crystn. solvent	M. p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
$N(CH_3)_2$[a]	30% EtOH	84–85	$C_{16}H_{17}NO_3$	...	...	..	..	5.16	5.28
$N(CH_3)_3NEt_2$·HCl[b]	EtOH–EtOAc	64–65	$C_{21}H_{29}ClN_2O_3$	64.19	63.57	7.44	7.61	7.13	7.21
$N(CH_2)_2N(CH_2CH_2)_2O$·HCl	EtOAc	146–148	$C_{20}H_{25}ClN_2O_4$	61.14	60.89	6.37	6.58	7.13	7.00
$OCH_2CH_2N(CH_3)_2$·H_2O	EtOAc[c,d]	108–110	$C_{18}H_{23}NO_5$	64.86	64.78	6.90	6.99	4.20	4.11
$OCH_2CH_2NEt_2$·HCl[e]	EtOAc	144–145	$C_{20}H_{26}ClNO_4$	63.26	63.15	6.85	6.87	3.68	3.67
$OCH_2CH_2NC_5H_{10}$·HCl[e]	EtOH–EtOAc	134–136	$C_{21}H_{26}ClNO_4$	64.35	64.05	6.69	6.62	3.57	3.52
$OCH_2CH_2N(CH_2CH_2)_2O$·HCl	C_6H_6	105–106	$C_{20}H_{24}ClNO_5$	60.98	60.33	6.14	6.09	3.56	3.61
	C_6H_6–Et_2O	79–84	$C_{23}H_{30}ClNO_4$	...	...	...	...	3.52	3.34
$O(CH_2)_3NEt_2$·HCl	C_6H_6	115–117	$C_{21}H_{28}ClNO_4$	64.03	62.63	7.16	7.23	3.56	3.83

[a] Needles. [b] Hygroscopic. [c] The hygroscopic hydrochloride was decomposed with bicarbonate solution, the base extracted into ether, and the solvent allowed to evaporate slowly at room temperature in order to give the hydrated material. [d] The anhydrous ester is liquid, b. p. 165–175° (3 mm., dec.). [e] Flakes. [f] The 3-(α-methylpiperidino)-propanol used in the preparation of this compound was kindly supplied by Eli Lilly & Co.

stripped and the remaining oil was fractionated. The esters were hydrolyzed by refluxing with 3 to 12% ethanolic sodium hydroxide solution for four to six hours, most of the ethanol was removed, non-acidic products were extracted into ether, and the substituted cyclopropanecarboxylic acids were precipitated with hydrochloric acid as solids, or oils which usually solidified soon.

The amphoteric 2-(2-pyridyl)-cyclopropanecarboxylic acid could be obtained by neutralization of the saponification mixture to *p*H 6.6 and continuous extraction with ether. Hydrolysis of the ester with concentrated hydrochloric acid, evaporation of the reaction mixture and recovery of the hydrochloride of the carboxylic acid was more advantageous.

Stereochemically homogeneous samples were produced by boiling the acids with thionyl chloride in benzene solution for two hours, and reconverting the acid chlorides to the acids by hydrolysis with hot water.[7]

The esters, amides and anilides of the acids were prepared from the acid chlorides in benzene solution by treatment with the corresponding reagent.

Basic Esters and Amides of Diphenoxyacetic Acid.—Eight parts of diphenoxyacetic acid[12] was refluxed in benzene solution with seven parts of purified thionyl chloride for six to seven hours, and the mixture was allowed to stand overnight. Benzene and thionyl chloride were stripped under reduced pressure, and the crude acid chloride[9] was used in the next step.

Equivalent amounts of diphenoxyacetyl chloride and the dialkylaminoalkanol, or dialkylaminoalkylamine, respectively, were mixed in benzene solution. After an initial exothermic reaction the hydrochlorides of the reaction products precipitated, and usually solidified after some standing. In selected cases, the bases were liberated with sodium bicarbonate solution, and purified if they were more readily handled than the salts.

Isoamyl *o*-Phenylenedioxyacetate.—The preparation of this ester was patterned on that reported for the ethyl ester.[13] The preparative modification described here produced the isoamyl ester in a yield of 16.7% as compared with 8% reported for the ethyl ester.[14]

To a hot solution of 106 g. of sodium in 1200 cc. of dry isoamyl alcohol was added a suspension of 254 g. of catechol in 250 cc. of isoamyl alcohol with stirring in an atmosphere of nitrogen. The resulting viscous white mass was heated at 120° and treated gradually with 362 g. of ethyl dichloroacetate at such a rate that the exothermic reaction subsided after about one-half of the ester had been added. The reaction mixture became fluid and turned purple. It was refluxed another sixteen hours, 700 cc. of isoamyl alcohol was distilled off at 20 mm. pressure, and the dark viscous residue was dissolved in 2 liters of ether. The ether solution was washed with several liters of an ice-cold calcium chloride solution, and then with two 500-cc. portions of cold 2% sodium hydroxide solution. The dark red ether layer was dried over calcium chloride, the solvent was distilled, and the residual oil was fractionated several times. The colorless fraction boiling finally at 149–152° (20 mm.) weighed 90 g. (16.7%). It consisted of practically pure isoamyl *o*-phenylenedioxyacetate but gave a weak test for catechol. Repeated fractionation to b. p. 122–124° (2 mm.) furnished a satisfactory analytical sample.

(12) Auwers and Haymann, *Ber.*, **27**, 2795 (1894).

(13) Christiansen and Dolliver, THIS JOURNAL, **66**, 312 (1944).

(14) Dolliver, private communication.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78. Found: C, 66.05; H, 7.00.

***o*-Phenylenedioxyacetic Acid.**—A mixture of 13 g. of isoamyl *o*-phenylenedioxyacetate and 75 cc. of 8% sodium hydroxide solution was heated at 90° for forty-five minutes; isoamyl alcohol was extracted with ether, and the colorless solution was acidified and extracted with ether. After drying over sodium sulfate, the solvent was removed, and the residual oil was allowed to crystallize from petroleum ether. The yield of colorless flakes, m. p. 104–106°, was 6 g. (65.6%). The material gave no ferric chloride test for catechol, and did not depress the melting point of an authentic sample[13].

***o*-Phenylenedioxyacetamide.**—When dry ammonia was passed through isoamyl *o*-phenylenedioxyacetate at 100°, the ester became cloudy, and the product cleared and solidified after thirty minutes. The colorless amide crystallized from ether–petroleum ether, m. p. 105–106°. It gave no color test with ferric chloride, and could be hydrolyzed with 25% sodium hydroxide solution at room temperature.

Anal. Calcd. for $C_8H_7NO_3$: N, 8.41. Found: N, 8.62.

The amide could also be prepared in poor yields, from *o*-phenylenedioxyacetyl chloride which was obtained from the acid and thionyl chloride in benzene solution. This acid chloride could not be purified but served also as the starting material for the preparation of the unstable diethylaminoethyl *o*-phenylenedioxyacetate.

Summary

The condensation of several aromatically and heterocyclically substituted ethylene derivatives with ethyl diazoacetate furnished the ethyl esters of the corresponding cyclopropanecarboxylic acids. Dialkylaminoalkyl esters of some of these acids were prepared as potential antispasmodics.

A series of dialkylaminoalkyl diphenoxyacetates and diphenoxyacetamides was prepared for comparison with the isosteric derivatives of dibenzylacetic acid. The chemical stability of the acetal type derivatives of diphenoxyacetic acid was compared with that of similar compounds derived from *o*-phenylenedioxyacetic acid.

CHARLOTTESVILLE, VIRGINIA RECEIVED MARCH 23, 1949

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Synthesis of Some 1-Cyclopentenealdehydes

BY JAMES ENGLISH, JR., AND GEORGE W. BARBER[1]

In many of the possible synthetic approaches[2] to molecules having structures analogous to auxin a[3] substituted 1-cyclopentenealdehydes are necessary starting materials. The preparation of such substances has therefore been undertaken with a view to their eventual utilization in a synthetic program.

1-Cyclopentenealdehyde itself has been prepared by the rearrangement of cyclohexene peroxide[4] and from adipic aldehyde obtained by ozonolysis of cyclohexene.[5] Urion obtained this substance also by treatment of divinylglycol with alumina at 300°.[6] These methods, however, are not easily adapted to the preparation of substituted 1-cyclopentenealdehydes and in our experience have given unsatisfactory yields. The process finally developed is shown in the equations.

The 3-*n*-propyl- and 3,5-di-*n*-propylpyrocatechols were prepared from the corresponding allyl derivatives by hydrogenation; the allyl pyrocate-

(1) Present address: Cox Medical Research Institute, University of Pennsylvania. Taken from a thesis submitted by George W. Barber to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the Ph.D. degree.

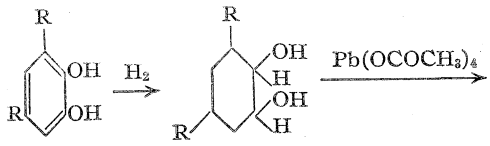
(2) J. English and J. D. Gregory, THIS JOURNAL, **69**, 2123 (1949).

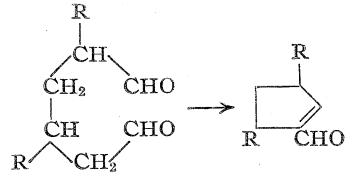
(3) F. Kogl, *Ber.*, **68***A*, 16 (1935).

(4) E. W. Farmer and A. Sundralingham, *J. Chem. Soc.*, 121 (1942).

(5) A. Wohl and H. Schweiger, *Ber.*, **39**, 895 (1906).

(6) E. Urion, *Ann. chim.*, [11] **1**, 5 (1934).





chols in turn were obtained from guaiacol and eugenol, respectively, as described in the literature. Pyrocatechol and its mono- and di-propyl derivatives were hydrogenated with Raney nickel to give the corresponding cyclohexanediols in 84–86% yields. No attempt was made to separate the *cis* and *trans* forms of these compounds, but the redistilled mixtures were oxidized with lead tetraacetate in benzene or chloroform. It was found that by the addition of anhydrous potassium carbonate to the reaction mixture to maintain neutrality, the losses in handling the resulting adipic aldehydes were much decreased in comparison with those experienced in the original procedure of Criegee.[7]

After considerable experimentation the method of Wohl and Schweitzer[5] was found most effective for the cyclization of adipic aldehydes and yields of about 50% of the corresponding 1-cyclopentenealdehyde were obtained directly from the lead tetraacetate oxidation mixture without the necessity of isolating the intermediate adipic aldehydes. In the case of 3,5-di-*n*-propyladipic aldehyde cyclization took place during the oxidation reaction, especially in chloroform solution, and a yield of 80% of 3,5-di-*n*-propyl-1-cyclopentenealdehyde was obtained directly.

The structures proposed for the cyclization products of the 3-*n*-propyl- and 3,5-di-*n*-propyladipic aldehydes are supported by the loss of water of the intermediate aldols during the cyclization. By analogy with other aldol condensations as reported in the literature,[8] no such dehydrations would have been expected if the cyclization had involved the tertiary alpha carbon atom. In analogous base-catalyzed cyclizations of the Dieckmann type a similar phenomenon is observed.[9] Here again a secondary alpha carbon atom rather than a tertiary one seems always to be involved.

Attempts were made to separate the 3,5-di-*n*-propyl-1-cyclopentenealdehyde into its *cis* and *trans* forms. The hydrogenation of pyrocatechol has been found[10] to give a mixture of isomers and similar behavior might have been expected in this case. However, neither extensive fractional crystallization of the semicarbazone or a careful fractional distillation produced any evidence of the existence of significant amounts of an isomer in the purified material. It therefore seems probable that this substance is homogeneous, and that the hydrogenation of disubstituted catechols leads to a predominance of one stereoisomer, probably *trans* with respect to the alkyl groups.

On standing at room temperature all three 1-cyclopentenealdehydes were observed to polymerize, becoming yellow and viscous in the course of a few days. Preliminary experiments indicate that the freshly prepared propyl-1-cyclopentenealdehydes react normally in the Reformatski reaction with ethyl bromoacetate.

Experimental[11]

3-*n*-Propylpyrocatechol.—A mixture of 442 g. of 6-propylguaiacol, b. p. 80–82° at 1.5 mm., prepared from 6-allylguaiacol[12] by hydrogenation with platinum oxide at 50 p. s. i. in ethanol, was refluxed for twelve hours in a solution of 750 g. 48% hydrobromic acid in 1 liter of glacial acetic acid. After removal of the excess hydrobromic acid and solvent the residue was distilled. There was obtained 382 g. (95% of theory) of colorless 3-propylpyrocatechol, b. p. 112–113° at 1.5 mm. On recrystallization from ethanol the product melted at 72°. Kurosawa[13] reported the melting point of this substance as 70–72°.

3,5-Di-*n*-propylpyrocatechol.—Diallylguaiacol, prepared by the method of Claisen and Eisleb[14] was hydrogenated in ethanol with platinum oxide at 60 p. s. i. The product, obtained in quantitative yield was 4,6-di-*n*-propylguaiacol, b. p. 107–108° at 1 mm., $n^{20}D$ 1.5123. A dinitrobenzoate was prepared m. p. 117.5°. *Anal.* Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.13; H, 9.72. A mixture of 208 g. of this product was refluxed with 300 cc. of 48% hydrobromic acid and 800 cc. of glacial acetic acid for eight hours. After evaporation of the residual hydrobromic acid and solvent *in vacuo*, the product was distilled, b. p. 115–120° at 1 mm., as a viscous liquid that slowly crystallized. On recrystallization from petroleum ether (b. p. 30–60°) by cooling in Dry Ice there was obtained 169 g. (87%) of crystalline 3,5-di-*n*-propylpyrocatechol, m. p. 39–40°. The pure product melts at 41.5°.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19, H, 9.34. Found: C, 74.18; H, 9.04.

Hydrogenation of Pyrocatechols.—Pyrocatechol and the above substituted pyrocatechols were hydrogenated in 100 g. batches with 50 cc. of absolute ethanol, 10 g. of Raney nickel and a pellet of sodium hydroxide.[15] The reaction was carried out at about 2000 p. s. i. and at a temperature of 140 to 160°. Six to nine hours were required for complete hydrogenation, the higher homologs requiring the longer times. The products were taken up in petroleum ether, washed with 10% sodium hydroxide to remove any unchanged pyrocatechol, and the residues distilled after evaporation of the solvent. The properties and yields of the mixtures of stereoisomeric cyclohexanediols obtained were:

	B. p. °C.	Mm.	Yield, %	M. p., °C.
1,2-Cyclohexanediols[16]	110–115	5	84	72–80

(7) R. Criegee, *Ber.*, **64**, 264 (1931).

(8) A. Lieben, *Monatsh.*, **22**, 289 (1901).

(9) W. Dieckmann, *Ann.*, **317**, 27 (1901); A. Kötz and P. Schuller, *Ann.*, **350**, 234 (1906); R. Cornubert and C. Bonel, *Bull. soc. chim.*, [4] **47**, 300 (1930).

(10) L. W. Covert, R. Connor and H. Adkins, THIS JOURNAL, **54**, 1658 (1932).

(11) All melting and boiling points are corrected.

(12) L. Claisen, *Ber.*, **45**, 3161 (1912).

(13) J. Kurosawa, *ibid.*, **48**, 1603 (1915).

(14) L. Claisen and O. Eisleb, *Ann.*, **401**, 21 (1913).

(15) H. E. Ungnade and D. V. Nightingale, THIS JOURNAL, **66**, 1218 (1944).

(16) Amatatsu, *J. Chem. Soc. Japan*, **52**, 585 (1931); *Chem. Abstr.*, **26**, 5084 (1931).

	B. p. °C.	Mm.	Yield, %	M. p. °C.
3-*n*-Propyl-1,2-cyclohexanediols	121–122	4	87	
3,5-Di-*n*-propyl-1,2-cyclohexanediols	135–150	2	86	

Adipic Aldehyde.[7]—Twenty grams (0.17 mole) of the above 1,2-cyclohexanediol preparation was dissolved in 200 cc. of dry benzene and 50 g. anhydrous potassium carbonate added. The mixture was stirred vigorously while 76 g. (0.17 mole) of lead tetraacetate was added in 5 g. portions over the course of one hour. A nitrogen atmosphere was maintained during the addition and subsequent distillations. The mixture was stirred for an additional hour after the addition was complete and then filtered. The mixture of salts was extracted thoroughly with benzene and the combined filtrates dried briefly over sodium sulfate. The benzene was then removed in vacuum and the product distilled. There was obtained 13.4 g. (68%) of colorless adipic aldehyde, b. p. 68–70 at 3 mm., $n^{20}D$ 1.4350. There was always observed a higher boiling fraction of polymerized material and a non-volatile residue.

1-Cyclopentenealdehyde.[5]—Nineteen grams of freshly distilled adipic aldehyde was heated with 115 cc. of distilled water in a bomb at 110° for five hours. After cooling, the solution was then extracted thoroughly with ether and the product isolated by distillation. There was obtained 10 g. of 1-cyclopentenealdehyde (62%), b. p. 57–59° at 23 mm., $n^{20}D$ 1.4866.

An over-all yield of 52% was obtained by treating the crude adipic aldehyde as obtained above on evaporation of solvent with water at 110° in the same manner. The product in both cases polymerized on standing. Urion reported the properties of this substance as: b. p. 48° at 11 mm., $n^{20}D$ 1.4828.

2-*n*-Propyladipic Aldehyde.—The 3-*n*-propylcyclohexane-1,2-diol mixture described above (30 g.) was oxidized in the same manner as described above for cyclohexanediol. There was obtained 19.5 g. (68%) of 2-*n*-propyladipic aldehyde, b. p. 124–127° at 15 mm. Careful fractionation gave a product b. p. 83° at 2 mm., $n^{20}D$ 1.4478, d_{20} 0.9580; molecular refraction calcd., 43.8; found, 43.6.

The 2,4-dinitrophenylhydrazone prepared in the usual manner melted at 178–179° after recrystallization from glacial acetic acid.

Anal. Calcd. for $C_{21}H_{24}N_8O_8$: C, 48.84; H, 4.68. Found: C, 49.42; H, 4.63.

2-*n*-Propyladipic acid[17] was prepared by heating 5.2 g. of 2-*n*-propyladipic aldehyde in 100 cc. of water and 50 cc. of alcohol with 20 g. of fresh silver oxide and 3 g. of sodium hydroxide. After two hours of refluxing and stirring the mixture was filtered and extracted with ether. After acidification with hydrochloric acid, the solution was again extracted with ether yielding, on removal of the solvent, an oil that crystallized partially after standing some time. On recrystallization from petroleum ether (b. p. 30–60°) 2-*n*-propyladipic acid m. p. 53–54° was obtained.

Anal. Calcd. for: $C_9H_{16}O_4$: C, 57.43; H, 8.57; neut. equiv., 94.1. Found: C, 57.38; H, 8.55; neut. equiv., 95.1.

3-*n*-Propyl-1-cyclopentenealdehyde.—A 63% yield of this substance was obtained from 15 g. of 2-propyladipic aldehyde by the procedure described above for 1-cyclopentenealdehyde. By treating the undistilled 2-propyladipic aldehyde directly with water at 110° as described above, an over-all yield of 52% of 3-propyl-1-cyclopentenealdehyde b. p. 86–88° at 15 mm. was obtained. The semicarbazone prepared in the usual manner and recrystallized from dilute ethanol melted at 188–189°.

Anal. Calcd. for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.58; H, 8.86; N, 20.91.

Steam distillation of a mixture of 7.8 g. of this semicarbazone with 7 g. of oxalic acid in 200 cc. of water yielded pure 3-*n*-propyl-1-cyclopentenealdehyde (3.5 g.), b. p. 54–55° at 2 mm., $n^{20}D$ 1.4780; d_{20} 0.9285; molecular refraction calcd. 41.11, found 42.13 (exaltation 2.5%). The 2,4-dinitrophenylhydrazone was obtained by crystallization from dilute alcohol as bright red needles, m. p. 149°.

3,5-Di-*n*-propylcyclopentenealdehyde.—Oxidation of 50 g. of the 3,5-di-*n*-propylcyclohexane-1,2-diol mixture in 300 cc. of dry chloroform containing 40 g. of anhydrous potassium carbonate in the same manner as described for the oxidation of cyclohexanediol, yielded on distillation 35.9 g. (80%) of 3,5-di-*n*-propyl-1-cyclopentenealdehyde b. p. 106–107° at 3.5 mm., $n^{20}D$ 1.4730. Under these conditions there seemed to be little if any of the di-*n*-propyl adipic dialdehyde formed. When benzene was substituted for chloroform, the details being otherwise the same, there was obtained 24.8 g. of material boiling at 95–120° at 2 mm.; refractionation yielded in addition to 3,5-di-*n*-propylcyclopentenylformaldehyde about 3 g. of a higher fraction, b. p. 112° at 2 mm., $n^{20}D$ 1.4554, which was presumably the di-*n*-propyladipic dialdehyde. This fraction was not further investigated. The semicarbazone, prepared in dilute alcohol and recrystallized from alcohol, melted at 124.5–125°.

Anal. Calcd. for $C_{13}H_{23}N_3O$: C, 65.79; H, 9.77; N, 17.71. Found: C, 65.72; H, 9.55; N, 17.57.

An attempt at separation of the possible stereoisomers by fractional crystallization of the semicarbazones yielded only the product described above and a small amount of non-crystalline oil. This oil may have contained other isomeric forms, but has not been investigated further. Careful fractional distillation of 35 g. of freshly prepared 3,5-di-*n*-propylcyclopentenylformaldehyde yielded an apparently homogeneous product, b. p. 89–90° at 3.5 mm., n 1.4735 to 1.4740; a total of 19 fractions were collected arbitrarily from a 40 cm. column packed with steel helices (about 25 theoretical plates) and 24.5 g. of material fell within the range given above. The remainder was largely polymerized residue in the still pot. Semicarbazones from these fractions melted at 124–125° as before. On standing at room temperature the free aldehyde became viscous due to polymerization.

Ethyl 3-(3-*n*-Propyl-1-cyclopentenyl)-3-hydroxypropionate.—A solution of 9 g. of 3-*n*-propyl-1-cyclopentenealdehyde and 16.7 g. of ethyl bromoacetate in a mixture of 16 cc. of dry benzene and 4 cc. of ether was added slowly under nitrogen to 7 g. of activated[18] zinc dust. The rate of addition was adjusted to maintain gentle reflux. After the addition the mixture was heated for one hour, the excess zinc removed and 100 cc. of ether added. The mixture was shaken alternately with dilute sulfuric acid and sodium bicarbonate until no cloudiness appeared on bicarbonate treatment and the product finally distilled under reduced pressure. After careful fractionation 6.6 g. (45%) of pure ethyl 3-(3-*n*-propyl-1-cyclopentenyl)-3-hydroxypropionate, b. p. 128 at 2 mm., $n^{20}D$ 1.4688, d_{20} 0.9975 was obtained.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.46; H, 9.93.

Ethyl 2-(3,5-Di-*n*-propyl-1-cyclopentenyl)-3-hydroxypropionate.—This ester was prepared in the same way from 3,5-di-*n*-propylcyclopentenealdehyde and ethyl bromoacetate. The ester, obtained in 50% yield, was carefully fractionated in vacuum. Pure ethyl (3,5-di-*n*-propyl-1-cyclopentenyl)-3-hydroxypropionate boiled at 124° at 1 mm., $n^{20}D$ 1.4686, d_{20} 0.9688.

Anal. Calcd. for $C_{16}H_{28}O_3$; C, 71.60; H, 10.52. Found: C, 70.69; H, 10.17.

The free acids corresponding to both of the above hydroxy esters were prepared by hydrolysis in alcoholic potassium hydroxide at room temperature. Both were obtained as liquids which defied attempts at crystallization. The product obtained from the monopropyl analog gave

(17) J. W. Mellor, *J. Chem. Soc.*, **79**, 131 (1901).

(18) R. L. Shriner, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. I, p. 16.

evidence of containing some lactone. The nature of these compounds will be further investigated.

Summary

A practical synthesis of substituted 1-cyclopentenealdehydes has been developed and applied to 1-cyclopentenealdehyde, 3-*n*-propyl-1-cyclopentenealdehyde and 3,5-di-*n*-propyl-1-cyclopentenealdehyde.

The substituted 1-cyclopentenealdehydes have been shown to undergo the Reformatski reaction.

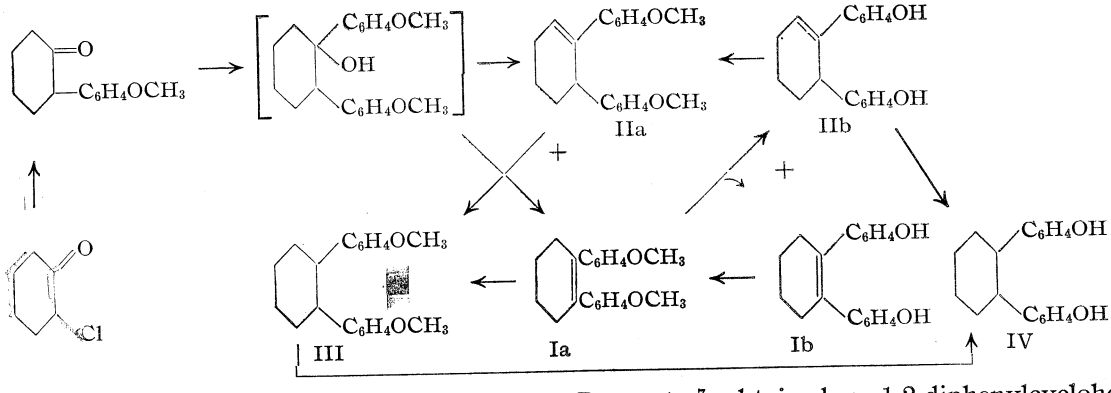
NEW HAVEN, CONNECTICUT RECEIVED MARCH 17, 1949

[CONTRIBUTION NO. 67 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Synthesis of Cyclohexestrol[1]

BY GEORGE P. MUELLER AND ROY MAY[2]

Much of the search for new synthetic estrogens has consisted either of substituting groups within the essentially intact hexestrol skeleton, or of building other structures also supposedly capable of simulating the nuclear form of the estrogenic hormone. The synthesis of the cyclohexane analog, for which previous attempts have been reported,[3] has been completed.



The formation of 2-substituted cyclohexanones from 2-chlorocyclohexanones has been studied more recently by Mousseron[4] and by Newman[5] who have shown that the alkyl or aryl group from an attacking Grignard reagent may become attached either to the carbonyl or the halogen-bearing carbon. Our results indicate further either that a 2-substituted cyclohexanone or cyclohexene oxide is formed and subject to further attack as in the formation of tertiary alcohols from carboxylic esters, or that the halogen-bearing and carbonyl carbons are attacked simultaneously. Thus, although clean separations of products were difficult, a 2:1 mole ratio of *p*-methoxyphenylmagnesium bromide to 2-chlorocyclohexanone favored the formation of bis-(*p*-methoxyphenyl)-cyclohexenes, Ia and IIa, over that of 2-*p*-methoxyphenylcyclohexanone,[6] and conversely for a 1:1 ratio.

The mixture of cyclohexenes must have been formed by spontaneous dehydration during the reaction or on hydrolysis of the magnesium salts, since the isomer Ia was on one occasion crystallized directly from the crude products before application of the usual dehydrating conditions.

Parmerter[7] obtained a 1,2-diphenylcyclohexene after dehydrating the crude hydrolysis product from phenylmagnesium bromide and 2-phenylcyclohexanone, but he did not confirm the actual presence of a carbinol. Further evidence of the activating effect of the *p*-methoxyphenyl group in this connection was observed during a synthesis of 2-*p*-methoxyphenylcyclohexanone through perbenzoic acid oxidation of 1-*p*-methoxyphenylcyclohexene. Here, distillation of the acid-free oxidation product to purify the 1-*p*-methoxyphenylcyclohexene oxide yielded instead the cyclohexanone. 1-Phenylcyclohexene oxide was reported however as being purified in this way and requiring acid catalysis to effect the rearrangement.[8]

Two bis-(*p*-methoxyphenyl)-cyclohexenes, Ia and IIa, were isolated and separately hydrogenated to the same cyclohexane, III, which was demethylated in alcoholic alkali to 1,2-bis-(*p*-hydroxyphenyl)-cyclohexane IV. We have called

(1) The main portion of this paper was presented at the American Chemical Society meeting at Washington, D. C., September, 1948.

(2) Present address: T. V. A., Health and Safety Dept., Wilson Dam, Alabama.

(3) (a) Price and Mueller, THIS JOURNAL, **66**, 628 (1944); (b) **66**, 632 (1944).

(4) Mousseron, Granger, Winternitz and Combes, *Bull. soc. chim.*, 610 (1946).

(5) Newman and Booth, *J. Org. Chem.*, **12**, 737 (1947).

(6) Shortly after its preparation in this laboratory this ketone was reported by Bachmann and Wick at the American Chemical Society Meeting, Chicago, Ill., 1948.

(7) Parmerter, THIS JOURNAL, **71**, 1127 (1949).

(8) Sherwood, Short and Woodcock, *J. Chem. Soc.*, 323 (1936).

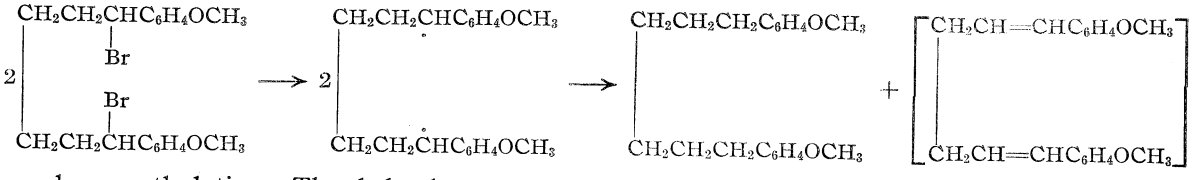
the latter "cyclohexestrol," although its low physiological activity may, perhaps, not warrant such a cognomen. Similar demethylation of the cyclohexene, Ia, gave both of the phenolic cyclohexenes, Ib and IIb, identified with the methoxy-isomers by remethylation. The skeletal structure of the series was confirmed through dehydrogenation of the mixed bis-(*p*-methoxyphenyl)-cyclohexenes to 4′,4″-dimethoxy-*o*-terphenyl.[3b]

Placement of the double bond in the isomeric series, I and II, as shown is provisional. It seems likely that the carbinol intermediate would have a *trans* configuration favorable to the formation of Ia, as the preponderant isomer, by *trans* elimination of water.[9] Conflicting evidence arises from the appearance of the two phenolic cyclohexenes during alkaline demethylation at 200° of the isomer Ia. If there were not some doubt, arising from isolation difficulties and hence the qualitative nature of the experiment, one could only conclude that migration of the bond from the unsymmetrical to the symmetrical and completely conjugated position had occurred.[10] Establishment of these structures through oxidation studies is continuing.

The two phenolic cyclohexenes as well as cyclohexestrol were tested and found to possess definite, though weak, estrogenic activity. Whether the latter has the *dl* or *meso* configuration can only be inferred from hydrogenation experiments with diethylstilbestrol.[11] Up to this date the compound has eluded resolution.

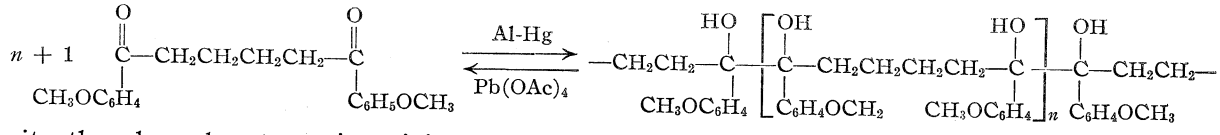
Several attempts to synthesize cyclohexestrol by ring-closure of 1,6-bis-(*p*-methoxyphenyl)-hexane derivatives were unsuccessful but yielded curious results which illustrate the steric resistance offered by aryl substituents on the carbons to be joined. The methods tried were analogous to those previously used in preparing hexestrol, dienestrol and related compounds.[12]

Treatment of 1,6-bis-(*p*-methoxyphenyl)-1,6-dibromohexane with phenylmagnesium bromide and cobaltous chloride was expected to produce a 1,6-diradical and then a 1,2-bis-(*p*-methoxyphenyl)-cyclohexane. We submit that while the mechanism of free radical formation here was that previously suggested, the disposition of the radical itself may rather be the result of a disproportionation.[13]



The isolation and positive identification of 1,6-bis-(*p*-methoxyphenyl)-hexane, aside from the ever-present biphenyl and *p*-terphenyl, was all that could be accomplished with the intractable, highly unsaturated products. Again, treatment of the dibromohexane with sodium, magnesium and sodium amide led in each case to unsaturated oils from which no recognizable compound could be isolated.

Another approach to the ring-closure was the aluminum-amalgam reduction of 1,4-bis-(*p*-methoxybenzoyl)-butane to the anticipated 1,2-bis-(*p*-methoxyphenyl)-1,2-dihydroxycyclohexane.[14] Similar cyclic 1,2-diaryl pinacols have been formed in which the ring was already extant.[15] Only a polymeric product was recovered, however, despite attempts to isolate crystalline material from the purification liquors. This resin was poly-1,6-bis-(*p*-methoxyphenyl)-1,6-dihydroxyhexamethylene, as shown by its rapid and quantitative oxidation with lead tetraacetate to the original 1,6-diketone.



The formation of this interesting polypinacol under such mild conditions and the facile reversal of the reductive-polymerization offers attractive possibilities. The study of this reaction and of the chemical and physical properties of the product is continuing.

Experimental

Reduction of 1,4-bis-(*p*-Methoxybenzoyl)-butane.—1,4-bis-(*p*-Methoxybenzoyl)-butane, 25.0 g., was hydrogenated in 125 ml. of ethyl alcohol over copper-chromium oxide at 2000 p. s. i. and 100°, giving 22.4 g. of crystalline material, m. p. 100–140°. After three recrystallizations from methyl alcohol the melting point was 132–150°. Similar mixtures were obtained by using Raney nickel at 2000 p. s. i. and 130°. Aluminum isopropoxide reduction of 9.9 g. of the diketone and recrystallization of the product once from benzene gave 7.5 g. of solid, m. p. 105–140°. In order to confirm the reduction work, 48.6 g. of magnesium turnings, 216 g. of freshly-distilled tetramethylene bromide and 408 g. of anisaldehyde were treated in a man-

(9) Price and Karabinos, THIS JOURNAL, **62**, 1159 (1940).
(10) Farmer, *Trans. Faraday Soc.*, **38**, 356 (1942).
(11) Wessely and Welleba, *Ber.*, **74**, 777, 785 (1941).
(12) (a) Kharasch and Kleiman, THIS JOURNAL, **65**, 491 (1943); (b) Docken and Spielman, *ibid.*, **62**, 2163 (1940); (c) Bernstein and Wallis, *ibid.*, **62**, 2871 (1940); (d) Kharasch, Nudenberg and Fields, *ibid.*, **66**, 1276 (1944).
(13) Kharasch, Sayles and Fields, *ibid.*, **66**, 481 (1944).
(14) *Cf.* (a) Dodds, Golberg, Lawson and Robinson, *Nature*, **141**, 247 (1938); (b) Newman, THIS JOURNAL, **62**, 1683 (1940); (c) Niederl and Silverstein, *J. Org. Chem.*, **14**, 10 (1949).
(15) Maitei and Bogdan, *Ber.*, **67B**, 1834 (1934).

ner similar to that of Schmidt,[16] yielding 100 g. of the 1,6-glycols, m. p. 115–138°, after two recrystallizations from ethyl alcohol. Oxidation of 3.3 g. of such a product with 10 g. of concentrated sulfuric acid, 5 g. of potassium dichromate and 20 ml. of water at 100° for twenty-five minutes yielded 1 g. of 1,4-bis-(*p*-methoxybenzoyl)-butane, identified through mixed melting points of the diketone and its oxime with authentic samples. The glycols, therefore, were mixtures of *dl* and *meso* forms of 1,6-bis-(*p*-methoxyphenyl)-1,6-dihydroxyhexane.

1,6-bis-(*p*-Methoxyphenyl)-1,6-dibromohexane.—The mixture of 1,6-bis-(*p*-methoxyphenyl)-1,6-dihydroxyhexanes, 5 g., was suspended in 20 ml. of dry benzene and dry hydrogen bromide was introduced, causing solution of the glycol accompanied by slight warming. The water formed was removed and the solution cooled overnight; the white, crystalline powder was collected and weighed 5.5 g.; m. p. 99–102°. An additional recovery by concentrating the benzene solution *in vacuo* made the total yield 6.2 g. (88%). This bromide, recrystallized from anhydrous ether, melted at 102–103° with decomposition.

Anal. Calcd. for $C_{20}H_{24}O_2Br_2$: C, 52.65; H, 5.30. Found: C, 52.84; H, 5.36.

At room temperature the bromide decomposed in a few days, but was stable for several months under refrigeration. A dark green oil was the impurity associated with the bromide, either accompanying certain preparations or appearing on decomposition after standing or melting. Since the pure bromide was not greatly soluble in boiling ether, although more so in ether–acetone mixtures, from which it crystallized less completely, purification for preparative purposes was best accomplished by washing with a very little cold acetone and several times with ether. The colored material was thus removed, leaving generally 85–90% of white crystalline material from very impure-looking preparations. Decomposition accompanied attempts to recrystallize from hot benzene or ethyl alcohol. A pure sample precipitated silver bromide instantly from alcoholic silver nitrate.

The oily residues remaining from crystallization of the solid 1,6-glycols yielded 76% of the same pure dibromohexane.

1,6-bis-(*p*-Methoxyphenyl)-1,6-dichlorohexane.—The mixture of solid 1,6-glycols, 10 g., was suspended in 20 ml. of dry benzene and 20 ml. of petroleum ether (b.p. 95–96°); 8 g. of thionyl chloride was added and the solution warmed gently at reflux for forty-five minutes until gas evolution had ceased and the solid dissolved. After cooling overnight 7.2 g. (65%) of gray-white crystals were collected; m. p. 105–108°. After five recrystallizations from dry ether the dichlorohexane melted at 108–112°, or up to 116° upon rapid heating, with decomposition. *Anal.* Calcd. for $C_{20}H_{24}O_2Cl_2$: C, 65.40; H, 6.59. Found: C, 65.35; H, 6.79. It gave instantaneous precipitation in alcoholic silver nitrate. As before, the oily 1,6-glycols by the same procedure yielded 53% of the dichloro compound.

Attempts to Cyclize 1,6-bis-(*p*-Methoxyphenyl)-1,6-dibromohexane.—Using a procedure similar to that of Kharasch and Kleiman for coupling anethole hydrobromide,[11] the dibromohexane, 22.8 g., was suspended in 300 ml. of dry benzene and 300 ml. of dry ether. This suspension was added to a solution of 75 ml. of phenylmagnesium bromide (0.15 mole) in ether which had previously been treated with 1.0 g. of freshly-fused, powdered cobaltous chloride and cooled in ice–hydrochloric acid. The cooling bath was then removed, stirring continued five hours at room temperature and the mixture finally decomposed with 300 g. of ice and 10 ml. of concentrated hydrochloric acid. The dried ethereal extracts yielded 23.2 g. of an oil which was distilled to give 8.1 g. of biphenyl, b. p. 107–120° (8–11 mm.), m. p. 69–70° and 10.13 g. of an oil, b. p. 210–250° (1 mm.). Subjection of the latter fraction to a long series of distillations and crystallizations from toluene, ether, ligroin and methyl alcohol permitted isolation of 0.4 g. of *p*-terphenyl, m. p. 209–211°, and 0.5 g. of 1,6-bis-(*p*-methoxyphenyl)-hexane, m. p. 70.1–72.5°. The mixed melting points of the latter with biphenyl and with 1,2-bis-(*p*-methoxyphenyl)-cyclohexane (see below) were depressed, but not with a synthetic sample of the known 1,6-bis-(*p*-methoxyphenyl)-hexane,[17] for which compound the analysis also was correct.

Pinacol Reduction of 1,4-bis-(*p*-Methoxybenzoyl)-butane.—A suspension of 25 g. of the diketone in 400 ml. of moist ethyl acetate was added to 9.5 g. of aluminum foil, freshly amalgamated. The temperature remained at 38° with stirring, for two hours as the reaction proceeded slowly, then rose to 48° and finally had dropped back to 30° after four hours. The mixture was worked up in the usual way, the organic solution dried over anhydrous magnesium sulfate and evaporated *in vacuo* leaving 20.7 g. of a tan-colored glass, soluble in warm ethyl acetate and precipitated therefrom by benzene or petroleum ether. The product was not soluble in methyl alcohol, ethyl alcohol or acetone. It was dissolved in 100 ml. of ethyl acetate and the resulting solution filtered into 250 ml. of methyl alcohol. The freshly precipitated polymer was gummy, but on standing in the mother liquors became friable and when dried resembled colorless rosin. The dry polymer was introduced into 100 ml. of ethyl acetate where it first swelled, then formed a gel and finally dissolved on heating; it was precipitated again in 250 ml. of methyl alcohol, collected and dried. The powdered polymer was hygroscopic and difficult to dry to a constant weight even over phosphorus pentoxide. It melted at 170–185° with foaming until residual moisture had evaporated. The viscous amber liquid cooled to form a brittle glass. *Anal.* Calcd. for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 72.03; H, 7.39; redried: C, 72.14; H, 7.64. The finely-powdered polymer, 0.66 g. (0.002 mole), and 0.90 g. (0.002 mole) of lead tetraacetate gave a heavy, insoluble suspension in 5 ml. of glacial acetic acid. However, on stirring, the entire mass was brought into solution in two minutes. After centrifuging to remove traces of insoluble matter, this was poured into cold water and the precipitated solid collected and dried, giving 0.66 g. of ketone. This was recrystallized twice from ethyl acetate and melted at 144.0–146.0°, not depressing the melting point of an authentic sample of 1,4-bis-(*p*-methoxybenzoyl)-butane.

2-(*p*-Methoxyphenyl)-cyclohexanone.—The procedure used previously in preparing phenylmethylcyclohexanones served as a guide.[5] 2-Chlorocyclohexanone,[18] 41 g. (0.31 mole), in 100 ml. of dry ether was added with stirring and cooling to the Grignard reagent prepared from 56 g. (0.30 mole) of *p*-bromoanisole and 7.55 g. (0.31 mole) of magnesium in 100 ml. of ether. Xylene, 155 ml., was added to the mixture on the next day and ether distilled away until the internal temperature reached 95–100°, when heating was continued at total reflux with stirring for eight hours. The cooled mixture was hydrolyzed with ammonium chloride solution and the organic layer removed, washed, dried and distilled, yielding 19.9 g. (33%) of 2-(*p*-methoxyphenyl)-cyclohexanone; b. p. 156–166° (1 mm.), m. p. 88.5–89.5° after crystallization from ligroin. *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.01, 75.97; H, 7.65, 7.77. This ketone failed either to form a bisulfite addition compound or to react with Schiff reagent. It did react slowly with Fehling solution and the usual ketone reagents. The 2,4-dinitrophenylhydrazone was prepared and recrystallized three times from ethyl alcohol; m. p. 143–144°. *Anal.* Calcd. for $C_{19}H_{20}O_5N_4$: C, 59.37; H, 5.25. Found: C, 59.10; H, 5.25. Its structure was confirmed by oxidizing 1.0 g. of the ketone suspended in 25 ml. of water and heated to 90° with the dropwise addition of 1.0 g. of potassium permanganate in 25 ml. of water. The cooled solution was extracted with ether and the residual ether removed from the aqueous solution which was then acidified with dilute sulfuric acid and permitted to stand in the cold until crystallization of the δ-(*p*-methoxy-

(16) Schmidt, *Ann.*, **547**, 103 (1941).

(17) Plant and Tomlinson, *J. Chem. Soc.*, 1092 (1935).

(18) Newman, Farbman and Hipsher, *Org. Syntheses*, **25**, 22 (1945).

benzoyl)-valeric acid was complete. This was collected and recrystallized successively from alcohol and ethyl acetate; 0.5 g., m. p. 127.0–127.5°,[17] neutral equivalent 238 (calcd., 236).

Another preparation of 2-(*p*-methoxyphenyl)-cyclohexanone involved oxidation of 1-(*p*-methoxyphenyl)-cyclohexene[19] with perbenzoic acid in chloroform solution. However, the oxidation products from 19.3 g. were oily and yielded as crystalline products 2 g. of an unidentified substance, m. p. 122–124° [*Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.65, 73.51; H, 6.77, 6.62] and only 2 g. of the desired cyclohexanone after distillation at 3 mm. of the unpurified oxide intermediate.

The bis-(*p*-Methoxyphenyl)-cyclohexenes, Ia and IIa.—A solution of 19 g. (0.093 mole) of 2-(*p*-methoxyphenyl)-cyclohexanone in 300 ml. of dry ether was added to the Grignard reagent prepared from 18 g. (0.096 mole) of *p*-bromoanisole and 2.34 g. (0.096 mole) of magnesium in 40 ml. of ether, slowly, to maintain gentle refluxing. The mixture stood overnight, was hydrolyzed with ammonium chloride solution and the crude product recovered as an oil from the dry ethereal extract. This oil was heated at reflux for one hour with 20 g. of acetic anhydride. Removal of the excess anhydride and acetic acid left an oil, separable into 10.9 g. of viscous, greenish-yellow oil, b. p. 209–214° (1 mm.), crystallizing slowly on dilution with alcohol. The yield was 9.1 g. (33%) of crystalline product, m. p. 75–87°. Microscopic observation showed two crystal forms present after eight recrystallizations from ethyl alcohol, which raised the melting point to 86–88°. The analysis was correct for a mixture of bis-(*p*-methoxyphenyl)-cyclohexenes; this mixture was almost entirely the isomer Ia with very little IIa.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.54. Found: C, 81.30, 81.46; H, 7.39, 7.44.

In an alternative preparation 21 g. (0.16 mole) of 2-chlorocyclohexanone in 50 ml. of dry ether was added to the Grignard reagent prepared from 61 g. (0.32 mole) of *p*-bromoanisole and 7.9 g. (0.32 mole) of magnesium in 100 ml. of ether; 150 ml. of xylene was used in the manner described above. After hydrolysis and separation, the dried xylene extracts were treated with 10 ml. of acetic anhydride for three hours at room temperature and the solvent and acetic acid removed *in vacuo*. Fractional distillation yielded 2.1 g. (6.4%) of 2-(*p*-methoxyphenyl)-cyclohexanone and 17.8 g. of green oil, b. p. 210–215° (1 mm.), of which 9.2 g. (19.7%) crystallized readily from alcohol. This was the principal product, melting at 88.5–90.0° (micro)[20] after three recrystallizations. This was bis-(*p*-methoxyphenyl)-cyclohexene, Ia.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.54. Found: C, 81.44; H, 7.43.

The mother liquors from purification of the isomer Ia yielded 0.25 g. of the other isomer, m. p. 88.0–89.5° (micro) after five crystallizations from alcohol. This was bis-(*p*-methoxyphenyl)-cyclohexene, IIa; a mixture of equal weights of Ia and IIa melted at 67–86°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.54. Found: C, 81.57; H, 7.49.

In an attempt to isolate the intermediate, 1,2-bis-(*p*-methoxyphenyl)-cyclohexanol, the acetic anhydride treatment was omitted, but instead the heavy oil remaining after removal of the xylene *in vacuo* allowed to stand until partly crystallized. With the aid of petroleum ether some crystals were freed from oil and purified from methyl alcohol. They proved to be the cyclohexene, Ia.

Dehydrogenation of 0.3 g. of the mixture of cyclohexenes, m. p. 75–87°, was accomplished by heating with 0.065 g. of sulfur for five hours at 200–250°. Zinc dust was added at 250° to destroy excess sulfur and the melt cooled and extracted with hot methyl alcohol. The recovery of white needles, m. p. 103–105° was 0.14 g.; when purified further from methyl alcohol this product melted at 105–106° and did not depress the melting point of 4′,4″-dimethoxy-*o*-terphenyl.[3b]

The bis-(*p*-Hydroxyphenyl)-cyclohexenes, Ib and IIb.—A solution of 3.0 g. of bis-(*p*-methoxyphenyl)-cyclohexene, Ia, m. p. 86–88°, in 25 ml. of ethyl alcohol and 10 g. of potassium hydroxide was heated in a steel autoclave at 200–210° for twenty-four hours.[13a] Acidification of the cooled, diluted solution precipitated 2.65 g. (98%) of crude phenols, m. p. 165–220°. Fractional crystallization from methyl alcohol finally gave two pure products, the first isolated being bis-(*p*-hydroxyphenyl)-cyclohexene, IIb, 0.4 g., crystallizing in long needles and subliming into short staffs at 224° just before melting at 226.6–228.6° (micro). *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.18; H, 6.81. Found: C, 81.14; H, 6.77. The diacetate resulted from heating 50 mg. of the phenol with 2 ml. of acetic anhydride and 0.1 g. of fused sodium acetate. It was purified from methyl alcohol; m. p. 149.0–150.4° (micro). *Anal.* Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.07; H, 6.65. This phenolic cyclohexene, IIb, did not depress the melting point of 4′,4″-dihydroxy-*o*-terphenyl. However, 4′,4″-diacetoxy-*o*-terphenyl, m. p. 186°[3b] was clearly different from and depressed the melting point of the cyclohexane derivative. Moreover, saponification of the acetate, in 5% sodium hydroxide, m. p. 149–150°, gave the original phenol almost quantitatively. Methylation of 50 mg. of this phenol, m. p. 224–228°, by alternate addition in two portions of a total of 2 ml. of 20% sodium hydroxide and 2 ml. of dimethyl sulfate, destroying the excess with concentrated ammonia, yielded a gummy, white solid. This was recrystallized three times from methyl alcohol; m. p. 90.8–91.4° (micro); m. m. p. with bis-(*p*-methoxyphenyl)-cyclohexene, Ia, 70–87°; m. m. p. with the cyclohexene, IIa, 89.5–90.9° (micro). Hydrogenation of the phenolic cyclohexene, IIb, 18 mg., over 10% palladium-on-charcoal catalyst[21] in ethyl alcohol at 80 p. s. i. yielded 12 mg. of 1,2-bis-(*p*-hydroxyphenyl)-cyclohexane, IV, m. p. 177–179° (see below).

The second compound isolated from the demethylation products crystallized on slow evaporation of the liquors from phenolic cyclohexane IIb. This melted at 160–220° but finally yielded 0.5 g. of micro-needles, m. p. 171.0–173.5° (micro), from the same solvent. It depressed to 158° the melting point of 1,2-bis-(*p*-hydroxyphenyl)-cyclohexane and is bis-(*p*-hydroxyphenyl)-cyclohexene, Ib. *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.18; H, 6.81. Found: C, 81.33, 81.15; H, 6.90, 6.66. The diacetate, prepared as above, was purified from methyl alcohol; m. p. 140.5–141.5° (micro). *Anal.* Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.45; H, 6.36. Methylation of this phenol in like manner furnished bis-(*p*-methoxyphenyl)-cyclohexene, Ia, m. p. 88.8–89.8° (micro); m. p., with the isomer Ia isolated from the Grignard reaction, 88.3–90.4° (micro).

1,2-bis-(*p*-Methoxyphenyl)-cyclohexane, III.—The mixture of bis-(*p*-methoxyphenyl)-cyclohexenes, 3.2 g., in 50 ml. of acetone was shaken with 0.5 g. of 10% palladium-on-charcoal catalyst for six hours at 50 p. s. i. of hydrogen. Following filtration and removal of acetone the residue was crystallized from alcohol, giving 2.9 g. (90%) of 1,2-bis-(*p*-methoxyphenyl)-cyclohexane, m. p. 67–69°. *Anal.* Calcd. for $C_{20}H_{24}O_2$: C, 81.02; H, 8.17. Found: C, 80.92, 80.91; H, 8.06, 7.92. Hydrogenation, likewise, of the pure isomeric bis-(*p*-methoxyphenyl)-cyclohexenes, Ia and IIa, resulted in the same cyclohexane from each in comparable yields.

1,2-bis-(*p*-Hydroxyphenyl)-cyclohexane, IV.—Demethylation of 8.0 g. of 1,2-bis-(*p*-methoxyphenyl)-cyclohexane with 20 g. of potassium hydroxide in 150 ml. of alcohol at 200–210° for twenty-four hours yielded 7.0 g. of acid-precipitated product, m. p. 176–178°. Two recrystallizations from 50% aqueous methyl alcohol, with

(19) This was prepared by dehydration of the carbinol, *cf.* Sherwood, *et al.*, *J. Chem. Soc.*, 1832 (1932); 323 (1936), and the melting point was as given by v. Braun, *Ann.*, **472**, 1 (1929).

(20) All micro-melting points were observed at fifty magnifications in the Kofler apparatus as supplied by the Arthur H. Thomas Co., Philadelphia, Pa., and calibrated in terms of standard samples accompanying the instrument.

(21) Hartung, THIS JOURNAL, **50**, 3370 (1928).

addition of Norite, gave 6.5 g. (88%) of the phenol, m. p. 177.5–179.5°, which produced no color with ferric chloride. *Anal.* Calcd. for $C_{18}H_{20}O_2$: C, 80.54; H, 7.53. Found: C, 80.56, 80.54; H, 7.41, 7.20.

1,2-bis-(*p*-Acetoxyphenyl)-cyclohexane, m. p. 114.8–116.2° (micro), was prepared and purified just as described for the corresponding unsaturated compounds. *Anal.* Calcd. for $C_{22}H_{24}O_4$: C, 74.96; H, 6.88. Found: C, 74.88, 75.00; H, 6.81, 6.75.

Physiological Activity.—On subcutaneous injection into rats[22] of an oil solution, bis-(*p*-hydroxyphenyl)-cyclohexene, Ib, showed 300 I. U./mg.; bis-(*p*-hydroxyphenyl)-cyclohexene, IIb, 150 I. U./mg.; and 1,2-bis-(*p*-hydroxyphenyl)-cyclohexane, 200 I. U./mg. of estrogenic activity.

(22) We are grateful to Parke Davis and Company, Detroit, Michigan, for testing these compounds.

Summary

1,2-bis-(*p*-Hydroxyphenyl)-cyclohexane and two intermediate cyclohexenes together with their methyl and acetyl derivatives have been prepared. The phenols have moderate estrogenic activity. The hindrance to ring closure of 1,6-diarylhexamethylene derivatives has been indicated and the formation of a polypinacol discussed.

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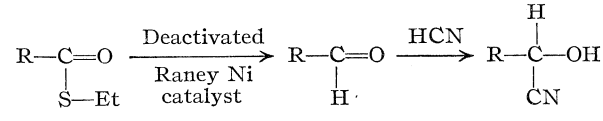
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Steroid Acids and their Transformation Products. VI. Some New Aldehydes and Their Derived Cyanohydrins

BY A. VERN MCINTOSH, ANNA MAE SEARCY, ELIZABETH M. MEINZER AND ROBERT H. LEVIN

Preparation of steroid aldehydes by the desulfurization of thiol esters of 3β-hydroxy-5-cholenic acid, 3β-hydroxybisnor-5-cholenic acid and desoxycholic acid with acetone deactivated W-1[1] Raney nickel catalyst has been reported in previous papers of this series.[2] We have now prepared aldehydes starting with the thiol esters of nor-desoxycholic acid, lithocholic acid, 12α-hydroxycholanic acid, and 3α-hydroxy-11-cholenic acid, in yields of 39 to 78%. These aldehydes have been converted to cyanohydrins in excellent yields, completing the sequence of reactions



Ethyl 3α,12α-diacetoxynorthiolcholanate has been used as a model for the study of variations in the desulfurization procedure. The information gained from the experiments on the desulfurization of this compound is summarized very briefly below, excluding data which have been previously reported in this series.

A number of attempts were made to prepare 3α,12α-diacetoxynorcholan-23-al from the thiol ester without deactivation of the nickel. It was found that five parts of W-4 Raney nickel, or twenty parts of W-1 or commercial active Raney nickel, would reduce the thiol ester in alcohol quantitatively to 3α,12α-diacetoxynorcholan-23-ol at either room temperature or at reflux. When ten parts of W-1 Raney catalyst was heated with one part of ester in alcohol solution, a mixture of 3α,12α-diacetoxynorcholan-23-ol and ethyl 3α,12α-diacetoxynorthiolcholanate was obtained, besides about a 1% yield of aldehyde isolated as the semicarbazone.

Next, an experiment was devised to analyze the products obtained by use of Raney nickel which had been deactivated by reaction with the thiol ester. A mixture of Raney nickel and Celite filter-aid was placed in a chromatogram column and a solution of the thiol ester was filtered through and collected in portions. When 10 g. of W-4 Raney nickel was used, 2.1 g. of very pure 3α,12α-diacetoxynorcholan-23-ol was obtained in the first several fractions, then alcohol–ester mixtures followed. The time of contact of the solution in the column was about a minute, indicating a very rapid reaction at room temperature. Using W-1 Raney nickel, a little less than half the yield of alcohol given by the W-4 nickel was obtained, followed by some gummy mixtures, then the pure thiol ester. A very small amount of aldehyde semicarbazone was obtained on working up the mixtures, besides both alcohol and ester.

Without deactivation of the Raney nickel before the reaction with the thiol ester not more than 1% of aldehyde was obtained, isolated as the semicarbazone. Pretreatment of the Raney nickel in acetone under reflux proved by far the most suitable of the methods of deactivation tried.[2] When deactivated with acetone W-1 and W-4 Raney nickels, prepared in this Laboratory, and a commercial active Raney nickel[3] were used successfully as desulfurizing agents. A commercial pelleted Raney catalyst was found to be entirely inactive. Within experimental error the yields obtained when the commercial active Raney nickel was used were the same as were obtained with the W-1 catalyst. The W-4 catalyst gave consistently lower yields of aldehyde although different deactivation and reaction times were tried. However, for reduction of thiol esters to alcohols the W-4 nickel was best, giving nearly quantitative

(1) Adkins and Pavlic, THIS JOURNAL, **69**, 3039 (1947).

(2) (a) Spero, McIntosh and Levin, *ibid.*, **70**, 1907 (1948); (b) McIntosh, Meinzer and Levin, *ibid.*, **70**, 2955 (1948).

(3) Raney Active Nickel Catalyst, in water, obtained from the Gilman Paint and Varnish Co., Chattanooga, Tenn. This catalyst is analogous to W-1 or W-2 catalysts in activity.

TABLE I

THIOL ESTERS OF STEROID ACIDS

Compound, ethyl	M. p., °C.[b]	Rotation[c] $[\alpha]_D$ deg.	Yield, %	Molecular formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Calcd.	Sulfur Found
3α-Acetoxythiolcholanate	97–102	+36[d]	76	$C_{28}H_{46}O_3S$	72.68	72.39	10.02	9.79	6.93	7.05
3α-Hydroxythiolcholanate[a]	81–82	+20[e]	..[a]	$C_{26}H_{44}O_2S$	74.23	74.04	10.54	10.08	7.62	7.22
3α-Acetoxy-11-thiolcholenate	81–82.5	...	74	$C_{28}H_{44}O_3S$	72.99	73.05	9.63	9.39	6.98	7.09
12α-Acetoxythiolcholanate	.....[h]	+66[f]	65	$C_{28}H_{46}O_3S$	72.68	72.81	10.02	9.78	6.93	7.04
12α-Formoxythiolcholanate	.....[h]	+69[g]	88	$C_{27}H_{44}O_3S$	72.27	72.15	9.89	9.74	7.15	7.45
3β-Methoxybisnor-5-thiolcholenate	86–90	...	40	$C_{25}H_{40}O_2S$	74.20	74.11	9.96	9.65	7.92	8.18

[a] Prepared in 80% yield by passing ethyl 3α-formoxythiolcholanate over alumina. [b] All melting points taken on the Fisher–Johns block and corrected. [c] Rotations taken in chloroform with a 1-dm. tube. [d] 42.96 mg. in 10 ml. α_D +0.156°. [e] 106.6 mg. in 10 ml., α_D +0.21°. [f] 80.2 mg. in 10 ml., α_D +0.532°. [g] 69.4 mg. in 10 ml., α_D +0.480°. [h] Not crystalline.

TABLE II

STEROID ALDEHYDES AND DERIVATIVES

Compound	M. p., °C.[a]	Rotation[b] $[\alpha]_D$ deg.	Yield, %	Molecular formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
3α-Acetoxycholan-24-al	113.5–115.5	+42[c]	39	$C_{26}H_{42}O_3$	77.56	77.34	10.52	10.20
2,4-Dinitrophenylhydrazone	201.5–202.5			$C_{32}H_{46}O_6N_4$[k]	65.95	65.88	7.96	7.73
3α-Formoxycholan-24-al	98–100	+47[d]	78	$C_{25}H_{40}O_3$	77.27	77.17	10.38	10.60
2,4-Dinitrophenylhydrazone	162.5–164.5			$C_{31}H_{44}O_6N_4$[l]	65.47	65.82	7.80	7.65
3α-Hydroxycholan-24-al	146–148	+20[e]	[i]	$C_{24}H_{40}O_2$	79.94	80.07	11.18	10.98
Semicarbazone	226–229			$C_{25}H_{43}O_2N_3$[m]	71.90	71.70	10.38	9.94
12α-Acetoxycholan-24-al	112–115	+64[f]	60	$C_{26}H_{42}O_3$	77.56	77.62	10.52	10.46
3α,12α-Diacetoxynorcholan-23-al	128–131	+88[g]	69	$C_{27}H_{42}O_5$	72.61	72.49	9.48	9.37
Semicarbazone	237–240			$C_{28}H_{45}O_5N_3$[n]	66.77	66.65	9.01	8.91
3α-Acetoxy-11-cholen-24-al	115–117.5	+49[h]	53	$C_{26}H_{44}O_3$	77.95	77.75	10.07	10.21
3α-Formoxy-5-cholen-24-al	130–134	−76[i]	78	$C_{25}H_{38}O_3$	77.70	77.60	9.91	9.97

[a] All melting points taken on the Fisher–Johns block and corrected. [b] Rotations taken in chloroform with a 1-dm. tube. [c] 112.51 mg. in 10 ml., α_D 0.473°. [d] 124.82 mg. in 10 ml., α_D +0.59°. [e] 82.54 mg. in 10 ml., α_D +0.161°. [f] 205.8 mg. in 10 ml., α_D +1.326°. [g] 156.27 mg. in 10 ml., α_D +1.38°. [h] 100.3 mg. in 10 ml., α_D +0.486°. [i] 66.1 mg. in 10 ml., α_D −0.50°. [j] Prepared from 3α-formoxycholan-24-al by hydrolysis in 2% methanolic potassium hydroxide for three hours at room temperature; yield 47%. [k] Calcd.: N, 9.62. Found: N, 9.55. [l] Calcd.: N, 9.85. Found: N, 9.7. [m] Calcd.: N, 10.06. Found: N, 9.81. [n] Calcd.: N, 8.34. Found: N, 8.53.

TABLE III

CYANOHYDRINS

Aldehyde	M. p., °C.[a]	Rotation[b] $[\alpha]_D$ deg.	Yield, %	Molecular formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
3α-Acetoxycholan-24-al	154.5–156	...	89	$C_{27}H_{43}O_3N$	75.48	75.47	10.09	10.05	3.26	3.39
3α-Hydroxycholan-24-al	146–149	+28[c]	95	$C_{25}H_{41}O_2N$	77.47	77.86	10.66	10.48	3.61	3.46
12α-Acetoxycholan-24-al	153–156	+71[d]	98	$C_{27}H_{43}O_3N$	75.48	75.56	10.09	9.96	3.26	3.38
3α,12α-Diacetoxynorcholan-23-al	164–165.5	+99[e]	97	$C_{28}H_{43}O_5N$	71.00	71.10	9.15	8.93	2.96	2.92
3β-Acetoxy-5-cholen-24-al	154–157	−55[f]	100	$C_{27}H_{41}O_3N$	75.83	75.97	9.67	9.58	3.28	3.11
3β-Formoxy-5-cholen-24-al	137–143	−53[g]	82	$C_{26}H_{39}O_3N$	75.50	75.43	9.50	9.24	3.39	3.57
3α-Acetoxy-11-cholen-24-al	162–163.5	+45[h]	100	$C_{27}H_{41}O_3N$	75.83	75.64	9.67	9.50	3.28	3.42

[a] All melting points taken on the Fisher–Johns block and corrected. [b] Rotations taken in chloroform in a 1-dm. tube. [c] 122.0 mg. in 10 ml., α_D +0.344°. [d] 89.8 mg. in 10 ml., α_D +0.641°. [e] 100.0 mg. in 10 ml., α_D +0.988°. [f] 158.47 mg. in 10 ml., α_D −0.872°. [g] 100.0 mg. in 10 ml., α_D −0.529°. [h] 89.3 mg. in 10 ml., α_D +0.404°.

yields in a few minutes at room temperature with alcohol or ether as the solvent.

In several less thorough series of experiments with thiol esters of other steroid acids the results were similar to those outlined above.

Commercial active Raney nickel[3] has been used in the desulfurization of most of the thiol esters reported in this series of articles,[2] in every case successfully. The conditions were those reported for ethyl 3α,12α-diacetoxynorthiolcholanate in the experimental section of this paper. Variation of the amount of catalyst used by about 20% in some cases slightly improved the yield. When the thiol ester is not sufficiently soluble in aqueous acetone[4] it may be added in dry acetone or dioxane.

Two examples of the separation of the aldehyde

(4) The water is not necessary for the reaction, but makes the reaction mixture easier to work up.

from the by-products of the reaction through formation of the sodium bisulfite complex[5] are given in the experimental section. Bisulfites of some steroid aldehydes, especially those containing free hydroxyl groups, tend to be both water soluble and relatively difficult to decompose with aqueous sodium carbonate. This is the case with 3α,12α-diacetoxynorcholan-23-al. When the complex is highly insoluble, *e. g.*, with 3α-formoxycholan-24-al, the aldehyde is more easily worked up.

The steroid aldehydes not previously reported are listed in Table II. Semicarbazones and 2,4-dinitrophenylhydrazones are included in the same table.

Cyanohydrins were prepared from the aldehydes described in this paper, as well as from several aldehydes reported previously.[2] These are listed in Table III. Three methods of preparation were investigated. In one the aldehyde bisulfite was suspended in excess 1.25% aqueous potassium cyanide and heated on the steam-bath five to ten minutes, then stirred for an hour and extracted with ether to obtain the product.[6] In a second the aldehyde was dissolved in a mixture of alcohol and acetic acid and treated with excess potassium cyanide at 0°.[7] The first method gave a good yield of cyanohydrin from 3β-acetoxy-5-cholen-24-al, but did not work well with 3α,12α-diacetoxynorcholan-23-al. Using the second method these results were reversed. In a third variation the aldehyde was dissolved in a small amount of dioxane and stirred with 40% aqueous sodium bisulfite, then excess solid potassium cyanide was added and the mixture was heated five minutes on the steam-bath, allowed to cool, and poured into water. This method gave good results with all the steroid aldehydes used, and is described in the experimental section.

3α,12α-Diacetoxynorcholan-23-al cyanohydrin and 3β-acetoxy-5-cholen-24-al cyanohydrin were found to be stable when chromatographed over alumina. This contrasts with the behavior of 20-ketosteroid cyanohydrins which Sarett[1] found to be dehydrated or split by passage over alumina columns.

A number of new steroid thiol esters prepared in the course of this research are listed in Table I.

Experimental[8]

Thiol Esters.—Six new thiol esters are listed in Table I. These were prepared by treating the corresponding steroid acid chlorides with ethyl mercaptan in the presence of pyridine,[9] with the exception of ethyl 3α-hydroxythiolcholanate which was obtained by passing ethyl 3α-formoxythiolcholanate[9] over Fisher adsorption alumina.[9,10]

(5) Centolella, Heyl and Herr, THIS JOURNAL, **70**, 2953 (1948).

(6) Heyl and Herr, personal communication, have previously prepared the cyanohydrin of 3β-acetoxybisnor-5-cholen-22-al by this method in high yield.

(7) Sarett, THIS JOURNAL, **70**, 1454 (1948).

(8) All m. p.'s taken on the Fisher–Johns block and corrected. Analyses and rotations by the Upjohn microanalytical and physics groups.

(9) Levin, McIntosh, Spero, Rayman and Meinzer, THIS JOURNAL, **70**, 511 (1948).

(10) Levin, McIntosh and Spero, *Science*, **108**, 82 (1948).

12α-Formoxy- and 12α-acetoxycholanic acids, used as starting materials, have not been reported previously. These were prepared from 12α-hydroxycholanic acid[11] by formylation following Moffett's procedure[12] and by acetylation in acetic anhydride–acetic acid mixture using anhydrous perchloric acid as a catalyst.[13]

12α-Formoxycholanic acid was crystallized from 1–1 dioxane–formic acid mixture, m. p. 145–147°; $[\alpha]^{24}D$ +75° (203.7 mg. in 10 ml. of chloroform, *l*, 1 dm.; αD +1.53).

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.22; H, 9.97. Found: C, 73.91; H, 10.08.

12α-Acetoxycholanic acid melted at 214–215° after crystallization from glacial acetic acid; $[\alpha]^{25}D$ + 71° (233.9 mg. in 10 ml. of chloroform, *l* 1 dm.; αD + 1.67°).

Anal. Calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.12. Found: C, 74.70; H, 10.16.

The Desulfurization Reaction.—The aldehydes prepared by treatment of steroid thiol esters with deactivated Raney nickel are listed in Table II. Two examples of the method are given below.

3α,12α-Diacetoxynorcholan-23-al.—A suspension of 30 g. of commercial active Raney nickel (washed alkali free) in 90 ml. of acetone was stirred and heated under reflux an hour, then 30 ml. of water was added, followed by a solution of 3.0 g. of ethyl 3α,12α-diacetoxynorthiolcholanate in 60 ml. of acetone. The reaction mixture was heated an hour, then was filtered hot. The Raney nickel was washed with hot acetone and the filtrate and washings concentrated *in vacuo* till a heavy precipitate formed. The precipitate (2.67 g.) was dissolved in a mixture of 45 ml. of ether and 40 ml. of methanol, then 100 ml. of 40% aqueous sodium bisulfite was added and the mixture was shaken for ten minutes. On standing three layers separated (some water may be required). The aldehyde bisulfite complex was richest in the middle layer. The two lower layers combined were brought to *p*H 10 by addition of saturated aqueous sodium carbonate and extracted with ether to give 1.76 g. of crystalline aldehyde. The ether layer, extracted a second time with bisulfite, gave 0.36 g. of aldehyde. A residue of 0.61 g. remained after evaporation of the ether. The crude aldehyde was crystallized from aqueous acetic acid to give 1.82 g. (69%) of 3α,12α-diacetoxynorcholan-23-al, m. p. 115–121°. After crystallization from Skellysolve "B" the aldehyde melted at 128–131°.

3α-Formoxycholan-24-al.—Desulfurization of 2.7 g. of ethyl 3α-formoxythiolcholanate with 30 g. of Raney nickel was carried out as described above. The acetone solution of the aldehyde was concentrated *in vacuo* to less than 30 ml. An oil separated. Water was added and the mixture was extracted with ether. The ether solution was concentrated to 30 ml., then 30 ml. of methanol and 75 ml. of saturated aqueous sodium bisulfite were added and the mixture was shaken ten minutes. A white precipitate formed, and was separated by centrifuging. The precipitate was shaken with ether and ice water and again centrifuged, then was suspended in 10% aqueous sodium carbonate under ether and agitated thirty minutes with a stream of nitrogen. The ether layer was washed with water, dried, and evaporated under nitrogen to give 1.50 g. (62%) of 3α-formoxycholan-24-al, m. p. 95–98°. After crystallization from Skellysolve "B," then aqueous acetic acid, the m. p. was 98–100°.

3α,12α-Diacetoxynorcholan-23-ol and Derivatives.—In the desulfurization of ethyl 3α,12α-diacetoxynorthiolcholanate the material remaining in the ether solution after extraction with aqueous sodium bisulfite was dissolved in benzene and passed over Fisher adsorption alumina. The fraction eluted with benzene consisted of ethyl 3α,12α-diacetoxynorthiolcholanate; a second fraction eluted with 2% methanol in benzene consisted of 3α,-12α-diacetoxynorcholan-23-ol. When the yield of alde-

(11) Wieland and Schlichting, *Z. physiol. Chem.*, **150**, 267 (1925).

(12) Hoehn and Moffett, THIS JOURNAL, **67**, 740 (1945).

(13) Whitman and Schwenk, *ibid.*, **68**, 1865 (1946).

hyde was highest the proportion of the two by-products was roughly equal, but even when the Raney nickel–ester ratios were varied from 5–1 to 20–1 both products were present.

The identity of the alcohol was checked by preparation of 3α,12α-diacetoxynorcholan-23-ol by direct reduction of ethyl 3α,12α-diacetoxynorthiolcholanate with W-4 Raney nickel in alcohol at room temperature.[2] The two alcohols were identical. The compound was crystallized both from aqueous alcohol and chloroform–hexane mixture; m. p. 148.5–151°; $[\alpha]^{26}D$ + 110° (100.0 mg. in 10 ml. of $CHCl_3$, *l* 1 dm.; αD +1.10°).

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.30; H, 9.89. Found: C, 72.49; H, 9.95.

3α,12α-Diacetoxynorcholan-23-ol refluxed for two hours in 1–1 pyridine–acetic anhydride gave a 70% yield of 3α,-12α,23-triacetoxynorcholane, m. p. 108–110° from aqueous acetic acid.

Anal. Calcd. for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Found: C, 71.05; H, 9.38.

3α,12α-Diacetoxynorcholan-23-ol was allowed to stand seven hours in a 5% solution of potassium hydroxide in 80% alcohol at room temperature. The product was precipitated by the addition of water, chromatographed and crystallized from aqueous alcohol to give a 70% yield of 3α,23-dihydroxy-12-acetoxynorcholane, m. p. 181.5–182°.

Anal. Calcd. for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.89; H, 10.32.

Hydrolysis of 3α,12α-diacetoxynorcholan-23-ol in 10% alcoholic potassium hydroxide under reflux for three hours gave 83% of 3α,12α,23-trihydroxynorcholane, m. p. 194–200°. On recrystallization from ethanol the compound melted at 209.5–211°.

Anal. Calcd. for $C_{23}H_{40}O_3$: C, 75.77; H, 11.06. Found: C, 75.67; H, 10.96.

The dinitrophenylhydrazones and semicarbazones reported in Table II were prepared as described in previous papers in this series.[2]

Cyanohydrins.—The preparation of the steroid aldehyde cyanohydrins listed in Table III is illustrated by the method used for **3α-acetoxycholan-24-al cyanohydrin.** A mixture of 0.500 g. of 3α-acetoxycholan-24-al, 1.5 ml. of dioxane, and 3 ml. of saturated aqueous sodium bisulfite was stirred at room temperature for thirty minutes, then 0.5 g. of solid potassium cyanide was added and the mixture was heated for five minutes on the steam-bath, then allowed to cool to room temperature for thirty minutes, with occasional stirring. The reaction mixture was poured into 50 ml. of water giving a gummy precipitate. This was crystallized from aqueous acetic acid to give 0.476 g. (85%) of crystals melting at 148–152°. After several crystallizations from aqueous acetic acid the m. p. was 154.5–156°.

Summary

3α-Hydroxycholan-24-al, its 3-acetyl and 3-formyl derivatives, 12α-acetoxycholan-24-al, 3α,-12α-diacetoxynorcholan-23-al, 3α-acetoxy-11-cholen-24-al, and 3β-formoxy-5-cholen-24-al have been prepared by the desulfurization of the corresponding thiol esters with acetone deactivated Raney nickel catalyst.

The cyanohydrins have been obtained by treating these aldehydes with sodium bisulfite and potassium cyanide in dioxane–water.

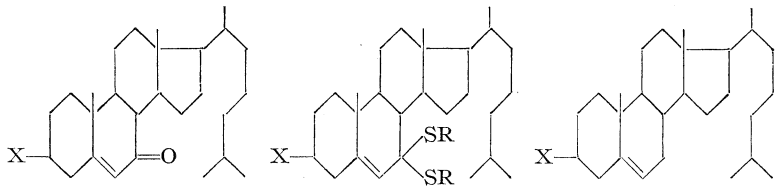
KALAMAZOO, MICHIGAN RECEIVED APRIL 28, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Addition of Mercaptans to Unsaturated Steroid Ketones

BY JACK W. RALLS,[1] R. M. DODSON[2] AND BYRON RIEGEL

Cholesterol that has been labeled with isotopic carbon in the nucleus would be useful for many biological investigations. A method for the introduction of the carbon isotopes into ring B of cholesterol (III-C) involves the intermediate 7-ketocholesterol (I-C). The final step would be the reduction of the 7-keto group to give the labelled cholesterol. This critical step was studied in some detail. Classical methods of reduction require strongly acid or basic conditions, which will cause the elimination of the group at the 3-position[3] with the formation of a second conjugated ethylenic linkage. Reduction of a carbonyl group without the simultaneous reduction of the α,β-unsaturation limits the methods that may be employed. The Wolff–Kishner reduction is unsatisfactory.



I II III

X A AcO—
B Cl—
C HO—

Recently Hauptmann[4] has prepared 4-cholestene from cholestenone by desulfurizing the dibenzyl mercaptole derivative. This method has also been used for the reduction of saturated steroid ketones[5] where the carbonyl group occupies the 3, 7, 12 and 17 positions.

The mercaptoles of 7-ketocholesteryl acetate (II-A) do not form readily. The best yield (40%) was obtained using ethanedithiol in

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(3) (a) H. Stavely and W. Bergmann, *J. Org. Chem.*, **1**, 567 (1936); (b) R. Marker, O. Kamm, G. Fleming, A. Popkin and E. Wittle, THIS JOURNAL, **59**, 619 (1937); (c) O. Wintersteiner and S. Bergstrom, *J. Biol. Chem.*, **137**, 785 (1941).

(4) H. Hauptmann, THIS JOURNAL, **69**, 562 (1947).

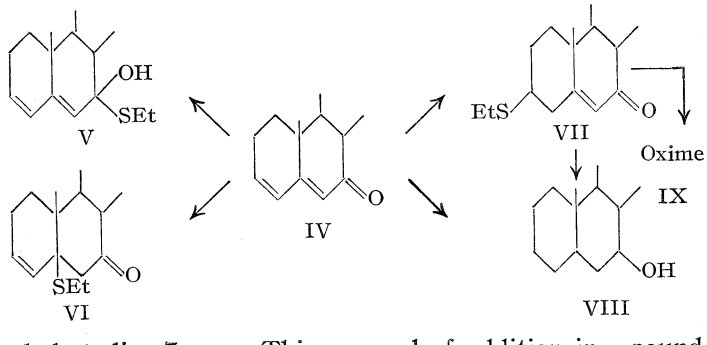
(5) (a) S. Bernstein and L. Dorfmann, *ibid.*, **68**, 1152 (1946); (b) L. Norymberska, J. Norymberski and A. Olade, *ibid.*, **70**, 1256 (1948); (c) R. H. Levin and J. L. Thompson, *ibid.*, **70**, 3140 (1948).

absolute ether with dry hydrogen chloride as the catalyst. The ethanedithiol derivative, melting at 188.2–188.8°, was reduced to cholesteryl acetate (III-A) which was isolated as the dibromide in a 40% yield. Because of the low yields on these final steps, this method did not appear feasible for the preparation of labelled cholesterol.[6]

However, when 7-ketocholesteryl acetate (I-A) was treated with ethyl mercaptan in an acetic–hydrochloric acid mixture, a good yield of a crystalline solid melting at 152–153° with a specific rotation of −106° was obtained. This compound was not the desired mercaptole. The elucidation of its structure and the course of the reaction established a new 1,6-addition.

The analytical data indicated that the substance resulted from the addition of one mole of ethyl mercaptan to 3,5-cholestadien-7-one (IV). Such a product could form if the 7-ketocholesteryl acetate had lost the elements of acetic acid to give 3,5-cholestadien-7-one which then added ethyl mercaptan. When 3,5-cholestadien-7-one was treated with ethyl mercaptan, a product identical with that from 7-ketocholesteryl acetate was obtained. The most likely compounds that would be formed by the addition of ethyl mercaptan to 3,5-cholestadien-7-one are V, VI and VII.

The presence of a carbonyl group was established when it was found that the adduct formed an oxime (IX). The addition product was unstable when heated with dilute methanolic potassium hydroxide solution. Under these conditions the adduct gave ethyl mercaptan and 3,5-cholestadien-7-one. This reversal of addition in the presence of bases is characteristic of compounds formed by 1,4-addition of mercaptans to α,β-unsaturated ketones.[7] By treating the addition product with Raney nickel in dioxane–water at 120° for twenty-four hours, complete removal of sulfur was accomplished and the product isolated was identified as 7-cholestanol (VIII). The formation of 7-cholestanol was found to be compatible with structures VI and VII when it was shown that 3,5-cholestadien-7-one gave a good yield of 7-cholestanol when reduced under the desulfuration conditions.



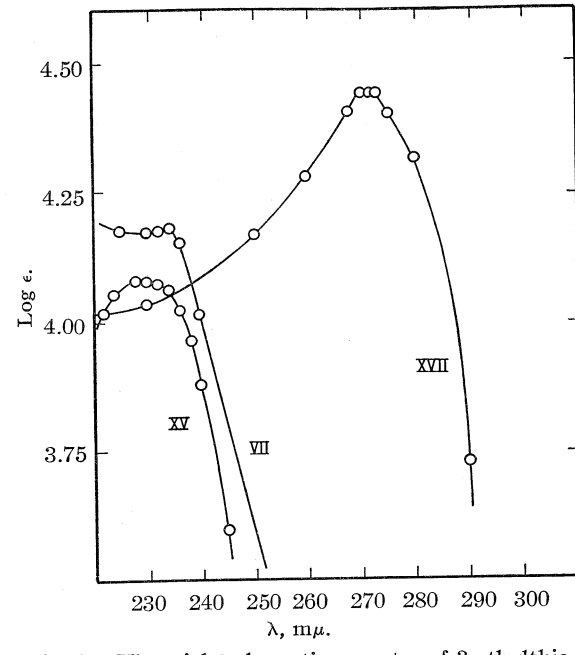


Fig. 1.—Ultraviolet absorption spectra of 3-ethylthio-5-cholesten-7-one (VII), 3-ethylsulfonyl-5-cholesten-7-one (XV), and 3-ethylthio-3,5-cholestadiene (XVII). All taken in dry ether.

An assignment of structure was made on the basis of the absorption spectrum of the adduct shown in Fig. 1. The spectrum indicates that structure VII is correct, since it is very similar to the spectra of 7-ketocholesteryl acetate and other α,β-unsaturated steroid ketones.[8] This compound, 3-ethylthio-5-cholesten-7-one (VII), would result from a 1,6-addition of ethyl mercaptan to 3,5-cholestadien-7-one. Since this type of addition has not been observed previously, a more rigorous structure proof was required.

The adduct (VII) was oxidized to a sulfone (XV) using excess hydrogen peroxide in dioxane at 100°. This compound melted at 190.0–192.0° and had a specific rotation of −64°. It would seem reasonable to expect that the sulfone (XV) would show absorption characteristics similar to VII. The absorption spectra are given in Fig. 1. The spectra are similar but the evidence was not as conclusive as we had hoped. Recently Fehnel and Carmack[9] have given an excellent presentation of the ultraviolet absorption spectra of organic sulfur compounds. However, they did not report a sulfur compound where the sulfur is attached to a bridgehead carbon atom.

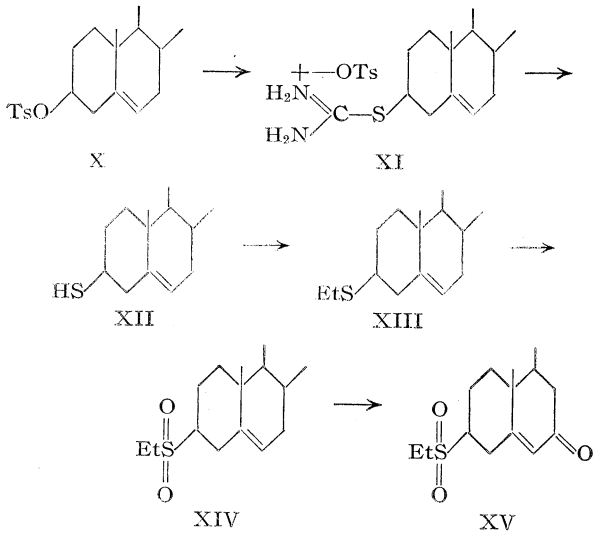
(6) Further work on these reactions was terminated when we learned from Dr. Seymour Lieberman that a similar study is in progress at the Sloan-Kettering Institute for Cancer Research.

(7) (a) B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931); (b) E. J. Morgan and E. Friedmann, *Biochem. J.*, **32**, 733 (1938).

(8) (a) H. Danneberg, *Preuss. Akad. Wiss. Math-naturw. Klasse*, No. 12 (1939); (b) I. M. Klotz, THIS JOURNAL, **66**, 88 (1944); (c) R. B. Woodward, *ibid.*, **63**, 1123 (1941).

(9) E. A. Fehnel and M. Carmack, *ibid.*, **71**, 84, 231 (1949).

To place the structure proof on a firm chemical basis, an independent synthesis of XV was carried out. The structures given in X to XV outline the method employed. By a modification of the



method of King, Dodson and Subluskey,[10] 3β-mercapto-5-cholestene (XII) was prepared. There seems to be little possible doubt that the structure of "thiocholesterol" is 3β-mercapto-5-cholestene. It has been prepared by several routes,[11–13] all of which yield the same isomer. The replacement reactions of 3β-toluenesulfonoxy-5-cholestene (X) have been studied extensively. It has been established that such replacements can lead to two isomeric products depending on the reaction conditions. Under basic (or buffered) conditions the product is predominantly the *i*-structure. Acid conditions favor replacement without inversion. In the reaction of 3β-toluenesulfonoxy-5 cholestene with thiocyanate[12] and thiourea[10] the authors have presented ample evidence that the products do not have the *i*-structure. These facts are the basis for the configurations assigned to the compounds reported in this paper. Additional evidence for these designations will be cited.

Alkyl cholesteryl sulfides are relatively unknown. The only such compound reported in the literature is the 3β-benzylthio-5-cholestene prepared by Wagner–Jauregg and Lennartz.[12] We have found that 3β-sodiothio-5-cholestene can be alkylated in excellent yield by ethyl bromide to give 3β-ethylthio-5-cholestene (XIII). This method appears to be a general one but we have not explored other possibilities. Compound XIII was prepared previously in this laboratory by the acid catalyzed rearrangement of *i*-cholesteryl methyl ether in a mixture of ethyl mercaptan and benzene.[14] Since this rearrangement is stereospecific,[15] the assignment of configuration of all the compounds reported in this paper is very probably correct.

The oxidation of 3β-ethylthio-5-cholestene (XIII) to the sulfone (XIV) was accomplished smoothly to give a compound melting at 150.8–151.6°. The sulfone when subjected to the allylic oxidation procedure[16] gave the 3β-ethylsulfonyl-5-cholesten-7-one (XV), m. p. 190.2–192.0°, $[\alpha]_D$ −64°. This material was identical with the sulfone obtained from the oxidation of the adduct formed from the addition of ethyl mercaptan to 3,5-cholestadien-7-one. Therefore, the 1,6-addition of an alkyl mercaptan to a multiple conjugated system has been established.

This type of 1,6-addition has not been observed previously. The addition of mercaptans to cinnamylideneacetophenone is stated to be a 1,4-addition,[17] although no proof of the structure of the adduct is presented. Since cinnamylideneacetophenone undergoes only 1,4-addition with a variety of reagents,[18] there is little question that the addition of mercaptans is also of this type. The 1,6-addition of ethyl mercaptan to 3,5-cholestadien-7-one is clearly a case of steric factors influencing the mode of addition. A 1,4-addition would necessitate the formation of an angular alkylthio group. Apparently the energetics of such a formation prohibit a 1,4-addition under mild conditions. This interpretation is consistent with the observation that cholestenone will not undergo a 1,4-addition of alkyl mercaptans.[4]

The generality of the reaction of 3-substituted 7-ketosteroids with ethyl mercaptan in an acetic–hydrochloric acid mixture was extended when it was found that 3β-chloro-5-cholesten-7-one (I-B) gave VII in good yield. These results suggest that this reaction may be used as a test for 7-ketosteroids which are oxygenated or halogenated in the 3-position. The applicability of this technique to mixtures has not been investigated. It has been found that cholesteryl acetate is unaffected by the reaction conditions employed. When *i*-cholestanone is treated under these conditions, only 3β-chloro-6-cholestanone results. 3-Cholestanone gives the diethyl mercaptole when the reaction time is extended. These data indicate that only the 3-ketosteroids form diethyl mercaptoles under mild conditions.

The smooth 1,6-addition of ethyl mercaptan under acid conditions was somewhat surprising. The analogous 1,4-addition of mercaptans to unsaturated ketones proceeds best when base catalyzed.[7a,19] When ethyl mercaptan was allowed to

(10) L. C. King, R. M. Dodson and L. A. Subluskey, THIS JOURNAL, **70**, 1176 (1948).

(11) H. R. Rosenberg and S. G. Turnbull, U. S. Patents 2,375,873, 2,375,874, *C. A.*, **39**, 5049 (1945).

(12) T. Wagner-Jauregg and T. Lennartz, *Ber.*, **74**, 27 (1941).

(13) A. Muller and E. Batyka, *ibid.*, **74**, 705 (1941).

(14) J. C. Colbert, Ph.D. Thesis, Northwestern University, 1946, p. 51.

(15) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).

(16) A. Windaus, H. Lettre and F. Schenk, *Ann.*, **520**, 98 (1935).

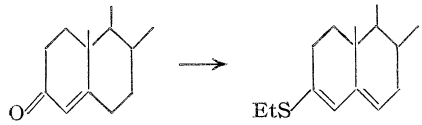
(17) S. Ruhemann, *J. Chem. Soc.*, **87**, 17, 461 (1905).

(18) E. P. Kohler and F. R. Butler, THIS JOURNAL, **48**, 1036 (1926).

(19) S. Ruhemann, *Proc. Chem. Soc.*, **20**, 251 (1904); **21**, 123 (1905).

react with 3,5-cholestadien-7-one under basic conditions, 3-ethylthio-5-cholesten-7-one was obtained but the yield was poor. Hauptmann[4] has reported that cholestenone (XVI) does not add benzyl mercaptan under basic conditions. We have found that ethyl mercaptan does not add to cholestenone under the same basic conditions which lead to 3-ethylthio-5-cholesten-7-one from the addition of ethyl mercaptan to 3,5-cholestadiene-7-one.

Under the acid conditions generally employed in this work, cholestenone (XVI) combined with ethyl mercaptan to give a good yield of the sub-



XVI XVII

stance previously reported by Bernstein and Dorfman.[5a,20] They tentatively assigned structure XVII or 3-ethylthio-3,5-cholestadiene to this material. Evidence that this structure was the correct one was obtained from the rotation and the absorption spectrum. The specific rotation of −129° was that expected of a 3-substituted 3,5-cholestadiene.[21] The absorption spectrum is reproduced in Fig. 1. The auxochromic effect of the –SEt group is apparent as the maximum of 238 mμ shown by 3-acetoxy-3,5-cholestadiene[8a] is shifted toward the higher wave lengths to a degree consistent with the effect in simpler compounds.[22]

Acknowledgment.—The authors would like to express their appreciation to Professor Irving M. Klotz for helpful discussions in the determination and interpretation of the absorption spectra.

Experimental[23]

5,6-Dibromocholestanyl Acetate from 7-Ketocholesteryl Acetate.—A solution of 1.0 g. of 7-ketocholesteryl acetate[16] and 2.0 g. of ethanedithiol (b. p. 59° (30 mm.)) in 20 ml. of dry ether was prepared. A slow stream of hydrogen chloride gas was passed into the solution. A crystalline solid started to precipitate after twenty minutes. More dry ether was added to maintain a constant volume, and the addition of hydrogen chloride was continued until a red color started to develop (thirty minutes). The crystalline solid was removed by filtration and washed with cold methanol. The yield of material melting at 188.2–188.8° was 0.48 g. (40%). This compound could be crystallized from methanol without changing the m.p.; it gave a positive test for sulfur and a negative test for chlorine.

The desulfuration of this derivative was carried out in two experiments. **A.** A solution of 0.30 g. of mercaptole was prepared in 50 ml. of a two-year old Raney nickel suspension containing 9.6 g. of the catalyst. After the addition of 5 ml. of water, the mixture was heated under reflux for nine hours. The nickel components were removed by filtration and washed with ether. Removal of the solvents *in vacuo* gave a mixture of solid and gum. The solid was taken up in 20 ml. of 95% ethanol; the gum (0.037 g.) was insoluble. Diluting the ethanolic solution and cooling gave 0.065 g. of an amorphous solid which melted over a wide range (109–122°). It was thought that alcoholysis of the acetyl group had taken place. The very poor yield of organic material indicated that considerable adsorption of the steroid fraction to the catalyst had taken place. With these preliminary results available a second experiment was run.

B. A mixture of 0.178 g. of the ethanedithiol addition product, 3.0 g. of freshly prepared Raney nickel catalyst,[24] 25 ml. of purified dioxane[25] and 5 ml. of water was heated under reflux for eight hours. The catalyst was removed by filtration and washed with two portions of hot dioxane. Removal of the solvents *in vacuo* gave 0.111 g. of amorphous solid which melted at 75–95°, gave a negative test for sulfur and a positive Liebermann–Burchard reaction. A solution of 0.074 g. of this material in 5 ml. of ether–acetic acid (2:3) was treated with a dilute solution of bromine in acetic acid until a slight excess of bromine was present. Removal of the ether by evaporation, addition of a few drops of water, and cooling gave 0.052 g. of crystalline solid melting at 112–114°. The mixed m. p. with an authentic sample of cholesteryl acetate dibromide was 112–114°.

3-Ethylthio-5-cholesten-7-one (VII).—**A.** To a solution of 1.0 g. of 7-ketocholesteryl acetate in 25 ml. of glacial acetic acid there was added 2.0 ml. of concentrated hydrochloric acid. The steroid was precipitated. Complete solution was effected by adding 10 ml. of acetic acid and warming slightly. The solution was cooled to room temperature and 5.0 ml. of ethyl mercaptan was added. A red color developed immediately and after five minutes a crystalline solid began to deposit. After standing for thirty minutes, the solid was removed by filtration and washed with cold methanol. The dried crystalline solid weighed 0.73 g. and melted at 148–149°. Cooling the filtrate and washings gave an additional 0.10 g. melting at 146–148°. Total yield was 0.83 g. (83%). Crystallization from acetone–methanol gave long needles which melted at 152.2–152.8°; $[\alpha]^{25.4}D$ −105.8° (44.6 mg. made up to 2 ml. with $CHCl_3$, $\alpha = -4.73°$, l, 2 dm.); $\lambda_{max.} = 234$ mμ (log $\epsilon = 4.19$); solvent, dry ether.

Anal. Calcd. for $C_{29}H_{48}OS$: C, 78.32; H, 10.88; S, 7.21. Found: C, 78.25; H, 11.02; S, 7.00.

B. A solution of 0.50 g. of 3,5-cholestadien-7-one[3a] in 18 ml. of glacial acetic acid and 1.0 ml. of concentrated hydrochloric acid was treated with 2.5 ml. of ethyl mercaptan. The color immediately changed to red-orange. After five minutes a solid formed. The mixture was cooled for thirty-five minutes in an ice-bath. The solid was removed by filtration (after the solvent had melted) and washed with cold methanol. The air dried material weighed 0.53 g. (91%) and melted at 148–150°. There was no depression in melting point when this material was mixed with the product from A.

C. The preparation starting with 3β-chloro-5-cholesten-7-one[3b] was carried out as above. From 1.0 g. of the steroid there was obtained 0.95 g. of crystalline solid melting at 144–149°. This material gave a negative Beilstein test for halogen and was not depressed in melting point when mixed with the products described above. Recrystallization from methanol–acetone gave 0.84 g. (80%) melting at 147–149°.

D. A solution of 0.50 g. of 3,5-cholestadien-7-one in 20 ml. of pyridine was treated with 5.0 ml. of ethyl mercaptan. After two hours at room temperature 0.20 g. of

(20) Compare *Soc. pour l'ind. chim. à Bâle*, British Patent 554,940.

(21) (a) E. Schwenk, G. Fleischer and B. Whitman, THIS JOURNAL, **60**, 1702 (1938); (b) U. Westphal, *Ber.*, **70**, 2128 (1937).

(22) E. A. Braude, *Ann. Reports Chem. Soc.* (London), **42**, 105 (1946).

(23) Melting points are uncorrected. Microanalyses by Misses M. Hines, J. Gibbs and V. Hobbs of Northwestern University and Mr. C. W. Beazley of Micro-Tech. Laboratories, Skokie, Illinois.

(24) The catalyst was prepared according to the directions of R. Mozingo, *Org. Syn.*, **21**, 15 (1941), except after the addition of the alloy the mixture was allowed to stand at 25–30° for fourteen to sixteen hours before washing. The alkali-free catalyst was dried by azeotropic distillation with purified dioxane.

(25) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath & Co., New York, N. Y., 1941, p. 368.

commercial sodium methoxide powder was added. After an additional two and one-half hours of standing, the orange mixture was poured onto cracked ice. The orange solid was taken up in ether and the ether layer washed with three portions of water. The ether layer was dried over anhydrous sodium sulfate and the ether removed. The yellow gummy solid was dissolved in 40 ml. of methanol–acetone (3:1). On cooling, a deposit of small crystals formed; these were collected and washed with cold methanol. The yield was 0.20 g. (36%), m. p. 141–146°. The filtrate and washings gave some additional material on concentration and cooling. This melted at 95–105° and was apparently a mixture of starting material and adduct.

Desulfuration of 3-Ethylthio-5-cholesten-7-one.—A. A mixture of 0.50 g. of 3-ethylthio-5-cholesten-7-one, 3.0 g. of Raney nickel catalyst, 40 ml. of purified dioxane, and 2 ml. of water was heated under reflux for three hours. The catalyst was removed by filtration and washed with warm dioxane. Removal of the solvents *in vacuo* gave 0.498 g. of white solid which melted at 106–135°. This material was dissolved in 125 ml. of boiling methanol. After standing for twenty-four hours at room temperature 0.24 g. of crystalline solid (m. p. 148–149°) had deposited. After standing at −10° for twenty-four hours, the filtrate deposited 0.050 g. of crystals melting at 142–145°. The filtrate was evaporated to a volume of 30 ml. When cooling to room temperature produced no precipitate, the solution was heated to boiling and water added to the point of turbidity. Cooling the solution gave 0.18 g. of white solid which melted at 100–108°. Crystallization of this material from methanol–butanone gave 0.10 g. of white solid which melted at 104–110°. Later observations indicated the more soluble fraction consisted largely of 7-cholestanol (m. p. 119–120°) mixed with 3-ethylthio-5-cholesten-7-one. On the basis of the recovery of 60% of relatively pure 3-ethylthio-5-cholesten-7-one, it was estimated that only about 25% desulfuration had taken place under these conditions.

B. A mixture of 0.500 g. of 3-ethylthio-5-cholesten-7-one, 5 g. of Raney nickel catalyst, 35 ml. of purified dioxane, and 1.0 ml. of water was sealed in an 100-ml. Carius tube. The mixture was heated in a bomb furnace at 120 ± 1° for twenty-four hours. There was a slight positive pressure on opening the tube. The nickel components were removed by filtration and the solvent removed *in vacuo*. A white solid remained. This was taken up in ether, the ether solution dried over anhydrous sodium sulfate and the ether removed. The crystalline solid which remained weighed 0.424 g. (96.5%) and melted at 109–112°. This material was sulfur free. Recrystallization of 0.40 g. from ethanol gave 0.227 g. (55%) of needles melting at 119–120° which had an $[\alpha]^{26}D + 38.1°$. This substance gave a negative Liebermann–Burchard reaction. These constants were somewhat different from those reported by Heilbron and co-workers[26] who give the melting point of 7-cholestanol as 119° and the rotation as +50.6°. The identity was proven by oxidation of the alcohol to 7-cholestanone following the directions of Marker, *et al.*[3b] From 0.20 g. of the alcohol there was obtained 0.16 g. of shiny plates which melted at 116.2–117.0°. This ketone was reduced to 7-cholestanol by the method of Heilbron, *et al.* The material was difficult to purify and after several crystallizations the needles obtained melted at 116.2–116.8°. This substance showed a marked depression in melting point when mixed with the starting ketone. A mixture with the alcohol (m. p. 119–120°) melted at 116.4–118.8°.

Stability of 3-Ethylthio-5-cholesten-7-one to Acid Conditions.—A. A mixture of 0.20 g. of 3-ethylthio-5-cholesten-7-one, 30 ml. of 95% ethanol, and five drops of concentrated hydrochloric acid was heated under reflux for three hours. When cooled the solution deposited long needles (0.20 g.) which melted at 150.8–151.8°. A mixed melting point with the starting material gave no depression.

(26) I. Heilbron, W. Shaw and F. Spring, *Rec. trav. chim.*, **57**, 529 (1938).

B. A mixture of 0.20 g. of 3-ethylthio-5-cholesten-7-one, 15 ml. of 95% ethanol and 5 ml. of concentrated hydrochloric acid was heated under reflux for six hours. The mixture had a faint red tinge and a mercaptan odor. After cooling 0.16 g. (80%) of starting material was recovered.

3-Ethylthio-5-cholesten-7-one Oxime (IX).—A mixture of 0.335 g. of 3-ethylthio-5-cholesten-7-one, 5 ml. of pyridine, 5 ml. of dry ethanol, and 0.50 g. of hydroxylamine hydrochloride was heated under reflux. Complete solution was effected when the mixture reached reflux temperature. After an eight-hour reflux period, considerable solid had formed. The mixture was cooled and the solid removed by filtration. This was washed with water and cold methanol and crystallized from dioxane–water to give 0.32 g. (92%) of crystalline solid which melted at 146–147°. The mixed melting point with the starting material was 119–129°. Recrystallization from 2-propanol gave micro needles which melted at 147.2–148.0°. The oxime gave a positive test for sulfur.

Anal. Calcd. for $C_{29}H_{49}OSN$: N, 3.05. Found: N, 3.22.

Reversal of Mercaptan Addition by Base.—A suspension of 0.40 g. of 3-ethylthio-5-cholesten-7-one in a solution of 0.50 g. of potassium hydroxide in 25 ml. of methanol was prepared. After standing for fourteen hours at room temperature, the mixture was heated under reflux. Complete solution was effected after one and one-half hours. The orange solution smelled strongly of ethyl mercaptan. After an additional one and one-half hours of heating, the solution was poured onto cracked ice and the organic material extracted with ether. The ether layer, after washing, drying, and evaporation yielded an orange solid. This substance was crystallized from methanol to give as a first crop (0.203 g.) of yellow crystalline material which melted at 105–107°. The mixed melting point with 3,5-cholestadien-7-one was 105–109°. The reversal was not complete under these conditions. The mixture was proven to be composed of the mercaptan adduct and 3,5-cholestadien-7-one when it was found that 0.190 g. of the mixture gave 0.189 g. of pure 3-ethylthio-5-cholesten-7-one melting at 150–151.5°. A second crop of 0.056 g. melting at 100–104° was obtained but was not investigated further.

7-Cholestanol.—The reduction of 3,5-cholestadien-7-one was carried out as described for 3-ethylthio-5-cholesten-7-one. The crude alcohol was recrystallized from ethanol and gave 0.30 g. (60%) of crystalline solid which melted at 119.2–120.2°. When the filtrate was evaporated and the residue crystallized from acetone, an additional 0.145 g. (29%) was obtained. This material melted at 115.5–117.0°. When mixed with the first fraction, the melting point was 116.0–117.5°. The total yield was 0.445 g. (89%).

Cholesterylisothiouronium *p*-Toluenesulfonate (XI).[10]—A suspension was prepared from 10.8 g. (0.02 mole) of 3β-*p*-toluenesulfonoxy-5-cholestene, 8.0 g. (0.105 mole) of thiourea and 140 ml. of 99% 2-propanol. The mixture was heated under reflux for four hours. Water (50 ml.) was added to the clear boiling solution at a rate which maintained ebullition. The resulting suspension was cooled to room temperature and then allowed to stand overnight in the cold room. The crystalline product was removed by filtration and washed with two 25-ml. portions of acetone (25°). The solid was dried for one hour in the air and for four hours *in vacuo* over phosphorus pentoxide at room temperature (30°). The yield of material melting at 227.5–229.0° was 11.8 g. (96%).

3β-Mercapto-5-cholestene (XII) was prepared according to the directions of King, Dodson and Subluskey.[10] From 9.84 g. of cholesterylisothiouronium *p*-toluenesulfonate there was obtained 6.10 g. (95%) of 3β-mercapto-5-cholestene, m. p. 88–95°. This material gave satisfactory results in the following preparation.

3β-Ethylthio-5-cholestene (XIII).—A solution of sodium ethoxide was prepared from 1.0 g. of sodium metal dissolved in 50 ml. of absolute ethanol. To this solution

there was added 4.10 g. (0.010 mole) of 3β-mercapto-5-cholestene. The mixture was heated to reflux temperature and the resulting solution cooled. Cold ethyl bromide (20 ml., 0.126 mole) was added and the resulting mixture heated under reflux for two hours. The mixture was poured onto 500 g. of ice and the resulting suspension extracted with ether. The ether layer was washed with water, 1.2 *N* hydrochloric acid, water, 5% sodium bicarbonate, and water. The dried ether layer was evaporated and the solid crystallized from acetone–ethyl acetate (4:1). The yield of material melting at 129.8–131.6° was 4.30 g. (98%). Recrystallization from acetone gave an analytical sample, m. p. 131.6–132.6°, $[\alpha]^{30}D$ −30.1° (0.0369 g. made up to 2.0 ml. with chloroform, αD −1.11°).

Anal. Calcd. for $C_{29}H_{50}S$: C, 80.85; H, 11.70. Found: C, 81.08; H, 11.76.

3β-Ethylsulfonyl-5-cholestene (XIV).—A solution of 2.15 g. (0.005 mole) of 3β-ethylthio-5-cholestene in 50 ml. of purified dioxane was prepared. The solution was cooled and 5.0 ml. of 30% hydrogen peroxide was added. The mixture was allowed to stand at room temperature for twenty-three hours and then heated under reflux for eight hours after the addition of 3.0 ml. of 30% hydrogen peroxide. The resulting solution was cooled and poured onto cracked ice. The suspension was extracted with two 200-ml. portions of ether. The ether layer was washed with 5% sodium bicarbonate and then with water. The solid resulting from the removal of the ether was dissolved in 110 ml. of 95% ethanol. Cooling produced a crystalline solid which melted at 149–152°. The yield was 1.4 g. (60%). Recrystallization from acetone gave an analytical sample, m. p. 150.8–151.6°, $[\alpha]^{33}D$ −18.9° (0.0456 g. made up to 2.0 ml. with chloroform, α −0.86).

Anal. Calcd. for $C_{29}H_{50}SO_2$: C, 75.27; H, 10.91. Found: C, 75.68; H, 10.98.

3β-Ethylsulfonyl-5-cholesten-7-one (XV): A. Oxidation of the Adduct.—A solution of 0.37 g. (0.864 mmole) of the adduct in 39 ml. of purified dioxane was prepared. After the addition of 3.0 ml. of 30% hydrogen peroxide, the mixture was allowed to stand for twenty-three hours at room temperature and then heated under reflux for nine hours. The resulting solution was poured onto ice. After standing overnight, the solid was removed by filtration. Crystallization from acetone–methanol gave 0.21 g. (52%) of solid melting at 186.5–188.5°. Another crystallization gave the analytical sample m. p. 190.0–192.0°, $[\alpha]^{27}D$ −64.2° (0.0340 g. made up to 2.0 ml. with chloroform, α −2.18°).

Anal. Calcd. for $C_{29}H_{48}SO_3$: C, 73.06; H, 10.15. Found: C, 72.91; H, 10.05, $\lambda_{max.}$ = 229 mμ, log $\epsilon_{max.}$ = 4.08 (in dry ether).

B. Oxidation of 3β-Ethylsulfonyl-5-cholestene.—A suspension of 1.00 g. (2.2 mmole) of 3β-ethylsulfonyl-5-cholestene in 15 ml. of glacial acetic acid was stirred vigorously and maintained at 55–58° while a solution of 0.75 g. of chromic oxide in 0.5 ml. of water and 1.5 ml. of glacial acetic acid was added over a period of forty minutes. The mixture was stirred and heated for an additional three hours. After addition of ethanol (1 ml.) to destroy the excess oxidizing agent, the warm solution was carefully diluted with 10 ml. of water. After standing overnight at 5°, the suspension was filtered and the solid washed with small portions of cold methanol until it was nearly colorless. The slightly grey solid was crystallized from acetone–methanol (1:2) to yield 0.25 g. (24%) of solid melting at 190.2–192.0°. The mixed melting point with the product from A gave no depression. The rotation was $[\alpha]^{33}D$ −64.2° (0.0385 g. made up to 2.0 ml. with chloroform, α −2.47°).

Reaction of Other Steroids with Ethyl Mercaptan in Acetic Acid–Hydrochloric Acid: A. Cholesteryl Acetate.—One gram of cholesteryl acetate was dissolved in a mixture of 35 ml. of acetic acid and 2 ml. of concentrated hydrochloric acid. Then 5 ml. of ethyl mercaptan was added to the cooled solution and the mixture allowed to stand for two hours at 0°. The solid was removed by filtration and washed with cold methanol. The dry solid (0.90 g., 90%) melted at 113–115°. Mixed melting point with starting material was 114–115°.

B. *i*-Cholestanone (3β-Chloro-6-cholestanone).—A solution of 0.105 g. of *i*-cholestanone[27] in 10 ml. of acetic acid and 0.5 ml. of ethyl mercaptan was prepared. Twenty drops of concentrated hydrochloric acid were added to the cold solution. After fifteen minutes, 5 ml. of methanol was added and the solution cooled. When no solid resulted from this treatment, water was carefully added. This resulted in the separation of a white solid. The mixture was cooled for two hours and the solid was removed by filtration and washed with cold methanol. After air drying, the solid melted at 127–129°. The mixed m. p. with 3β-chloro-6-cholestanone[15] was 127–128°. The yield was 0.090 g. (80%).

C. 3-Cholestanone (3-Cholestanone Diethyl Mercaptole).—A mixture of 0.49 g. of 3-cholestanone, 18 ml. of acetic acid, and 1.0 ml. of ethyl mercaptan was prepared. Addition of five drops of concentrated hydrochloric acid gave a cloudy suspension. Cooling for forty minutes gave a solid mixture. Addition of 15 ml. of methanol caused the solid to change to an oil. Cooling for an hour and scratching produced a solid. This was removed by filtration and washed with cold methanol. The air dried solid weighed 0.56 g. (93%) and melted at 76–78°. This was 3-cholestanone diethyl mercaptole.[5a]

D. Cholestenone (3-Ethylthio-3,5-cholestadiene).—Ten drops of concentrated hydrochloric acid was added to a mixture of 20 ml. of acetic acid, 2 ml. of ethyl mercaptan, and 1.10 g. of cholestenone. The solution soon became cloudy. Scratching and cooling gave a white solid. The mixture was cooled for one-half hour. The solid was removed by filtration and washed with three 5-ml. portions of cold methanol. The finely divided solid weighed 1.08 g. (88%) and melted at 94–95°. Recrystallization from 35 ml. of acetone gave 0.95 g. (78%) of crystalline solid melting at 97.4–98.2°. The analysis of the material corresponded to that reported by Bernstein and Dorfman[5a] when calculated on the basis of the correct formula, $C_{29}H_{48}S$; $[\alpha]^{26.4}D$ −128.8° (69.3 mg. made up to 4.93 ml. with $CHCl_3$, α −4.93°, *l*, 2 dm.); $\lambda_{max.}$ = 272 mμ (log ϵ = 4.41), taken in dry ether.

Summary

1. The keto group of 7-ketocholesteryl acetate has been reduced by converting to the ethylene mercaptole and desulfurizing.

2. In an acetic–hydrochloric acid solution, 7-ketocholesteryl acetate, 7-ketocholesteryl chloride and 3,5-cholestadien-7-one react with ethyl mercaptan to give 3-ethylthio-5-cholesten-7-one. 3,5-Cholestadien-7-one is the common intermediate for this reaction.

3. The reaction of ethyl mercaptan with 3,5-cholestadien-7-one is a new 1,6 addition.

4. The structure of 3-ethylthio-5-cholesten-7-one was established by conversion to 3-ethylsulfonyl-5-cholesten-7-one which was prepared by an independent synthesis.

5. Improved procedures are described for the preparation of 7-cholestanol, diethyl mercaptole of 3-cholestanone and for 3-ethylthio-3,5-cholestadiene (from cholestenone).

EVANSTON, ILLINOIS RECEIVED MARCH 25, 1949

(27) A. Windaus and O. Dalmer, *Ber.*, **52**, 162 (1919).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MARYLAND]

A Spectrophotometric Study of Ferric Thiocyanate in Isodielectric Mixtures of Various Aqueous–non-Aqueous Solvent Pairs[1]

BY SIDNEY BALDWIN AND W. J. SVIRBELY

Woods and Mellon[2] recently made a spectrophotometric study of ferric thiocyanate in acetone–water solutions at various volume concentrations. Their work showed that as the volume per cent. of acetone in the solution was increased, the corresponding absorption curve, plotted as per cent. transmittancy *versus* wave length, had a consistently deeper minimum. This decrease in transmittancy with increasing concentration of acetone was attributed to the lower dielectric constant of the solution.

The present study was undertaken in order to clarify the role of the dielectric constant of the medium in the ferric thiocyanate system. It would seem that if the intensity of color is solely a function of the dielectric constant of the solvent, with the other variables, such as concentrations and temperature kept constant, the absorption curves for this system should be identical in all isodielectric mixtures, regardless of the solvent pair. Accordingly, the absorption spectra of ferric thiocyanate was investigated at various fixed dielectric constants in the following solvent pairs: acetone–water, methanol–water, ethanol–water, isopropyl alcohol–water, ethylene glycol–water and dioxane–water.

Materials

Nitric Acid.—J. T. Baker Analyzed nitric acid was distilled from an all-glass apparatus, collecting the middle 50%. The distillate was allowed to remain twenty-four to thirty-six hours under a hood to remove dissolved nitrogen dioxide. A nitric acid solution, 6.04 *N*, was prepared from the distillate. The standardization was with sodium tetraborate decahydrate, using methyl red as an indicator; d^{25}_4 1.1933. The solution was stored in a dark, cool place.

Ferric Nitrate.—J. T. Baker Analyzed (99.8% pure) iron wire (0.1 g.) was dissolved in about 10 ml. of the 6.04 *N* acid. Hydrogen peroxide (30%) was added to insure complete oxidation to ferric ion. The solution was evaporated to dryness on a steam-bath. The residue was dissolved in exactly 10 ml. of 6.04 *N* nitric acid and diluted to 1 liter. A 100-ml. aliquot portion of this solution was diluted to 250 ml., giving a solution containing 40 p. p. m. of iron in 0.024 *N* nitric acid. The solution was stored in a cool, dark place; d^{25}_4 1.0015.

Ammonium Thiocyanate.—J. T. Baker Analyzed salt was used without further purification: 100 g. of ammonium thiocyanate was dissolved in 400 g. of water. The resulting solution contained 20% of ammonium thiocyanate by weight; d^{25}_4 1.0452. It was stored in a cool, dark place.

Methyl Alcohol.—A liter of Mallinckrodt acetone-free methanol was refluxed[3] over 15–20 g. of magnesium turnings for three hours. The methanol was then fractionally distilled through a 50-in. Fenske column. The middle 500-ml. portion was collected: $n^{20}D$ (obsd.) 1.3285, $n^{20}D$ (lit.) 1.3288.

Ethyl Alcohol.—A liter of U. S. Industrial commercial absolute alcohol was refluxed[4] over 7 g. of sodium and 27.5 g. of diethyl phthalate for one hour. It was then fractionally distilled, collecting the middle 500-ml. portion, $n^{20}D$ (obsd.) 1.3610, $n^{20.5}D$ (lit.) 1.3610.

Acetone.—About 2.5 liters of J. T. Baker Analyzed acetone was treated[5] with 100 ml. of 85% phosphoric acid. The acetone was distilled through an 18-in. Vigreux column, collecting the middle 2-liter portion. This portion was dried for forty-eight hours over anhydrous potassium carbonate and then fractionally distilled, collecting the middle 1500-ml portion: $n^{20}D$(obsd.) 1.3586; $n^{20}D$ (lit.) 1.3591.

Dioxane.—About 2 liters of U. S. Carbon and Carbide dioxane was purified by a standard procedure.[4] The middle 1-liter portion was collected after fractionation: $n^{20}D$(obsd.) 1.4215; $n^{20}D$(lit.) 1.4221.

Isopropyl Alcohol.—About 2 liters of Eastman Kodak Co. (98–99%) isopropyl alcohol was fractionally distilled, collecting the middle 80%. This was then dried for eighteen hours over anhydrous sodium sulfate in a refrigerator. It was then refractionated; $n^{20}D$(obsd.) 1.3768, $n^{20}D$(lit.) 1.3776.

Ethylene Glycol.—About 2 liters of Eastman Kodak Co. Technical grade was fractionated. The fraction boiling between 197–198° was collected and dried over sodium sulfate for a week in a refrigerator. This portion was then vacuum-distilled and the fraction boiling between 107–108° at 9.5 mm. pressure was collected: $n^{20}D$ (obsd.) 1.4309; $n^{20}D$ (lit.) 1.4318.

Experimental Method

The weight percentage of water at 25°, corresponding to dielectric constants of 30, 40, 50, 60 and 70, were obtained from the literature.[5] From calculations involving density data, the correct volumes of organic solvent and water required to give the desired dielectric constant were determined.

After the reagents had attained thermal equilibrium in a thermostat, the following procedure was used in preparing a solution: five ml. of ferric nitrate solution, 5 ml. of nitric acid solution and 2 ml. of ammonium thiocyanate solution were placed, in the order listed, in a thermostated, calibrated, 50-ml. volumetric flask. Allowing for the water already present in the reagents used, the calculated volumes of organic solvent and water required to give a definite dielectric constant were added to the flask. Dilution, to the mark, was made by a previously prepared mixture of the solvent-pair having the desired dielectric constant. The above procedure allowed the maintaining of a constant iron concentration of 4 p. p. m. in all cases and also kept the *p*H of the solution within the desirable limits[2] of 0.70 to 0.25. The solution was thoroughly mixed and the absorption data were obtained within one-half hour after development of the color. Very little fading was observed in that time limit. The blank consisted of a solution of the same solvent-pair made up to the same dielectric strength.

All absorption measurements were made with a Beckman Model D U Quartz Spectrophotometer, using specially matched corex cells. These cells, 0.998 cm. in depth, were thoroughly rinsed 3 or 4 times with the solution to be measured, and the faces wiped dry with a lintless cloth. Per cent. transmittancy values were read at 10 mμ inter-

(1) Part of a thesis submitted by Sidney Baldwin to the Graduate School of the University of Maryland in partial fulfilment of the requirements for the degree of Master of Science.

(2) Woods and Mellon, *Ind. Eng. Chem., Anal. Ed.*, **13**, 551 (1941).

(3) Bjerrum and Zechmeister, *Ber.*, **56**, 894 (1923).

(4) Fieser, "Experiments in Organic Chemistry," D. C. Heath & Co., Boston, Mass., 1941.

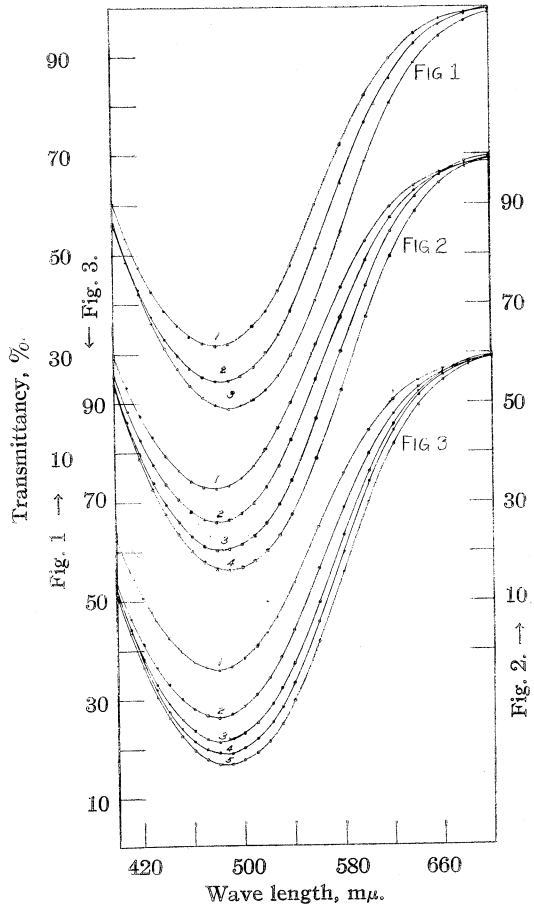
(5) Åkerlöf, THIS JOURNAL, **54**, 4132 (1932).

vals from 400 to 540 mμ and at 20 mμ intervals from 540 to 700 mμ. The instrument was operated at maximum sensitivity and at narrow slit width (0.02 mm.). Two runs were made at each dielectric strength for each solvent pair. If the values checked within 1–2% at each wave length, no further runs were made. The average of the two runs was used.

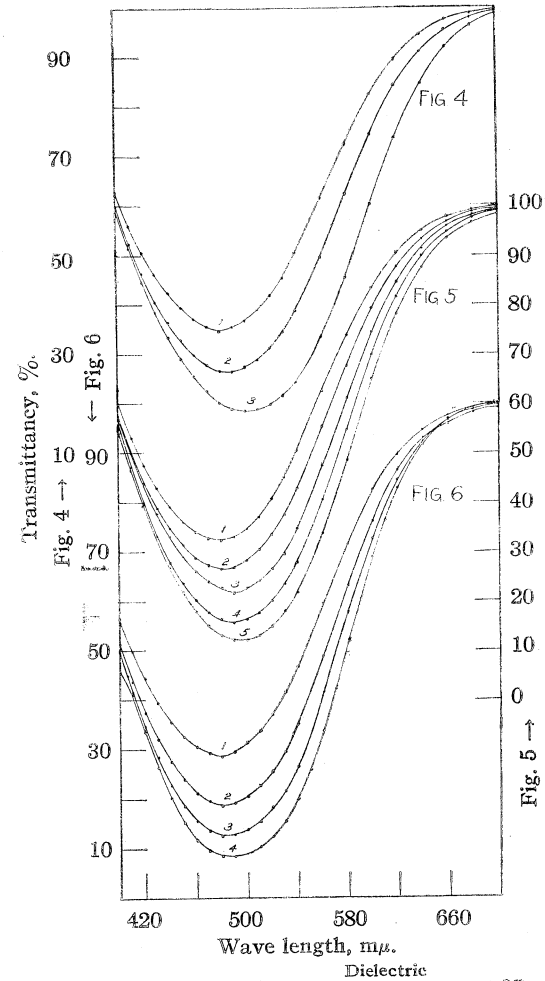
A Coleman Model 4D *p*H meter was used for measuring the acidity of the solutions after the transmittancy curves were taken in order to check the *p*H.

The wave length scale of the spectrophotometer was not calibrated. The photometric scale was checked using a solution of potassium chromate in 0.05 *N* potassium hydroxide. The values obtained checked very well with those reported by previous workers.[6]

During absorption measurements, the cuvettes were not temperature controlled, due to conditions not under our control. The room temperature was essentially constant during each run. The temperature range, in which all the measurements were made, was 28.0 ± 1.2°. The calculated volumes of non-aqueous solvent and water used in the various mixtures, gave the desired dielectric constant at 25°. It was realized that, owing to the dissolved electrolytes and to the difference in temperatures, the value of the existing dielectric constant would differ from the desired value. Nevertheless, it was assumed that, since the same concentrations of reagents were used in all the determinations, and since the experimental temperatures in all except a few cases were reasonably close



	Curve	Dielectric constant	°C.
Fig. 1.—Methanol–water solutions	1	70	29.0
	2	60	28.0
	3	50	28.0
Fig. 2.—Ethanol–water solutions	1	70	27.2
	2	60	26.8
	3	50	26.8
	4	40	27.2
Fig. 3.—Isopropyl alcohol–water solutions	1	70	27.5
	2	60	27.8
	3	50	27.8
	4	40	27.4
	5	30	27.5



	Curve	Dielectric constant	t °C.
Fig. 4.—Ethylene glycol–water solutions	1	70	28.3
	2	60	28.1
	3	50	29.2
Fig. 5.—Dioxane–water solutions	1	70	28.4
	2	60	28.6
	3	50	29.1
	4	40	28.6
	5	30	28.6
Fig. 6.—Acetone–water solutions	1	70	28.1
	2	60	28.1
	3	50	28.3
	4	40	29.0

(6) Von Halban and Siedentopf, *Z. physik. Chem.*, **100**, 208 (1922).

to 28°, both effects would cause almost an equal variation in any fixed, calculated, dielectric constant. Consequently, the solutions prepared should have the same relative dielectric strength even if the absolute values referred to in our data are not strictly valid.

Discussion of Data

The spectrophotometric curves for the six solvent pairs are shown in Figs. 1–6. In all cases, the absorption decreases as aqueous conditions are approached. In general, there is a larger difference between the minima at the higher dielectric constant values than at the lower values. Figures 1–6 also show that there is a slight hypsochromic effect, *i. e.*, there is a shift in the peak of the absorption band toward lower wave lengths as aqueous conditions are approached. This is in agreement with the work of Woods and Mellon[2] in acetone–water solvents. It contradicts the observations of Schlesinger and Van Valkenburgh,[7a] who claim that there is no difference in the absorption spectra of aqueous solutions of ferric thiocyanate and of non-aqueous solutions of ferric thiocyanate.

TABLE I

WAVE LENGTHS WHERE MINIMA OCCUR

Solvent pairs	Dielectric constant 30	40	50	60	70
Acetone–water		490	483	480	480
Methanol–water			492	483	480
Ethanol–water		490	487	485	480
Isopropanol–water	485	485	480	480	480
Ethylene glycol–water			503	488	480
Dioxane–water	495	490	490	483	480

Our data for the hypsochromic effect are summarized in Table I.

An examination of the transmittancy curves for the various isodielectric mixtures also shows that acetone–water mixtures have lower per cent. transmittancy values than any of the other corresponding isodielectric media. Furthermore, reference to Table I shows that the minima did not usually occur at the same wave length in the various isodielectric media. Thus it is evident that specific solvent effects are also in operation in addition to any operating dielectric effect.

Before attempting to explain the above observations, we would like to call attention to Table II, which is a summary of conclusions concerning the nature of the species causing the color in the ferric thiocyanate system. In regard to absorption work, the following observations have been made. Frank and Ostwalt[7g] showed that the positive complex $Fe(SCN)^{++}$ had an absorption minimum at about 447.5 mμ. Woods and Mellon[2] observed that as the ammonium thiocyanate added was increased from 0.5 to 5.0 ml., (SCN^-/Fe^{+3} changed from 76 to 765), the intensity increased and the peak of the absorption band shifted from 460 to 480 mμ. They also observed that the absorption band of a solution obtained by extracting the ferric thiocyanate complex with a mixture of equal volumes of amyl alcohol and ethyl ether had about the same intensity as that of an acetone solution of the same concentration of iron. However, the peak of the absorption band of the extract was at 500 mμ. Since in non-aqueous solvents[7a,e] the iron exists as the dimer, $Fe_2(SCN)_6$, one concludes that the absorption maximum at 500 mμ must be due to the dimer. Absorption maxima between 447 mμ and 480 mμ depend on the nature of the complex ion present.

TABLE II

SUMMARY OF CONCLUSIONS CONCERNING NATURE OF COLORED SPECIES

Reference 7	Solvent	Fe^{+3} (*M*)	SCN^{-1} (*M*)	$\frac{SCN^{-1}}{Fe^{+3}}$	Nature of colored species
a	Aqueous				$Fe(SCN)_6^{-3}$
a	Ether or benzene				$Fe[Fe(SCN)_6]$
b	Aqueous				$Fe(SCN)^{++}$, $Fe(SCN)_2^+$, $Fe(SCN)_3$ and possibly $Fe(SCN)_4^-$ at high thiocyanate concn.
c	Aqueous	0.003582	0.000109 to 0.6322	0.03–176	$Fe(SCN)^{++}$, $Fe(SCN)_2^+$
d	Non-aq.				Dimer, $Fe_2(SCN)_6$
d	Aqueous	.1	4	40	$Fe(SCN)_4^-$
e	96% Ethanol	.1	0 to 0.80	0–8	Dimer, $Fe_2(SCN)_6$
e	96% Ethanol	0–0.50	.5	0–1	Dimer, $Fe_2(SCN)_6$
f	Aqueous	.002	.01–0.02	5–10	Positive complexes $Fe(SCN)^{++}$, $Fe(SCN)_2^+$
f	Aqueous	.002	.2–0.4	100–200	Negative complexes $Fe(SCN)_4^-$ to $Fe(SCN)_6^{-3}$
g	Aqueous	.001–0.008	.0003	0.3–0.0375	$Fe(SCN)^{++}$
g	Aqueous	.0003	.003	10	Higher complexes
h	Organic solvent–water mixture	$.0716 \times 10^{-3}$	.11	1540	Probably $Fe_2(SCN)_6$ and negative complexes

(7) (a) Schlesinger and Van Valkenburgh, THIS JOURNAL, **53**, 1212 (1931); (b) Møller, *Kem Maanedsblad*, **18**, 138 (1937); *C. A.*, **33**, 9179 (1939); (c) Bent and French, THIS JOURNAL, **63**, 568 (1941); (d) Schlesinger, *ibid.*, **63**, 1766 (1941); (e) Uri, *J. Chem. Soc.*, 336 (1947); (f) Babko, *J. Gen. Chem.* (*U. S. S. R.*), **16**, 1549 (1946); *C. A.*, **41**, 4732 (1947); (g) Frank and Ostwalt, THIS JOURNAL, **69**, 1321 (1947); (h) present study.

TABLE III

Compound	450 mμ Regression equation[a]	δest_T[b]	480 mμ Regression equation[a]	δest_T	520 mμ Regression equation	δest_T
Acetone	$\log T = 0.0117D + 0.700$	0.74	$\log T = 0.0177D + 0.216$	0.51	$\log T = 0.0161D + 0.446$	0.31
	$T = 8.56 \times 10^{-7}D^4 + 13.2$	.57	$T = 9.47 \times 10^{-7}D^4 + 6.29$	.26	$T = 11.6 \times 10^{-7}D^4 + 10.1$	1.33
Ethanol	$\log T = 0.00641D + 1.10$	.81	$\log T = 0.010D + 0.808$	.39	$\log T = 0.0103D + 0.893$	0.50
Methanol	$\log T = 0.00617D + 1.12$	1.07			$\log T = 0.0116D + 0.774$	0.54
	$T = 5.04 \times 10^{-7}D^4 + 23.5$	0.56	$T = 6.52 \times 10^{-7}D^4 + 15.5$	.10		
Glycol	$\log T = 0.00671D + 1.12$	.82	$\log T = 0.0121D + 0.699$	.32	$\log T = 0.0162D + 0.498$	1.87
	$T = 5.92 \times 10^{-7}D^4 + 25.2$	.10				
Dioxane	$\log T = 0.00549D + 1.17$	.90	$\log T = 0.0101D + 0.818$	1.30	$\log T = 0.0109D + 0.862$	1.06
Isopropanol	$T = 7.24 \times 10^{-7}D^4 + 21.8$	.82	$T = 7.96 \times 10^{-7}D^4 + 16.4$	0.57	$T = 9.50 \times 10^{-7}D^4 + 21.7$	0.67

[a] Where D = dielectric constant. T = per cent. transmittancy; [b] δest_T = unbiased standard error of estimate of T found from the regression equation.

Therefore, based on the hypsochromic effect, in light of the conclusions of other investigators concerning the nature of the colored species, we can conclude that in this investigation (the ratio of thiocyanate to iron was 1540) the color forming species is mainly a mixture[8] of $Fe_2(SCN)_6$ and various negative complex ions. On approaching non-aqueous conditions, $Fe_2(SCN)_6$ predominates,[7d,e] while on approaching aqueous conditions, the negative complexes, in particular $Fe(SCN)_6^{-3}$ become more important.

If one assumes that the following equilibrium reaction exists $Fe(SCN)_6^{-3} + Fe^{+3} \leftrightarrows Fe_2(SCN)_6$, (1) then the increase in color intensity on approaching non-aqueous conditions is explainable if the color of $Fe_2(SCN)_6$ is assumed to be more intense than that of the negative complex. Furthermore, the equilibrium serves to explain the specific solvent effects. If there is a tendency for the solvent to donate a free electron pair to Fe^{+3}, then a strong electron donating solvent would favor the dissociation of $Fe_2(SCN)_6$ into ions, while a weaker electron donating solvent would favor association into $Fe_2(SCN)_6$, thereby producing a greater color intensity. Acetone, according to this study, thus would have a weak electron donating tendency compared to the other organic solvents used. The concept that acetone is a poorer electron donor is tantamount to saying that it is a weaker base than the other organic solvents used in this study. Measurements of Koch[9] based on solvation activity coefficients of Ag^+ in various solvents, placed the solvents in the following order of decreasing basicity: methanol, ethanol and acetone. The same order holds equally well for the basicity with respect to H^+ and it seems reasonable to expect it to hold also for Fe^{+3}. Although there are no values listed for the other organic solvents used in this study, it appears likely that they should have electron donating tendencies not too far different from methanol and ethanol. Thus, acetone should favor the equilibrium in reaction (1) to the right to a much greater extent than any of the other solvents used.

In trying to correlate per cent. transmittancy with some property of the solvent, we obtained two general empirical relations, if the dielectric constant was treated as the independent variable, namely

$$T = mD^4 + b \quad (1)$$

$$T = a10^{cD} \text{ or } \log T = \log a + cD \quad (2)$$

where T is the per cent. transmittancy, D is the dielectric constant and m, b, a and c are empirical constants which were evaluated by the method of least squares. The results are given in Table III. We would like to state, however, that it is impossible to distinguish between specific solvent effects and dielectric effects. These equations serve to generalize the data. No trend was observed when either weight per cent. or mole-fraction of water was used as the independent variable.

Acknowledgment.—The authors are indebted to Dr. A. Kramer of the Department of Horticulture, University of Maryland, for his permission to use the Beckman Spectrophotometer in that department.

Summary

1. The absorption curves for ferric thiocyanate at an iron concentration of 4 p. p. m., at relative dielectric constants of 30, 40, 50, 60 and 70 have been measured in the range of 400 to 700 mμ in the following solvent pairs: methanol–water, ethanol–water, isopropyl alcohol–water, ethylene glycol–water, dioxane–water, and acetone–water. The work was carried out at about 28° with a Beckman Model DU Spectrophotometer.

2. In general, on approaching aqueous conditions a decrease in intensity of color and a shifting of the absorption peak to a lower wave length are observed. These experimental observations are accounted for by postulating that $Fe_2(SCN)_6$ and $Fe(SCN)_6^{-3}$ are the species causing the color and that the former has a more intense color than the latter.

3. The increased intensity in acetone–water solutions compared to other solvent–water mixtures is attributed to the feeble, basic character of acetone compared to the other organic solvents used.

4. Equations have been obtained empirically showing the correlation of per cent. transmittancy with the dielectric strength of the solution.

(8) The possibility of existence of other complex ions is not denied. In light of the work summarized in Table II, it appears that in our case the highly negative complexes would be the most important.

(9) Koch, *J. Chem. Soc.*, 269 (1928); *Phil. Mag.*, [7] **11**, 579 (1931).

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY AND THE INSTITUTE FOR NUCLEAR STUDIES, UNIVERSITY OF CHICAGO]

Applications of Radioactive Chlorine to the Study of the Mechanisms of Reactions Involving Changes in the Oxidation State of Chlorine

BY HENRY TAUBE AND HAROLD DODGEN

In the chlorine system of oxidation states in water solution representatives of each of the stages between −1 and +7, the +2 and +6 only excepted, are known. Thus each of the substances Cl^-, Cl_2, $ClO^-(HOCl)$, $ClO_2^-(HClO_2)$, ClO_2, ClO_3^- and ClO_4^- persists in water solution and can be well characterized. The reactions of these substances offer a rich field for kinetic investigations and unusual opportunities for reaching a detailed understanding of mechanisms. In this paper is presented an account of experiments which have been done on the mechanisms of some of the reactions using radioactive chlorine as a tracer. The changes studied were oxidation–reduction reactions, and in all cases both the oxidizing and the reducing agents contained chlorine. Experiments have been carried out on the following reactions: (a) the interaction of chlorous acid and chlorate ion, (b) the interaction of chlorine (or hypochlorite) and chlorite, (c) the interaction of chloride ion and chlorate (and the reverse reaction), and (d) the disproportionation of chlorous acid. Included also are experiments on the exchange of chlorine atoms between hypochlorite and chlorite ions and between chlorine and chlorate ion in acid solutions.

Some of the reactions here studied have been investigated kinetically by other workers. While the published data are for the most part incomplete and often conflicting, they are of value in reaching conclusions about the mechanisms of the reactions. In no case do the observations made thus far, including those reported here, suffice to establish mechanisms, but they do in every case lead to significant conclusions. It will be shown that the observations on reactions (b), (c) and (d) require that the activated complex be unsymmetrical in every case, and that the observations for the three reactions can be correlated if an intermediate of the type Cl—Cl<O/O (or Cl—O—Cl—O) is assumed to be present.

The present paper includes a discussion of earlier work as well as of that performed by us. It is offered as an orienting survey of the reactions in this field, and will be amplified by further experiments. These will include detailed studies of stoichiometry and rates, and will make further applications of isotopes as tracers.

An interesting feature of the reactions in acid solution is that chlorine dioxide is frequently a product. Although not a stable end-product, it persists for long periods of time; both the rate at which it disproportionates and the rate at which it reacts with chlorine in other oxidation states in acid at room temperature are slow. Chlorine dioxide appears in the disproportionation of chlorate in acid, in the reduction of chlorate by chloride ion, the oxidation of chlorite by chlorine or hypochlorous acid and in the disproportionation of chlorite in acid. The feature that chlorine dioxide is present in the system, or that it can readily be generated from some of the substances present, has greatly simplified the work. Chlorine dioxide can readily be separated from other chlorine species using extraction procedures, and most of the tests for radioactivity were therefore made with it. Experiments reported earlier[1] have established the necessary facts about the exchange of activity between chlorine dioxide and chlorine in other oxidation states.

General Experimental Procedures, Conditions, Definitions.—For the tracer experiments the isotope $_{17}Cl^{38}$ was used. It was produced by exposing the appropriate chlorine containing substance to the slow neutron radiation of the University of Chicago cyclotron. For experiments which required the radioactivity to be present in Cl^- or Cl_2, aqueous solutions of hydrogen chloride and of chlorine were exposed. The oxalic acid method previously described was applied in the preparation of Cl^*O_2.[1] A solution containing the chlorine radioactivity as ClO_3^- was prepared by disproportionation of radioactive chlorine in aqueous phosphate buffer at 95°, the chloride ion then being removed by adding silver ion and filtering off the precipitate of silver chloride.

Account of activity was kept in terms of specific activity,[1] $I_0/(100C)$. I_0 is the counting rate expressed in arbitrary units, and C is the concentration expressed as gram atoms per liter of the species containing radioactive chlorine. In all cases solutions in carbon tetrachloride were counted. Chlorine and chloride exchangeable activity were removed from solutions of Cl^*O_2 in carbon tetrachloride by extraction with portions of an aqueous solution 0.5 M in potassium chloride containing also phosphate buffer at a pH above 7. Where activity was present in Cl^-, the specific activity was established by exchanging with chlorine added in known amount, then counting chlorine in carbon tetrachloride and determining the concentration of chlorine in the solutions.

Unless otherwise stated, the temperature at which the experiments were conducted was 25 ± 2°.

The data used in calculating equilibrium constants, with the exception of those for ClO_2^- and

(1) Dodgen and Taube, THIS JOURNAL, 71, 2501 (1949).

$HClO_2$, are taken from Latimer "Oxidation Potentials."[2] For ClO_2^- and $HClO_2$ the newer values reported by Fontana and Latimer[3] are used. In all changes involving chlorine dioxide, the values for the equilibrium constants refer to the gas as the standard state for this substance. The value of the coefficient for the distribution of chlorine dioxide[4] between gas and water has been measured in these laboratories. The concentration in solution is 25 times as great as the concentration in the gas phase at 25°.

Results and Discussion

The Reaction: $2H^+ + ClO_2^- + ClO_3^- = H_2O + 2ClO_2$ (g). The present interest in the system ClO_2^-, ClO_3^-, and ClO_2 in acid was to learn something about the rate at which ClO_2^- and ClO_3^- interact in acid. Since the position of equilibrium and the rate of the reverse reaction are pertinent to a consideration of the rate of the forward reaction, a brief discussion of the observations on these aspects of the reaction is presented.

The equilibrium constant for the reaction as represented in the heading is 36. For the net change with $HClO_2$ replacing $H^+ + ClO_2^-$, it is 0.36. These constants show that at equilibrium in neutral solution chlorine dioxide would be almost completely disproportionated, and that even in fairly acid solution the disproportionation would be largely complete. It is known, however that the change is slow except in alkaline solution. For example, a solution in the dark at 0° initially 0.155 *M* in ClO_2, 0.0011 *M* in H^+ and also containing the catalyst chloride ion at 0.001 *M* was observed by Bray[5] to decompose only about 1% in seven weeks. The rate law for the disproportionation in alkali for concentrations of chlorine dioxide in excess of about 10^{-3} *M* was observed to be[5]

$$-d(ClO_2)/dt = k(ClO_2)^2(OH^-)$$

with the specific rate at 0° equal to 330 $l.^2$ $mole^{-2}$ $min.^{-1}$ and the temperature coefficient 1.81. These data show that disproportionation by this path in acid will be very slow, amounting to only about 10^{-80}% in one hour at 25° for a solution 0.1 *M* in ClO_2 and 1 *M* in H^+.

The rate of the forward reaction, $ClO_2^- + ClO_3^-$, has been the subject of considerable discussion. Bray[5] has reviewed the evidence which suggests that the reaction proceeds at an appreciable rate, and has concluded that there is but a single observation which supports this view. This observation[6] is that ClO_3^- enhances the rate at which chlorine dioxide is formed in an acidified solution of chlorite. However, the data reported in his paper indicate no appreciable difference in the rate of decomposition of $HClO_2$ for two solutions in which the concentrations of ClO_3^- are widely different.

The fact that the rate of hydrolysis of chlorine dioxide is very slow in acid, coupled with the fact that the equilibrium constant is about unity requires that the rate at which $HClO_2$ and ClO_3^- react must also be very slow. A direct experimental demonstration, necessary perhaps because the equilibrium constants are probably not very accurate, that ClO_2 and $HClO_2 + ClO_3^-$ do not enter into a rapidly established equilibrium is our observation[1] that no measurable exchange takes place between ClO_2 and ClO_3^- in acid in a period of an hour. An even more direct check has been attempted—to discover whether any of the ClO_2 which forms when ClO_2^- disproportionates in acid in the presence of ClO_3^- is derived from the chlorate ion. This was done by using inert ClO_2^- mixed with radioactive ClO_3^- and testing for the appearance of radioactivity in the product ClO_2.

Experiment.—The initial composition of the reaction mixture of volume 23 cc. was: 0.14 *M* $Cl^*O_3^-$, 0.037 *M* chlorite, 0.73 *M* H_2SO_4 and 0.1 *M* H_3PO_4. After fifteen minutes had elapsed, during which time about 20% of the chlorite decomposed, 20 cc. of carbon tetrachloride was added and the mixture shaken. The carbon tetrachloride layer was drawn off, and chloride exchangeable activity removed by two successive washings with 5-cc. portions of the chloride + buffer solution. The specific activity of the chlorine dioxide was found to be 0 ± 10. To establish the specific activity of ClO_3^-, the residual chlorite in the water layer was decomposed by acidifying with hydrochloric acid, the chlorine dioxide formed removed with carbon tetrachloride, then $Cl^*O_3^-$ was reduced to Cl^*O_2 by making the solution strongly acid with sulfuric acid. The specific activity of the chlorine dioxide (which will be almost identical with that of chlorate ion—see below) was measured and found to be 2000 ± 61.

This experiment shows that in acid solution, the reaction of $HClO_2$ with ClO_3^- is very much slower than is the disproportionation of $HClO_2$. Under the conditions of our experiments, less than 3% of the chlorine dioxide was formed by the former reaction. If both are second order in the chlorine species, the specific rate of the $HClO_2 + ClO_3^-$ reaction is less than 1/100 that of the $HClO_2 + HClO_2$ reaction. The experiment confirms the conclusion for which other evidence has been cited above, that ClO_3^- and $HClO_2$ even in acid react only very slowly. The contrast in this respect for the system $HClO_2$–ClO_2–ClO_3^- with the analogous one in nitrogen chemistry is striking: HNO_2 is outstanding among ordinary reducing agents for the speed at which it reduces NO_3^-.

The Reaction of Chlorite (ClO_2^- or $HClO_2$) with Chlorine and with Hypochlorite.—Both chlorine dioxide and chlorate ion are products when chlorine reacts with chlorite in acid solu-

(2) Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938.

(3) Fontana and Latimer, THIS JOURNAL, **69**, 2598 (1947).

(4) Experiments by John W. Born and Edward F. Gurnee.

(5) Bray, *Z. anorg. allgem. Chem.*, **48**, 217 (1906).

(6) (a) Ref. 5, p. 238; (b) ref. 5, p. 241, *cf.* Expts. 2 and 6 of Table XV.

TABLE I

TEST OF MECHANISM FOR THE OXIDATION BY CHLORINE OF CHLORITE TO CHLORINE DIOXIDE AND CHLORATE ION[a]

Expt.	Reaction	(H⁺)	$\frac{I_0}{100C}$ obs.	$\frac{I_0 b}{100C\infty}$	%
1	$Cl_2^* + 2HClO_2 = 2ClO_2 + 2Cl^- + 2H^+$	0.3	7 ± 3	128	6 ± 2
2	$Cl_2^* + 2HClO_2 = 2ClO_2 + 2Cl^- + 2H^+$	0.25	9 ± 3	127	7 ± 2
3	$Cl_2^* + 2HClO_2 = 2ClO_2 + 2Cl^- + 2H^+$	0.30	258 ± 6	4560	5.6 ± 0.1
4	$HCl^*O + 2ClO_2^- = 2ClO_2 + Cl^- + OH^-$	5×10^{-8}	26 ± 11	583	5 ± 2
5	$HCl^*O + 2ClO_2^- = 2ClO_2 + Cl^- + OH^-$	10^{-8}	81 ± 8	1780	4.6 ± 0.5
6	$HCl^*O + ClO_2^- = ClO_3^- + Cl^- + H^+$	10^{-8}	156 ± 10	1780	8.8 ± 0.6

[a] Temperature 25°. Perchloric acid was used in the strongly acidic solutions, phosphate buffer for those of higher *p*H. Calculated for random distribution among the chlorine atoms present as Cl^-, Cl_2, HClO, $HClO_2$, ClO_2, ClO_3^-.

tion. In neutral or weakly alkaline solution, the chlorine is largely present as HClO and Cl^-. Under these conditions both ClO_2 and ClO_3^- still appear as products, but the ratio of ClO_3^- to ClO_2 is greater than for acid solutions. Typical observations on the stoichiometry with halogen in excess are the following. In a solution initially 0.4 *M* in perchloric acid, 0.020 *M* chlorine and 0.024 *M* chlorite, 7.8% of the chlorite is oxidized to ClO_3^-, the remainder to ClO_2. In a solution at *p*H about 7.5, with initial HClO at 0.020 *M*, and initial ClO_2^- at 0.024 *M*, 28% of the chlorite is oxidized to chlorate.

The equations expressing the net changes in acid are

$$Cl_2 + 2HClO_2 = 2ClO_2 + 2Cl^- + 2H^+ \quad \Delta F^0 = -6490$$

$$Cl_2 + HClO_2 + H_2O = ClO_3^- + 2Cl^- + 3H^+ \quad \Delta F^0 = -7050$$

and for solutions near the neutral point

$$HOCl + 2ClO_2^- = 2ClO_2 + Cl^- + OH^- \quad \Delta F^0 = -27{,}000$$

$$HOCl + ClO_2^- + OH^- = ClO_3^- + Cl^- + H_2O \quad \Delta F^0 = -31{,}870$$

From the values tabulated for the standard free energy changes, it is evident that equilibrium is far to the right in ordinary acidity ranges for all the changes represented.

The changes in acid and neutral solutions proceed very rapidly. Chlorine dioxide appears instantly in large amount when the solutions are mixed, and with one of the reactants in excess, the other is consumed almost completely within a minute or so after mixing. In very alkaline solution, however (*e. g.*, 0.1 *M* OH^-), where ClO^- rather than Cl_2 or HClO is the principal species, the reaction is very slow—periods of time of the order of hours being required for appreciable reaction to take place. Nothing appears to have been published on the kinetics of the reactions of chlorine and hypochlorite with chlorite, and in view of the high reaction rates, quantitative work would be difficult.

Two essentially distinct types of mechanism may be considered for this and for similar changes. In one of these, both reactants on primary interaction change to an oxidation state in which they become equivalent, and the intermediate substance thereby produced undergoes further change. In a second type of mechanism, the chlorine atom from the Cl_2 or HOCl at all stages remains distinct from the chlorine atom in ClO_2^-. Experiments making use of radioactive chlorine were undertaken to discover which of these two types operates. A report of these experiments follows.

Experiments.—For each experiment a solution containing radioactive chlorine was mixed with a solution containing non-radioactive chlorite. After reaction, the solution was buffered to a *p*H of 7–8 (unless already at that *p*H), carbon tetrachloride was added, the mixture shaken. The carbon tetrachloride layer was then treated as described earlier to measure the specific activity of the chlorine dioxide. The specific activity of the original chlorine was determined on a solution in carbon tetrachloride. Table I summarizes the results of the experiments.

The experiments show that for the most part in the three reactions studied, the atoms present initially in chlorine or hypochlorite appear as chloride ion, and those present in chlorite as chlorine dioxide. A small transfer of activity from chlorine or hypochlorite to the product chlorine dioxide is noted, however, and the effect appears to be real. In experiment 3 of Table I the extractions of the carbon tetrachloride solutions of chlorine dioxide by the aqueous Cl^- buffer solution were continued, the specific activity being measured after each extraction. No change in specific activity was observed —258 ± 6, 257 ± 9, 255 ± 12 — thus proving that the activity was present as chlorine dioxide. The possibility that Cl^*O_2 was formed in the bombardment of chlorine or chloride ion is ruled out on the basis of experiments reported elsewhere.[1] Irradiated chlorine shows no immediate exchange with chlorine dioxide. The relatively high transfer of activity noted in the reaction producing ClO_3^- is probably a result of the procedure followed in the experiment. After reaction, the chlorine dioxide was washed out, and the chlorate ion reduced to chlorine dioxide by adding sulfuric acid. The chloride ion was radioactive and, as is shown below, a slight transfer takes place in the $ClO_3^- + Cl^-$ reaction. The high value for the percentage transfer, 8.8, is probably due to the additional opportunity for exchange in generating chlorine dioxide from chlorate ion in the mixture.

The experiments prove that for the most part at

least, the reactions do not proceed by a path in which on primary interaction of chlorine or hypochlorous acid with chlorite a symmetrical intermediate is formed. Thus the mechanisms having as first steps

$$Cl_2 + ClO_2^- = {}_{O}\!\diagup\!Cl{-}Cl\!\diagdown_{O} \text{ (or } 2ClO) + Cl^-$$

$$HOCl + ClO_2^- + H^+ = {}_{O}\!\diagup\!Cl{-}Cl\!\diagdown_{O} \text{ (or } 2ClO) + H_2O$$

do not account for the major part of the reaction. The principal path must be one in which the chlorine atoms remain distinct, as for example one involving the intermediate $Cl{-}Cl\langle^{O}_{O}$ or $Cl{-}O{-}Cl{-}O$. There are at present no observations which distinguish the two formulations, and the reactions will be written for the substance $Cl{-}Cl\langle^{O}_{O}$.

Simple steps involving this intermediate which satisfy the observations on stoichiometry and those reported above are

$$Cl^*_2 + ClO_2^- = Cl^*Cl\langle^{O}_{O} + Cl^{*-}$$

or

$$H^+ + HOCl^* + ClO_2^- = Cl^*Cl\langle^{O}_{O} + H_2O$$

For the production of ClO_2, the following reaction may be formulated as

$$2Cl^*Cl\langle^{O}_{O} = Cl^*_2 + 2ClO_2$$

and for the production of chlorate ion as

$$Cl^*Cl\langle^{O}_{O} + H_2O = Cl^{*-} + ClO_3^- + 2H^+$$

The slight transfer of activity from Cl^*_2 or $HOCl^*$ to the product may result from the oxidation of $Cl^*Cl\langle^{O}_{O}$ to $ClO_2 + Cl^*O_2$, or from isomerization of $Cl^*Cl\langle^{O}_{O}$ to the symmetrical intermediate.

Test for Exchange in the System $ClO^- + ClO_2^-$.—An experiment was performed in which radioactive hypochlorite was mixed with chlorite ion in alkaline solution and the substances left in contact for a period of time. The rate of reaction is very slow when (OH^-) is as high as 0.1 *M*. The initial concentrations of ClO^-, ClO_2^- Cl^- and OH^- were 0.0171, 0.0478, 0.0171 and 0.1 *M* in order. At the end of forty-three minutes the solution was acidified, whereupon chlorine dioxide was liberated from the chlorite by hypochlorite. The specific activity of the chlorine dioxide was then measured as described above. It was observed to be 40 ± 13; if the activity had been uniformly distributed among Cl^-, ClO^- and ClO_2^-, the specific activity of the chlorine dioxide would have been 583.

The experiment shows that there was little transfer of activity from ClO^- to ClO_2^-. The slight amount appearing in the chlorine dioxide may be attributed to the transfer in the reaction of Cl^*_2 or $HOCl^*$ with ClO_2^- (see above). It may be concluded that the rate of exchange between ClO^- and ClO_2^- is very slow, less than 5% at the concentration above in forty-five minutes. Exchange could conceivably occur by oxygen atom transfer from one group to another. The experiment does not exclude the possibility that such exchange may occur in acid solution.

The System $4H^+ + 2Cl^- + 2ClO_3^- = Cl_{2aq} + 2ClO_2 + 2H_2O$.—The equilibrium constant for this reaction at 25° is 4.7×10^{-7}; thus, appreciable reduction of chlorate ion by chloride ion can be expected only in solutions of high acidity. The forward reaction proceeds fairly rapidly even at room temperature in solutions of high acidity when the concentrations of ClO_3^- and Cl^- are of the order of tenth molar. For example, in 4 *M* $HClO_4$, with ClO_3^- and Cl^- each 0.2 *M*, the color of ClO_2 becomes quite marked in about a minute. In the range of low chloride ion concentrations, the stoichiometry corresponds to that expressed by the equation above. At high chloride ion concentrations, however, relatively more chlorine is formed.

Considerable work on the kinetics of the forward reaction has been reported; much however is conflicting, and none as yet leads to any unambiguous conclusions about mechanism. Among the observations on kinetics which appear well established are the following. The reaction is inhibited by the product chlorine, but not by chlorine dioxide.[7] At low chlorine concentration a limiting rate is reached, and under these conditions the reaction is eighth order[8]

$$-d(ClO_3^-)/dt = k(H^+)^4(Cl^-)^2(ClO_3^-)^2$$

In the presence of iodide ion[9] the reaction reduces to one of simpler order

$$-d(ClO_3^-)/dt = k(H^+)^2(Cl^-)(ClO_3^-)$$

Since ClO_2^- and Cl_2 or HOCl are known to react to give ClO_3^- and Cl^- (as well as other products) it may be fruitful to consider the interaction of ClO_3^- and Cl^- in relation to the mechanism suggested for the above reaction. All the observations are consistent with a mechanism of this type formulated in the following way

$$Cl^- + ClO_3^- + 2H^+ \underset{(1')}{\overset{(1)}{\rightleftharpoons}} H_2O + Cl{-}Cl\langle^{O}_{O} \qquad \text{Equilibrium I reaction (1) forward reaction (1') reverse}$$

$$2Cl{-}Cl\langle^{O}_{O} \longrightarrow Cl_2 + 2ClO_2 \qquad (2)$$

Reaction 1 (*i. e.*, I in the forward direction) is the reverse of that written for the formation of chlo-

(7) Luther and MacDougall, *Z. physik. Chem.*, **55**, 477 (1906).
(8) Luther and MacDougall, *ibid.*, **62**, 199 (1908).
(9) Bray, *J. Phys. Chem.*, **7**, 112 (1903).

rate in the oxidation of ClO_2^- by Cl_2 or HOCl. It is evident that the pair $Cl^- + ClO_3^-$ can lead to the same intermediate as the pair $HOCl + ClO_2^-$ or $Cl_2 + ClO_2^-$. The mechanism as written leads to the eighth order rate law observed by Luther and MacDougall. The effect of chlorine on the rate may be explained as was done by Luther and MacDougall,[8] or by the assumption that chlorine or HOCl can reoxidize Cl—Cl(O)(O). The mechanism is consistent also with Bray's rate law if it be supposed that I^- reacts rapidly with Cl—Cl(O)(O) so that the forward reaction in Equilibrium I becomes rate determining. Finally, it may be pointed out that there is no inconsistency in stating that in the present system the substance Cl—Cl(O)(O) formed by reaction 1 reverts mainly to ClO_3^- and Cl^- by the reaction 1′ rather than reacting in the second step (this condition is necessary if I is to be maintained as an equilibrium) while in the system $Cl_2 + ClO_2^-$, it reacts principally to form $Cl_2^- + ClO_2$. The reaction $Cl_2 + ClO_2^-$ is much more rapid than is $Cl^- + ClO_3^-$, so that in the former system the steady state concentration of $ClClO_2$ is greater and the 2nd order reaction leading to the products $Cl_2 + ClO_2$ would therefore be favored above the first order reaction of the intermediate to give ClO_3^-.

These considerations show that the observations in the present system may be understood by postulating the same intermediate, Cl—Cl(O)(O) (or Cl—O—Cl—O), as was assumed for the reaction of chlorite with chlorine and hypochlorite. As a consequence of this type of mechanism, it would be expected that for the most part, the chlorine atoms in chloride and chlorate would remain distinct on interaction of the two ions, but that a small amount of exchange would occur. An account of the experiments testing this view follows.

Experiments.—Radioactive chloride ion was mixed with inert chlorate in strong acid (4.5 *M* H_2SO_4), the chlorine dioxide separated, and its specific activity determined as described above. In one experiment, with $(Cl^-)/(ClO_3^-)$, initially at 2, the specific activity of the chlorine dioxide liberated was found to be 7 ± 3; that calculated for random distribution among the chlorine atoms in the system 258. These numbers correspond to 3 ± 1% exchange. In a second experiment, $(Cl^-)/(ClO_3^-)$ was initially 0.5; the observed specific activity of the chlorine dioxide, and that calculated for complete exchange in the products were 8 ± 3 and 135, respectively, corresponding to 6 ± 2% of exchange.

As in the reaction of chlorine or hypochlorite with chlorite ion, the chlorine atoms for the most part remain distinct. Slight exchange is noted, however, about the same in magnitude as was observed for the previous reaction. It seems possible therefore that this small degree of exchange is the property of an intermediate common to both systems.

Only incomplete data on the rate and kinetics of the reverse reaction have been published, but those reported by Bray[10] suffice to show that over a limited range of the ratio $(ClO_2)/(Cl_2)$, the stoichiometry corresponds to that expressed by the equation. His data show, furthermore, that the rate of interaction is slow; thus at 18° in a solution in which ClO_2 and Cl_2 are initially of the order of tenths molar, (H^+) and $(Cl)^-$ 5×10^{-3} *M* and 2×10^{-3} *M*, respectively, only a few per cent. of ClO_2 reacts in eight days. Since the equilibrium constant is known, the specific rate and rate law for the forward reaction fix those for the reverse reaction (if the assumption be accepted that the rate law for the reverse reaction will be of the simplest form). The rate law proposed by Bray, similar in form to that found by Sand[11] at higher temperatures and agreeing with data published by Schacherl[12,13] taken together with the equilibrium constant would require a much higher rate for the $Cl_2 + ClO_2$ reaction than was observed by Bray. The observations can, however, be reconciled if the findings by Luther and MacDougall that the forward reaction is inhibited by chlorine is accepted.

An attempt was made to learn something about the rate of the reverse reaction for a system in which the concentrations of reactants and products approach equilibrium values. This was done by introducing radioactive chlorine dioxide into such a system, and observing the change in specific activity with time.

Experiment.—A solution was prepared containing initially 1 *M* $NaClO_3$, 4.2 *M* H_2SO_4 and 0.22 *M* HCl. This remained at room temperature for one day, after which time the concentrations of ClO_2 and Cl_2 were found by analysis to be 0.142 and 0.032 *M*, respectively. To 13 cc. of this solution was added 10 cc. of a carbon tetrachloride solution 0.098 *M* in Cl^*O_2 of known specific activity, and 0.074 *M* in Cl_2. The resulting mixture after shaking was allowed to stand for 86 min. and the specific activity of the chlorine dioxide determined. The results were as follows: the observed final specific activity of the ClO_2 was 81 ± 3, that expected if the only effect were dilution with the inert ClO_2 in the original aqueous solution 89 ± 3; that expected including also complete exchange with ClO_3^-, 19.

The experiment shows that in the time of the experiment, the exchange of chlorine dioxide with chlorate ion is far from complete, and that therefore the rate of reaction of chlorine and chlorine dioxide under the conditions of the experiment is

(10) Bray, *Z. anorg. allgem. Chem.*, **48**, 228 (1904).
(11) Sand, *Z. physik. Chem.*, **50**, 465 (1906).
(12) Ref. 10, p. 245.
(13) Schacherl, *Ann.*, **182**, 193 (1876).

slow. It should be pointed out that any decrease in specific activity observed sets only an upper limit on the rate of reaction, since adding carbon tetrachloride lowered the concentrations of chlorine and chlorine dioxide, and the net change while probably slight, proceeded in the direction of forming chlorine dioxide from inert chlorate ion. The slow rate observed is not compatible with the rate for the forward reaction far from equilibrium and the equilibrium constant, but is explained if the inhibiting effect of chlorine on the rate of the forward reaction is accepted.

Non-exchange in the System $Cl_2 + ClO_3^-$.—It has been shown that the equilibrium between $ClO_3^- + Cl^-$ and $ClO_2 + Cl_2$ is slow; furthermore, the chlorine atoms originating in ClO_3^- and Cl^- tend to remain distinct. It is also known that chlorine disproportionates to $ClO_3^- + Cl^-$ only slowly in acid. These facts made it seem worthwhile to reinvestigate the exchange between chlorine and chlorate ion in acid, since the rather rapid exchange noted by Libby[14] would therefore seem to imply some mechanism other than these orthodox equilibria for transfer of activity.

A record of the experiment on the exchange of Cl_2 and ClO_3^- is presented in Table II.

TABLE II

EXCHANGE IN THE SYSTEM $Cl_2^* + ClO_3^-$ IN STRONG ACID

($NaClO_3$)	(Cl_2^*)	(H_2SO_4)	Temp., °C.	Time, min.	$I_0/100C$ obsd.	$I_0/100C$ ∞ calcd.
1.0	0.025	2.0	25	1	379 ± 5	18
1	.025	2.0	25	68	375 ± 6	18
0.75	.015	4.5	25	2	300 ± 4	12
.75	.015	4.5	25	61	305 ± 7	12
.75	.015	4.5	25	83	290 ± 9	12
1.0	.0261	3.0	25	2	4250 ± 30	211
1[a]	.0261	3	93	32	3500 ± 150	211
1[a]	.0261	3	93	58	3600 ± 150	211

[a] Heated in sealed tubes.

The experiments were performed by using chlorine solutions of known specific activity, separating chlorine from the reaction mixture at the end of the experiment and determining its specific activity. The data show that at room temperatures there is no significant change in specific activity for periods of time up to approximately one and one-half hours. Even at 93°, the change in specific activity is slight, and probably is for the most part apparent rather than real. At this temperature, about 50% of the chlorine had disappeared at the end of the experiment, and the cell contents were colored slightly yellow. This yellow color was undoubtedly due to chlorine dioxide formed from the chlorate. Since the analysis did not distinguish between Cl_2 and ClO_2, the formation of chlorine dioxide would reduce the apparent specific activity of the chlorine.

The Disproportionation of Chlorite in Acid.—Chlorite is unstable and in acid solution it decomposes fairly rapidly. The principal products of the disproportionation reaction over the whole range of acid concentration in which the rate is appreciable are chlorine dioxide and chlorate ion as higher oxidation states and chloride ion as the lower oxidation state. If the chloride ion concentration remains low, the net change[15] approaches that expressed by the equation

$$4HClO_2 = Cl^- + 2ClO_2 + ClO_3^- + 2H^+ + H_2O$$

However, under most conditions the proportion of chlorate formed is somewhat in excess of that represented above. Small amounts of chlorine are also reported as products.[5] This is surprising in view of the rapid reaction of chlorine and chlorite ion. In an experiment done in this laboratory, differing from Barnett's in that the concentration of acid was much greater (1 M H^+ as compared to a maximum of about 0.2 M H^+ in Barnett's experiments), no measurable amount of chlorine was observed.

Experiment.—The solution was initially 1 M H_2SO_4 and 0.0540 M in total chlorite. After one and one-half hours had elapsed, the chlorine and chlorine dioxide were removed by repeated extraction with carbon tetrachloride. The carbon tetrachloride solution on analysis proved to have no noticeable amount of chlorine. The oxidizing agent which is left in the aqueous solution and which responds to iodide at low acid is chlorite. The chlorate formed is therefore measured by the decrease in total oxidizing power. Perchlorate ion is not a product in this reaction. The concentrations at the end of the time interval were: ClO_2, 0.0171 M; ClO_3^-, 0.0100 M; ClO_2^-, 0.0178 M; Cl_2, 0.000 M.

A study of the kinetics of the decomposition has been made by Barnett. His experiments were for conditions of fairly low acidity ($(ClO_2^-) > (HClO_2)$) and covered a range about twenty-fold in (ClO_2^-) and 3- to 4-fold in $(HClO_2)$. The rate law was found to be

$$-d(HClO_2)/dt = k(HClO_2)^2$$

and the value of k at 25°, 1.41. $mole^{-1}$ $min.^{-1}$.

Chloride ion catalyzes the disproportionation of $HClO_2$, and changes the stoichiometry of the reaction. Thus, in an experiment in which the solution was initially 0.472 M HCl and 0.0280 M $NaClO_2$, after eight minutes had elapsed, the total chlorite had fallen to 0.0149 M, and the concentrations of the products ClO_2 and ClO_3^- were 0.0091 and 0.0012 M, respectively. The fraction of the chlorite ion appearing as chlorate ion is much less in the chloride catalyzed reaction than it is in the uncatalyzed change.

The observations may all be understood on the basis that in the uncatalyzed reaction, the primary step is

$$2HClO_2 \longrightarrow HClO + H^+ + ClO_2^-$$

and in the catalyzed reaction

$$HClO_2 + Cl^- + H^+ \longrightarrow 2HClO$$

The oxidation of chlorite by HClO or chlorine as

(14) Libby, THIS JOURNAL, 62, 1930 (1940).

(15) Barnett, Thesis, University of California, 1935.

follow reaction yields mainly chlorine dioxide and accounts for the observed stoichiometry.

We have performed experiments to establish whether for the catalyzed reaction the chlorine atoms in the chloride ion remain distinct from those appearing in the product ClO_2. On the basis of the mechanism proposed above for the change, it is expected that they do remain distinct, since very little transfer of activity from HCl*O or Cl_2* to ClO_2 takes place in the reaction of these with ClO_2^-.

The experiments are outlined below, and show that in fact little mixing of activity between Cl^- and ClO_2^- is observed when the former acts as catalyst for the disproportionation of chlorite ion. The slight amount of exchange, about the same in extent as in the oxidation of chlorite by chlorine or hypochlorite, supports the view that the same intermediate is involved in both reactions.

Experiment.—The concentration of hydrochloride in each experiment was 0.58 *M*. The chloride ion was radioactive and its specific activity was determined before the reaction. After considerable chlorine dioxide had been formed, it was separated from other species as described above, and its specific activity determined. In one of the experiments, the specific activity of the chlorine dioxide formed was 4 ± 4, that expected if exchange with the halogen in the system were complete 50; in a second, these numbers were 27 ± 15 and 336. The results in the second experiment correspond to 8 ± 5% exchange. Thus the amount of exchange which takes place is about the same as in the oxidation of chlorite by chlorine or HOCl. Since the mechanism proposed includes as a step the oxidation of chlorite by HOCl or chlorine, slight transfer of activity to the product ClO_2 is expected.

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Summary

By experiments using radioactive chlorine as a tracer, the following observations have been made. (a) The oxidation of chlorite by chlorate in acid is much slower than the disproportionation of chlorite. (b) In the reaction of chlorite with chlorine (or hypochlorous acid) to form chlorine dioxide or chlorate and chloride ion, most of the chlorine atoms in the chlorine dioxide or chlorate are derived from the chlorite. (c) In the reaction of chloride ion with chlorate ion in acid to produce chlorine and chlorine dioxide, the chlorine atoms in the chlorine dioxide are for the most part derived from the chlorate. (d) In the disproportionation of chlorite in acid catalyzed by chloride ion, the chlorine atoms in the chlorine dioxide are for the most part derived from the chlorite. (e) In each of the changes under (b), (c) and (d), a small but definite degree of mixing of the chlorine atoms in the products has taken place. (f) The reverse reaction in the system (c) near its equilibrium composition is very slow. (g) The exchange of chlorine activity between ClO^- and ClO_2^- in base is very slow. (h) The exchange of chlorine with chlorate ion in acid at room temperature and at elevated temperatures is very slow.

The significance of these observations in relation to other published observations and in relation to reasonable mechanisms for the reactions has been discussed. An unsymmetrical intermediate, Cl—Cl<O/O (or Cl—O—Cl—O), common to the systems (b), (c) and (d) is postulated.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FRESNO STATE COLLEGE]

The Apparent and Partial Molal Volume of Copper Sulfamate in Aqueous Solutions

BY ELTON M. BAKER

The object of this investigation was to determine the apparent and partial molal volume of copper sulfamate at 25° for various concentrations of solutions from accurate density measurements. At infinite dilution the apparent molal volume becomes the partial molal volume. The literature contains limited data for salts of the type contained in this study.

Experimental

The experimental procedure consisted of determining densities of aqueous solutions of copper sulfamate in calibrated weld precision pycnometers of approximately 25 ml. capacity. These were calibrated using distilled water. The deviation was less than 0.005%. The density obtained for each concentration is the average of three determinations. The maximum deviation between values in any series was 0.005%. The densities were determined at 25 ± 0.02°. The temperatures were determined by a long mercurial thermometer of short range, calibrated by the National Bureau of Standards. Calibrated weights were used and weighings could be reproduced to ±0.05 mg. All weights were corrected to vacuum. Weighing was done in a room at 25 ± 1°.

Copper sulfamate was prepared by the interaction of C. P. sulfamic acid and basic copper carbonate. The blue copper sulfamate was recrystallized three times from distilled water. The copper content was determined by allowing an excess of potassium iodide to reduce weighed samples of the stock solution of copper sulfamate in an acid buffer. The released iodine was titrated using standard thiosulfate solution with potassium thiocyanate added

near the end-point. The accepted value was the average of three analyses in which the maximum deviation between analytical results for any concentration was less than 0.07%.

Molal concentrations were then obtained and molar concentrations were calculated with the use of densities.

A saturated solution was prepared by allowing a warm concentrated copper sulfamate solution to cool to 25°, then permitting it to come to equilibrium with the solid phase which separated. Weighed samples of the supernatant liquid were analyzed as before. The solubility was found to be 74.73 (±0.05) g. per 100 g. of water.

Treatment of Results.—The apparent molal volumes were calculated from the observed densities by means of the equation proposed by Gucker[1]

$$\phi(V_2) = 1000/c - 1/d_1[1000d/c - M_2] \quad (1)$$

where $\phi(V_2)$ is the apparent molal volume, M_2 is the molecular weight of the copper sulfamate, d_1 and d are the densities of the solvent and solution, respectively, and c is the concentration (moles of solute per liter of solution). The absolute density of water was used as 0.99707 g./ml. The densities and the corresponding values of concentration and apparent and partial molal volumes are shown in Table I.

TABLE I

Density	Concentration Molal	Concentration Molar	$\bar{V}_2$	$\phi(V_2)$	$d\phi(V_2)$
1.01340	0.08348	0.08283	59.86	58.77	−0.30
1.02316	.13394	.13250	60.40	59.00	− .10
1.10238	.56471	.54394	65.33	62.31	+ .02
1.18428	1.0484	.97910	68.86	64.72	+ .18
1.22814	1.3315	1.2199	71.14	66.51	− .27
1.28484	1.7130	1.5304	73.09	67.90	− .13
1.36007	2.2627	1.9495	75.54	69.74	− .05
1.44351	2.9221	2.4140	77.36	71.01	+ .38

(1) Gucker, *J. Phys. Chem.*, **38**, 307 (1934).

From the data a second order equation expressing $\phi(V_2)$ as a function of c was found. The value of the coefficients was obtained by the method of averages[2]

$$\phi(V_2) = 56.08 + 7.07c^{1/2} + 1.92c \quad (2)$$

In Column 6 are shown the deviations, $d\phi(V_2)$, of the observed values from those calculated from the equation.

Partial molal volumes were obtained using concentrations and calculated apparent molal volumes by the relation proposed by Gucker[1]

$$\bar{V}_2 = \phi(V_2) + c^{1/2}\left[\frac{1000 - c\,\phi(V_2)}{2000 + c^{3/2}\frac{\partial\phi(V_2)}{\partial c^{1/2}}}\right]\frac{\partial\phi(V_2)}{\partial c^{1/2}} \quad (3)$$

where $\phi(V_2)$ is the apparent molal volume and

$$\partial\phi(V_2)/\partial c^{1/2} = 7.07 + 3.84c^{1/2} \quad (4)$$

as obtained from equation (2).

The partial molal volume of copper sulfamate at zero concentration was determined as 56.08 ml. per gram molecular weight by the evaluation of the first constant in equation (2).

Summary

1. Densities at 25 ± 0.02° of copper sulfamate solutions ranging from 0.08 to 2.4 molar have been determined.

2. The solubility of copper sulfamate at 25° was determined: 74.73 g. per 100 g. of solvent.

3. The apparent and partial molal volumes of the solute have been calculated.

(2) Lipka, "Graphical and Mechanical Computation," John Wiley and Sons, Inc., New York, N. Y., 1921, pp. 126, 145.

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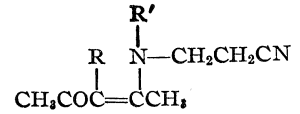
[JOINT CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA AND THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Infrared Spectra of Amino-substituted α,β-Unsaturated Ketones

BY NORMAN H. CROMWELL, FOIL A. MILLER,[1] AGATHA R. JOHNSON, ROBERT L. FRANK AND DAVID J. WALLACE

A recent study of some cyclizations involved the preparation of 4-(2′-cyanoethyl)-amino-3-penten-2-one (I), 4-(2′-cyanoethyl)-amino-3-methyl-3-penten-2-one (II) and 4-N-(2′-cyanoethyl)-methylamino-3-penten-2-one (III) and the possibility of their ring closure by the aldol condensation. The properties of these substances



I, R = R′ = H
II, R = CH_3, R′ = H
III, R = H, R′ = CH_3

have proved to be unusual and have prompted us to undertake a study of their infrared absorption spectra and those of a number of previously reported related compounds.

(1) Present address: Mellon Institute, Pittsburgh, Pennsylvania.

Preparation and Properties

Compounds I, II and III were readily prepared by condensation of the appropriate β-aminopropionitrile with acetylacetone or 3-methylacetylacetone. Assignment of the double bond in these structures to the position α,β to the carbonyl rather than β,γ between the carbon and nitrogen atoms, is based on their ultraviolet absorption maxima in the region characteristic of α,β-unsaturated carbonyl compounds and on a comparison of their infrared spectra with those of compounds VII through IX of known structure.

It is of interest that ammonia and β-aminopropionitrile fail to condense with 3,3-dimethylacetylacetone, a case in which the double bond of the product cannot take the position α,β to the carbonyl group.[2]

These amino ketones are structurally vinylogs of amides, and have been found to behave chemically more like amides than ketones. Our experiments performed mostly on 4-(2′-cyanoethyl)-amino-3-penten-2-one (I), show, for example, that they do not form phenylhydrazones; they fail to give a positive haloform reaction under the usual conditions; they fail to cyclize under conditions favorable for aldol condensation. Hydrolysis occurs in aqueous acid but not readily in water or aqueous alkali. Reaction with picric acid occurs only accompanied by cleavage to yield the picrate of the β-aminopropionitrile.

The preparation and properties of compounds IV,[2] V,[3] VI,[4] VII,[5] VIII,[5] IX,[5] X,[4] XI,[6,8,9] XII,[6,8,9] XIII,[5] XIV[7] and XV[9] have been described previously as indicated by the references.

Experimental

β-Aminopropionitrile.—The method of Ford, Buc and Greiner[10] was employed using 106 g. (2.00 moles) of acrylonitrile and 1 l. of 28% ammonium hydroxide. The yield was 81 g. (63%), b. p. 66–69° (5 mm.); $n^{20}D$ 1.4400. Its picrate had m. p. 178° (lit.,[11] 178°).

β-Methylaminopropionitrile.—The method of Whitmore and co-workers[11] for β-ethylaminopropionitrile was applied using 106 g. (2.00 moles) of acrylonitrile and 300 ml. of 35% aqueous methylamine (3.00 moles of amine), and gave 117.5 g. (70%) of product, b. p. 90° (30 mm.); $n^{20}D$ 1.4318.

4-(2′-Cyanoethyl)-amino-3-penten-2-one (I).—Addition of 13.5 g. (0.19 mole) of β-aminopropionitrile to 20.0 g. (0.20 mole) of acetylacetone resulted in an exothermic reaction. The product solidified on cooling to give a quantitative yield, 28.8 g.; m. p. 88°. An analytical sample was prepared by two recrystallizations from benzene–petroleum ether (3:1) to form white needles, m. p. 89.5–90°. These gave a purple color with ethanolic ferric chloride.

Anal.[12] Calcd. for $C_8H_{12}N_2O$: C, 63.16; H, 7.89. Found: C, 63.35; H, 7.68.

An alternative preparation involved the solution of 200 g. (2.00 moles) of acetylacetone in 150 ml. of 28% ammonium hydroxide, followed by addition of 106 g. (2.00 moles) of acrylonitrile. The mixture was refluxed for four hours and the excess water then removed under reduced pressure to yield several crops of crystals totaling 76 g. (25%), m. p. 88°.

The ultraviolet absorption spectrum was determined by Mrs. Calvin Brantley with a Beckman Model D spectrophotometer. A maximum occurs at 308 mμ with log ε = 4.265, where ε, the molecular extinction coefficient, is given by log $I_0/I = \epsilon \times c$ (moles/l.) × d(cm.). The solution employed contained 0.0006 g./l. in 95% ethanol.

Experiments designed to cyclize this compound to a dihydropyridine involved refluxing ethanolic solutions with piperidine, piperidine carbonate, sodium hydroxide, and sodium ethoxide; heating it with zinc chloride; heating it alone at temperatures up to 240°; and allowing it to stand with hydrochloric acid, acetic anhydride, and acetyl chloride. None of these attempts yielded a cyclized product. In most cases the starting material was recovered, although refluxing with 4% hydrochloric acid caused hydrolysis to β-aminopropionitrile hydrochloride.

Reaction with phenylhydrazine and with sodium hypoiodite according to the directions of Shriner and Fuson[13a,b] gave negative results. Reaction with picric acid[13c] gave the picrate of β-aminopropionitrile, m. p. 178° (lit.,[11] 178°).

4-(2′-Cyanoethyl)-amino-3-methyl-3-penten-2-one (II).—Mixing of 7.0 g. (0.060 mole) of 3-methylacetylacetone and 4.0 g. (0.057 mole) of β-aminopropionitrile and cooling of the hot reaction mixture gave the solid product. Recrystallization from benzene gave 9.0 g. (92%) of colorless needles, m. p. 109–110°. The compound forms a red color with ethanolic ferric chloride.

Anal. Calcd. for $C_8H_{14}N_2O$: C, 65.03; H, 8.43. Found: C, 65.25; H, 8.36.

The ultraviolet absorption spectrum, measured as reported for the preceding compound, had a peak of 327 mμ (log ε = 4.048; concentration 0.0092 g./l. in 95% ethanol).

4-N-(2′-Cyanoethyl)-methylamino-3-penten-2-one (III).—Twenty grams (0.20 mole) of acetylacetone and 17.0 g. (0.20 mole) of β-methylaminopropionitrile were mixed and heated on a steam cone for one half-hour. White needles (32.5 g., 98%) formed on cooling, m. p. 69–70°. These gave a purple color with ethanolic ferric chloride.

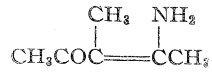
Anal. Calcd. for $C_8H_{14}N_2O$: C, 65.03; H, 8.43. Found: C, 64.85; H, 8.61.

The ultraviolet absorption spectrum, measured as described for the preceding compounds, had a maximum at 306 mμ (log ε = 4.357; concentration 0.0006 g./l. in 95% ethanol).

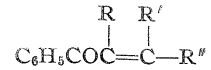
Infrared Absorption Spectra

The infrared spectra of compounds I-XV were measured from 650 to 3800 cm.$^{-1}$ with a Perkin–Elmer model 12B recording infrared spectrometer employing a sodium chloride prism. Table I summarizes the results. The samples were in the form of Nujol mulls, so the strong bands of Nujol at 1378, 1458 and about 2920 cm.$^{-1}$ appear in all the spectra. Since these bands are due to aliphatic C–H bending and stretching vibrations,[14] they would doubtless be present in the spectra of the compounds alone. They have therefore been included in the table and marked with an asterisk. Nujol also has a weak band at 720 cm.$^{-1}$ which probably would not be exhibited by the compounds. This has been observed in some of the spectra, and is also marked in the table. The accuracy of the wave length measurement is estimated to be ±1 cm.$^{-1}$ at 1000 cm.$^{-1}$, ±4 cm.$^{-1}$ at 1500 cm.$^{-1}$ ± 7 cm.$^{-1}$ at 2000 cm.$^{-1}$, and ±17 cm.$^{-1}$ at 3000 cm.$^{-1}$.

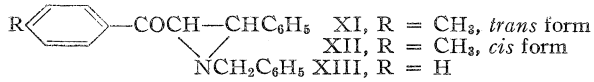
(2) Combes and Combes, *Bull. soc. chim.*, [3] **7**, 779 (1892).
(3) Cromwell and Witt, THIS JOURNAL, **65**, 308 (1943).
(4) Cromwell, *ibid.*, **62**, 2897 (1940).
(5) Cromwell, Babson and Harris, *ibid.*, **65**, 312 (1943).
(6) Cromwell and Hoeksema, *ibid.*, **71**, 708 (1949).
(7) Raiford and Peterson, *J. Org. Chem.*, **1**, 544 (1937).
(8) Cromwell and Wankel, THIS JOURNAL, **71**, 711 (1949).
(9) Cromwell and Hoeksema, *ibid.*, **71**, 716 (1949).
(10) Ford, Buc and Greiner, *ibid.*, **69**, 844 (1947).
(11) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, *ibid.*, **66**, 725 (1944).
(12) Microanalyses were carried out by Misses Emily Davis and Theta Spoor.
(13) (a) Shriner and Fuson, "Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 1948, p. 116; (b) p. 138; (c) p. 180.
(14) Rasmussen, *J. Chem. Phys.*, **16**, 712 (1948).



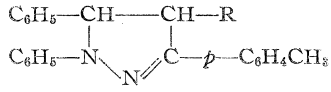
IV



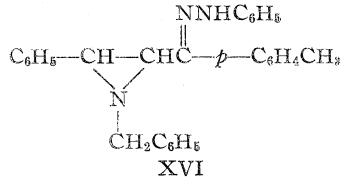
V, R = $N(CH_3)CH_2C_6H_5$, R′ = H, R″ = C_6H_5
VI, R = morpholino, R′ = H, R″ = C_6H_5
VII, R = H, R′ = $NHCH_2C_6H_5$, R″ = C_6H_5
VIII, R = H, R′ = cyclohexylamino, R″ = C_6H_5
IX, R = H, R′ = $NHCH_2C_6H_5$, R″ = CH_3
X, R = H, R′ = morpholino, R″ = C_6H_5



XI, R = CH_3, *trans* form
XII, R = CH_3, *cis* form
XIII, R = H

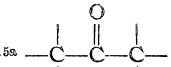


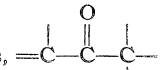
XIV, R = H
XV, R = $NHCH_2C_6H_5$

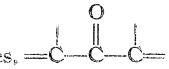


XVI

Compounds I-X.—We shall consider first the 1500–1700 cm.$^{-1}$ region of the spectra of compounds I-X. Here one expects to find bands due to the phenyl group, the carbonyl group, to C=C bonds, and to the N–H bending of amines. The phenyl bands occur very nearly at 1500 and 1600 cm.$^{-1}$.[15] They are characteristic and are rather easily identified by their intensity and shape. The carbonyl stretching vibration in ketones is found quite consistently at the following wave numbers

(a) Unconjugated ketones,[15a]  1705–1720[16,17,18,19]

(b) α,β-Unsaturated ketones, (including aryl ketones)  1665–1700[16,17,18,19]

(c) α,β,α′,β′-Unsaturated ketones, (including diaryl ketones)  1650–1670[16,17,18]

It is noteworthy that further extension of the conjugation to the γ,δ bond  has little additional effect on the carbonyl frequency. The C=C band is to be expected at 1600–1625 cm.$^{-1}$ in these compounds since it is in every case conjugated with the carbonyl group, and in some cases is also conjugated with a phenyl group.[15] The intensity of this band is known to vary greatly from one compound to another. Primary amines exhibit an N–H bending absorption at 1580–1640 (usually only one band is observed).[15] Little information seems to be available on secondary amines. Finally one often observes "extra" bands in this region which are due to combination tones and overtones. Their intensity may be enhanced by Fermi resonance so that they occasionally appear to be moderately intense.

Since our compounds I-X contain both keto and amino groups, it is convenient for discussion to classify them in several categories

	Examples
(1) α-Amino-α,β,α′,β′-unsaturated ketones	
(a) N-Disubstituted	V, VI
(2) β-Amino-α,β-unsaturated ketones	
(a) N-Unsubstituted	IV
(b) N-Monosubstituted	I, II
(c) N-Disubstituted	III
(3) β-Amino-α-β,α′,β′-unsaturated ketones	
(a) N-Monosubstituted	VII, VIII, IX
(b) N-Disubstituted	X

We now consider the bands which are observed experimentally in the double bond region. These are reproduced in Fig. 1 in the form of a line chart. The height of a line is a measure of the band intensity. The cross-hatched areas indicate the regions in which the carbonyl bands are expected to appear.

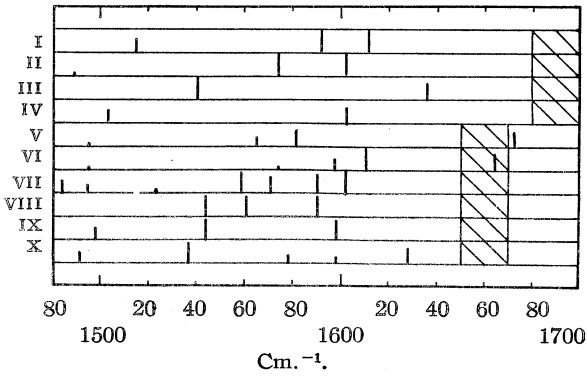


Fig. 1.—Infrared absorption spectra.

Only the two α-amino-α,β,α′,β′-unsaturated ketones (V and VI) have carbonyl bands in the expected range. The phenyl bands are rather

(15) Barnes, Gore, Stafford and Williams, *Anal. Chem.*, **20**, 402 (1948).

(15a) The upper limit of this range should be increased to 1760 cm.$^{-1}$ if the carbonyl group is in a strained ring, such as a four- or five-membered one. See: (a) reference 19a; (b) Whiffen and Thompson, *J. Chem. Soc.*, 1005 (1946).

(16) Barnes, Gore, Liddel and Williams, "Infrared Spectroscopy," Reinhold Publishing Corporation, New York, N. Y., 1944, p. 21.

(17) Thompson and Torkington, *J. Chem. Soc.*, 640 (1945).

(18) Unpublished research of Agatha R. Johnson and Foil A. Miller.

(19) (a) Jones, Williams, Whalen and Dobriner, THIS JOURNAL, **70**, 2024 (1948); (b) Jones, Humphries and Dobriner, *ibid.*, **71**, 241 (1949); (c) Rasmussen, Tunnicliff and Brattain, *ibid.*, **71**, 1068 (1949); (d) Hartwell, Richards and Thompson, *J. Chem. Soc.*, 1436 (1948).

TABLE I

INFRARED ABSORPTION SPECTRA

vw = very weak. w = weak. m = medium. s = strong. vs = very strong.

I		II		III		IV		V		VI		VII		VIII		IX		X		XI		XII		XIII		XIV		XV	
cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I	cm.$^{-1}$	I
739	vw	694	vw	762	w	878	w	681	vw	685	w	670	vw	683	vw	677	vw	674	vw	688	w	695	s	652	vw	678	vw	687	vw
760	s	770	w	769	vw	974	vs	692	m	691	m	680	vw	692	s	690	m	691	s	695	s	699	s	685	s	689	m	694	w
796	vw	813	m	808	s	1005	w	697	w	705	m	692	s	706	s	696	s	706	s	700	s	729	vs	697	vs	693	m	704	w
833	m	855	vw	904	vw	1011	vw	702	m	734	w	704	s	745	s	707	m	735	m	719*	m	753	s	708	s	712	vw	717*	vw
874	vw	920	vw	953	s	1092	vw	725	m	753	m	733	s	768	vw	731	s	770	s	729	s	778	w	738	s	743	s	746	m
905	vw	932	vw	998	m	1224	s	744	m	777	vw	748	s	777	m	751	s	783	s	751	s	795	w	748	vs	757	m	750	m
934	vw	975	s	1021	vs	1274	s	800	m	824	vw	764	m	794	vw	793	s	798	vw	757	w	813	m	763	w	790	vw	759	w
976	w	988	w	1050	s	1352	s	849	vw	848	vw	775	w	811	w	808	s	809	vw	795	w	821	w	775	m	819	s	819	w
999	vw	1009	vw	1133	s	1373*	s	894	vw	876	m	795	w	842	vw	833	w	823	w	802	w	848	w	819	vw	841	vw	823	vw
1011	w	1046	w	1181	vs	1460*	m	902	w	889	m	805	vw	891	m	849	vw	840	vw	821	m	854	vw	849	vw	868	vw	828	vw
1021	vw	1077	m	1216	w	1470	s	908	vw	894	w	845	vw	921	w	878	vw	847	vw	849	vw	871	vw	857	w	873	m	842	vw
1049	vw	1088	m	1250	w	1503	vs	912	vw	909	w	852	vw	924	w	897	vw	862	vw	858	vw	882	m	867	vw	876	w	869	vw
1109	w	1145	m	1278	w	1602	vs	956	m	935	m	894	vw	969	vw	925	vw	870	m	865	m	901	w	906	w	906	vw	876	vw
1206	m	1223	m	1355	s	2920*		971	vw	980	s	926	vw	977	w	974	m	898	m	871	vw	924	w	914	m	944	vw	944	vw
1211	m	1267	vs	1377*	vs	3120	s	991	m	1000	m	931	vw	1000	w	983	vw	923	vs	903	w	957	vw	920	m	955	vw	959	vw
1242	w	1298	s	1388	s	3265	vs	1003	w	1025	vw	963	m	1025	m	1002	vw	937	m	911	vw	988	w	936	m	996	w	968	vw
1274	m	1359	s	1419	vs			1026	vw	1050	vw	970	vw	1050	w	1016	vw	972	vw	926	w	1007	vw	950	vw	1002	vw	976	vw
1298	s	1376*	m	1459*	vs			1071	vw	1066	vw	973	vw	1060	m	1028	m	1001	w	957	w	1018	m	971	vw	1014	vw	991	vw
1356	m	1429	m	1541	vs			1078	vw	1076	vw	987	vw	1070	w	1066	m	1019	s	967	vw	1027	s	980	vw	1021	vw	1016	vw
1377*	m	1459*	s	1636	s			1103	vw	1120	vs	1005	vw	1085	m	1090	w	1034	s	981	vw	1038	m	993	vw	1026	vw	1029	vw
1435	m	1471	s	2255	w			1110	vw	1164	m	1025	m	1145	m	1105	vw	1061	m	1001	vw	1074	w	1001	vw	1030	vw	1034	vw
1461*	s	1489	vw	2920*				1153	vw	1198	s	1030	m	1152	w	1112	vw	1068	w	1008	w	1099	vw	1024	m	1040	vw	1076	w
1515	s	1574	vs					1173	m	1216	m	1061	s	1176	vw	1155	vw	1115	m	1018	w	1123	vw	1030	m	1071	vw	1081	vw
1592	vs	1602	vs					1187	m	1222	m	1078	vw	1186	vw	1177	vw	1126	s	1032	m	1156	vw	1052	s	1078	vw	1111	vw
1612	vs	2255	w					1195	w	1243	s	1087	vw	1225	m	1227	vw	1150	vw	1057	s	1184	s	1059	vs	1103	vw	1138	m
2250	w	2920*						1207	w	1270	s	1147	m	1250	m	1247	vw	1174	vw	1067	s	1204	w	1073	w	1111	vw	1160	vw
2920*								1229	m	1289	vw	1157	w	1277	vw	1276	m	1187	vw	1092	m	1215	vw	1087	w	1134	s	1177	vw
3090	w							1258	m	1303	vw	1177	vw	1294	w	1290	s	1210	vs	1096	m	1224	vw	1095	vw	1148	vw	1195	vw
3145	w							1289	vw	1315	vw	1183	vw	1306	vw	1310	vs	1227	s	1113	w	1241	s	1153	vw	1182	vw	1220	vw
3410	w							1312	w	1338	vw	1195	vw	1335	vs	1322	s	1256	s	1180	s	1273	vw	1174	m	1201	vw	1256	vw
								1358	w	1345	vw	1228	m	1378*	m	1372*	s	1271	m	1212	m	1280	vw	1182	w	1240	vw	1273	vw
								1367	m	1378*	m	1251	m	1459*	s	1439	s	1305	vw	1230	s	1301	vw	1213	w	1270	vw	1300	vw
								1376*	w	1401	w	1270	m	1473	s	1454*	vs	1339	m	1235	s	1311	vw	1224	vs	1279	vw	1327	w
								1414	m	1449	s	1286	m	1544	vs	1497	m	1361	m	1248	vw	1346	s	1232	s	1300	vw	1345	vw
								1424	m	1459*	s	1311	m	1561	vs	1544	vs	1379*	s	1263	w	1362	vw	1251	vw	1304	vw	1378*	w
								1457*	s	1495	vw	1338	s	1590	vs	1598	vs	1412	s	1285	w	1378*	m	1300	w	1327	s	1394	s
								1470	m	1574	vw	1365	m	1945	vw	2920*		1443	s	1307	w	1393	w	1311	w	1336	vw	1458*	s
								1495	w	1597	s	1379*	w	2920*		3025	vw	1459*	s	1313	vw	1413	vw	1357	m	1345	vw	1500	s
								1565	m	1610	s	1439	s	3025	vw	3060	vw	1491	s	1358	m	1457*	s	1380*	m	1378*	w	1574	w
								1581	vs	1664	vs	1453*	s	3045	vw	3190	vw	1536	vs	1378*	m	1496	m	1418	w	1395	s	1597	m
								1672	s	2920*		1459	s					1578	s	1407	vw	1608	s	1452	s	1413	w	2920*	
								2920*		3055	vw	1484	s					1598	m	1419	w	1651	s	1459*	s	1458*	s	3020	vw
								3010	vw			1495	m					1628	vs	1449	m	2920*		1497	m	1502	vs	3050	vw
								3050	vw			1523	w					2920*		1456*	s	3015	w	1578	vw	1554	vw		
												1559	vs					3055	w	1465	m	3040	w	1599	m	1575	vw		
												1571	vs					3490	w	1498	m			1685	vs	1599	s		
												1590	vs							1605	s			2920*		1666	vw		
												1602	vs							1678	vs			3020	w	2920*			
												2920*								2920*				3050	w	3020	vw		
												3040	w							3020	w					3060	vw		
																				3055	w								

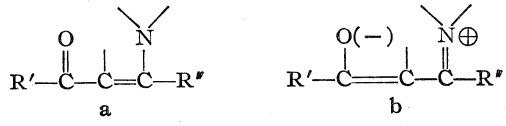
easily located in these two compounds, and the 1610 band in VI may well be due to the C=C vibration. The only puzzling questions are the explanation of 1565 cm.$^{-1}$ in V and the whereabouts of the C=C band in V.

In all the remaining compounds (I-IV and VII-X) the highest band in the 1500–1700 cm.$^{-1}$ region, which is presumably the C=O band, is lower than expected by from 20 to 80 cm.$^{-1}$. It is well known[19d] that hydrogen bonding will lower a carbonyl frequency. This effect can not be operative in III or X, however (nor in V or VI), because they are tertiary amines. One must therefore conclude that the substitution of an amino group in the beta position of these α,β-unsaturated ketones lowers the carbonyl frequency. This is particularly striking when one compares VI and X, since these compounds are identical except for the position of substitution.

Compound III should possess a C=C band. The only band in the double bond region besides the carbonyl band is an intense one at 1541, which is 60 cm.$^{-1}$ lower than expected. It can scarcely be due to a combination tone because of its marked intensity. In X one finds an analogous band in nearly the same position, 1537 cm.$^{-1}$. There are in addition phenyl bands at 1491 and 1598, and an unexplained band at 1578.

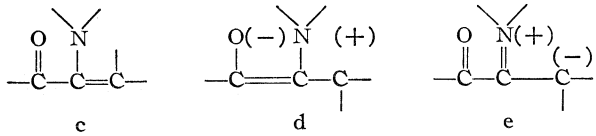
Let us now consider why in compounds III and X the carbonyl band is low, why the C=C band is missing, and what may be the origin of the band near 1540. One possibility is that the high band

is not really due to the C=O group, but that it is due to C=C and that the C=O band is missing. This is unlikely because (a) the carbonyl band is almost invariably a strong band, and (b) the 1540 band must still be explained. Another possibility is that with the amino group substituted on the β carbon atom, the ionic resonance form (b) can contribute appreciably to the ground state.



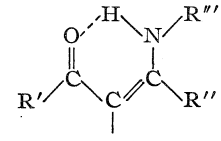
a b

This would have the effect of lowering the C=O frequency, lowering the C=C frequency, and raising the C—N frequency. Thus it does qualitatively fit the observed results. The 1540 band would then be explained as either the lowered C=C or the enhanced C—N frequency —probably the former. This explanation also makes it understandable that the α-amino ketones (V and VI) do not exhibit these anomalies, since the ionic resonance structures that one can write in this case (d and e) would be expected to contribute much less to the actual ground state of the molecule.[20]



c d e

The remaining compounds (I, II, IV, VII, VIII and IX) are further complicated by hydrogen bonding. It has been shown[21] that hydrogen bonding will lower a carbonyl frequency, and it has already been mentioned that this bonding cannot occur in compounds III, V, VI, nor X because they are tertiary amines. Now it is precisely in compounds III and X that the anomalous lowering of the carbonyl frequency is smallest. In the other β-amino ketones the effect of hydrogen bonding is apparently superimposed on this first effect. This is supported by the fact that no N–H stretching frequency is observed in the usual region around 3300 cm.$^{-1}$. The N–H band has probably been broadened and lowered to around 3000 cm.$^{-1}$ where it is hidden by the C–H bands. The spectrum of II was measured in chloroform solution and no shift to higher frequencies was observed. The hydrogen bonding must therefore be largely intramolecular. It will be noted that these compounds offer favorable opportunities for chelation.



In general the spectra of these remaining β-amino ketones show the same features as those of III and X except for having lower carbonyl bands. The phenyl bands can usually be found readily, and the C=C not at all if one assigns the highest frequency to C=O. Extra bands appear in many cases which may be due to the N–H bending vibration. And finally there is in nearly every case a strong band somewhere in the range 1500–1560 whose explanation is puzzling. We can think of no explanation for this other than the one already advanced.

When the spectra of compounds I-IV and VII-X were first measured, the compounds were suspected of being monosubstituted amides because of this strong band around 1540 cm.$^{-1}$. Richards and Thompson[22] give some general results for amides in the solid state

	Band "B"	C=O
R—CO—NH_2	1630	1655
R—CO—NHR	1530–1570	1640–1680
R—CO—NR_1R_2	....	1650

Band "B" near 1540 cm.$^{-1}$ is so characteristic of monosubstituted amides that it, in conjunction with an N–H stretching band near 3270 cm.$^{-1}$, serves as an excellent test for this class of compounds. We have already pointed out, however, that our compounds I-IV and VII-X are not amides but are vinylogs of amides.

The question now arises as to whether this 1540 cm.$^{-1}$ band might not have the same explanation in the monosubstituted amides and in the vinylogs. The origin of band "B" in amides is not settled. Richards and Thompson[22] discuss four possible explanations and conclude that it is due to the N–H bending motion. This is supported by its absence in disubstituted amides. These authors have pointed out that deuterization experiments should provide a critical test of this explanation. Should it be disproved, a possible alternative is to explain band "B" as the C-N stretching frequency enhanced by a large contribution from the ionic form g



f g

The analogy to the vinylogs (structures a and b) is evident, and affords some support for this idea. Nevertheless there are certain difficulties with this explanation. In the first place the ionic form must make a very important contribution

(20) Additional ionic resonance forms besides d and e are of course possible in the cases having phenyl groups attached to this system.

(21) The work of Thompson, *et al.*, reference 19d indicates that simple hydrogen bonding can lower the carbonyl frequency in some cases. Rasmussen, *et al.*, reference 19c, have found that intramolecular hydrogen bonding as in diacetone alcohol has almost no effect on the carbonyl vibrational frequency. On the other hand these latter authors state that "conjugated chelation" as in enolyzed beta-diketones produces a major shift of the carbonyl infrared band to about 1613 cm.$^{-1}$ with a considerable increase in intensity. The analogy between the structures of β-secondary or primary amino α,β-unsaturated ketones and the enols of β-diketones is obvious.

(22) Richards and Thompson, *J. Chem. Soc.*, 1248 (1947).

to the final ground state if the C–N stretching frequency is to be as high as 1540 cm.$^{-1}$. This should at the same time lower the carbonyl frequency markedly, since it acquires a large amount of single bond character. This frequency is indeed lower in amides than in aldehydes and unconjugated ketones, but by nowhere nearly the amount expected. Secondly one wonders why the 1540 cm.$^{-1}$ band is found only in monosubstituted amides, whereas with the vinylogs the 1500–1560 band appears regardless of whether the amine group is unsubstituted, monosubstituted, or disubstituted. We are therefore inclined to feel that the origin of the 1540 band is fundamentally different in the amides and in their vinylogs. Conversely if the origin is actually different, several of our unsaturated ketones might be expected to exhibit *two* bands between 1500 and 1600 cm.$^{-1}$ (in addition to any phenyl bands) ... namely the characteristic band at 1500–1560 cm.$^{-1}$ due to the resonance effect already described, and a second band due to the N–H bending in a secondary amine. Two bands are found in compounds I, VII and VIII, although there is only one in II and IX.

Compounds XI–XV.—Compounds XI and XII have been indicated to be the *trans* and *cis* modifications, respectively, of 1-benzyl-2-phenyl-3-*p*-toluylethyleneimine,[6,8,9] and it is of interest that while the *trans* form (XI) exhibits a carbonyl band in the normal region for α,β-unsaturated carbonyls (including aromatic unsaturation), the *cis* form (XII) has a band about 25 cm.$^{-1}$ below this region. These spectra help settle the relationship of the configuration of structure XIII to that of XI, inasmuch as its band in the α,β-unsaturated carbonyl region, 1680–1700 cm.$^{-1}$, resembles that of XI rather than XII.

Compound XV is the structure shown for the reaction product of phenylhydrazine with the ethyleneimine XII,[9] but the possibility was considered that the correct structure might instead be represented by XVI. A comparison of its infrared spectrum with that of the other four compounds (XI–XIV) confirms the previous conclusion that it has the pyrazoline structure (XV) rather than the ethyleneimine form (XVI). Thus for example it has the moderately strong bands at 1138 and 1394 cm.$^{-1}$ which have counterparts in XIV but not in XI, XII, nor XIII. Moreover it does not exhibit the strong bands at 1020–1060, 1175–1185, 1220–1240 and 1325–1360 cm.$^{-1}$ shown by each of XI, XII and XIII.

Summary

1. Certain β-amino α,β-unsaturated ketones have been shown to behave chemically more like amides, of which they are vinylogs, than like ketones or vinyl amines.

2. Infrared spectra of fifteen unsaturated amino ketones or derivatives thereof have been studied and their peculiarities discussed. The presence of an amino group (either substituted or unsubstituted) on the beta carbon atom of an α,β-unsaturated ketone lowers the carbonyl band by 20–80 cm.$^{-1}$.

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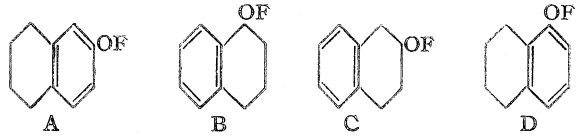
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

The Catalytic Dehydrogenation of 2-Substituted Tetrahydronaphthalene Derivatives

BY MELVIN S. NEWMAN AND J. ROGER MANGHAM[1]

The following report describes a continuation of studies designed to obtain more information about the liquid phase dehydrogenation over palladium-on-charcoal of oxygenated hydroaromatic compounds. The previous reports,[2,3] respectively, dealt with 6-substituted 1,2,3,4-tetrahydronaphthalenes, A, and 1-substituted 1,2,3,4-tetrahydronaphthalenes, B, where OF indicates the oxygenated function. Since the oxygenated functions of A and B differed both in their positions with respect to the point of ring fusion and in their relative positions with respect to the hydrogen to be removed, it is necessary to study compounds of type C and D before a complete discussion can be attempted. In this paper we describe the behavior of 2-substituted-1,2,3,4-tetrahydronaphthalenes, C, under the above conditions.



A B C D

In the discussion R will be used to designate the 1,2,3,4-tetrahydro-2-naphthyl radical and R′, the 2-naphthyl radical. In Table I are summarized the results with the following compounds: $RCOOCH_3$, I; RCH_2OH, II; RCH_2OCOCH_3, III; RCHO, IV; $R\overline{CHOCH_2CH_2O}$, V; $RCOCH_3$, VI; RCH_2COCH_3, VII; and $RCH_2CH_2COCH_3$, VIII.

(1) This work was taken from the dissertation submitted by J. R. Mangham to The Ohio State University in partial fulfilment of the requirements for the Ph.D. degree, December, 1948.

(2) Newman and Zahm, THIS JOURNAL, **65**, 1097 (1943).

(3) Newman and O'Leary, *ibid.*, **68**, 258 (1946).

TABLE I

DEHYDROGENATION EXPERIMENTS

No.	Compound	Time, hr.	Temp., °C.	H_2,[a] %	Products	Yield,[b] %
I	$RCOOCH_3$	3.5	290–320	100	$R'COOCH_3$	92
II	RCH_2OH	17.5	260–300	49[c]	R'H	28
					$R'CH_3$	60
III	RCH_2OCOCH_3	6.0	270–290	49	$R'CH_2OCOCH_3$	3[d]
					$R'CH_3$	83[e]
IV	RCHO	10.0	275–305	82[f]	R'H	97
V	$RCH\begin{matrix}OCH_2\\ |\\ OCH_2\end{matrix}$	4.0	295–305	28	$R'CH_3$	16[g]
VI	$RCOCH_3$	7.5	310	62	$R'COCH_3$	55
					$R'CH_2CH_3$	39
VII	RCH_2COCH_3	23.0	320	90	$R'CH_2COCH_3$	55
					$R'CH_3$	16[h]
VIII	$RCH_2CH_2COCH_3$	15.0	330	88	$R'CH_2CH_2COCH_3$	63
					$R'CH_2CH_3$	16[h]

[a] The yields of hydrogen are based on the assumption that each mole of tetralin derivative will evolve two moles of hydrogen during dehydrogenation. [b] Yields represent purified naphthalene derivatives, except as noted. [c] The theoretical amount of gas is four moles ($3H_2$ + 1 CO) per mole. [d] Yield based on index of refraction measurements. Recovered 9.0% of original acetate. [e] A portion of the yield was derived from a saponification equivalent determination. [f] The theoretical amount of gas is three moles ($2H_2$ + 1 CO) per mole. [g] Probably contaminated with 2-methyltetralin. Recovered 50.5% of the original acetal. [h] Yield based on slightly impure material.

Experimental[4]

Methyl 1,2,3,4-Tetrahydro-2-naphthoate, I.—A large scale synthesis of 1,2,3,4-tetrahydro-2-naphthoic acid, involving a modification of Baeyer's synthesis,[5] was carried out in 12 gallon Pyrex solution bottles. A solution of potassium hypochlorite was prepared from 8.11 kg. of commercial calcium hypochlorite (H. T. H., Mathieson Alkali Co.), 5.66 kg. of potassium carbonate, 1.62 kg. of potassium hydroxide and 43 l. of water. Since the 2.50 kg. (14.2 moles) of methyl 2-naphthyl ketone to be oxidized was much greater than that previously used,[6] it was added portionwise, during two hours, to the vigorously stirred oxidizing solution,[7] held between 60 and 70° by external cooling. After an additional one and one-half hours of stirring at this temperature, a solution of 1.40 kg. of sodium bisulfite in 3.5 l. of water was added. The 2-naphthoic acid was precipitated by the addition of 7.4 l. of concentrated hydrochloric acid and the liquid was removed by suction filtration with fritted filter sticks. The damp acid was dissolved in 18 l. of solution containing 825 g. of potassium hydroxide. With carbon dioxide bubbling in to control the basicity of the reducing medium,[5,8] 37.8 kg. of 3% sodium amalgam was added during eight hours. At this point reduction to the dihydro acids[9] was complete as indicated by an oxidation test[5] with cold dilute potassium permanganate. This solution was filtered free of insoluble material and combined with 9.2 l. of 18 *N* sulfuric acid. After removal of the liquid, the damp mixture of dihydro acids was dissolved in 28 l. of solution containing 4.83 kg. of sodium hydroxide. To this solution was added 4.46 kg. of Raney nickel–aluminum alloy[10] in portions during thirty hours. After removal of the nickel catalyst by filtration, the alkaline solution was divided into two equal amounts, each of which was allowed to siphon slowly into 19 l. of vigorously stirred concentrated hydrochloric acid. After the batches of precipitated acid had been freed of filtrate, dissolved in a total of 30 l. of water containing 650 g. of potassium hydroxide and combined, the solution was cooled to about 10° by the addition of ice. Potassium permanganate was added until no further decolorization occurred (500 ml. of saturated solution). After clarification with saturated sodium bisulfite solution, the solution was siphoned slowly into 4.5 l. of vigorously stirred concentrated hydrochloric acid. The solid was washed with water until free of aluminum salts.

Further purification was accomplished by fractional precipitation from alkaline solution.[9] After six fractions of impure acid had been obtained by addition of successive portions of 50 ml. of concentrated hydrochloric acid, the remainder of the product was precipitated, dried, and recrystallized from petroleum ether (b. p. 65–69°). The yield of 1,2,3,4-tetrahydro-2-naphthoic acid (RCOOH) from the last fraction was 1200 g., m. p. 96.0–96.6°. Fractions 1–6 were fractionally precipitated individually by a similar procedure and yielded an additional 179 g. of pure acid. The total yield was 1379 g. (53.2%). The methyl ester, I, boiled at 102–105° (1 mm.), $n^{20}D$ 1.5314.

Anal.[c] Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4. Found: C, 75.6, 75.6; H, 7.7, 7.6.

The acid chloride boiled at 122–126° at 2 mm. The amide melted at 138.0–138.8°.

Anal.[c] Calcd. for $C_{11}H_{13}ON$: N, 8.2. Found: N, 8.0.

Methyl 1,2,3,4-Tetrahydro-2-naphthyl Ketone, VI.—Into a solution made from 16.5 g. of metallic lithium, 200 g. of methyl iodide, and 900 ml. of ether[11] was slowly added a solution of 35.0 g. (0.2 mole) of RCOOH in 1.4 l. of ether. The mixture was treated with water and the neutral portion was distilled to yield 21.4 g. (61.7%) of the desired ketone, VI, as a colorless oil, b. p. 135–138° (4 mm.), $n^{20}D$ 1.5426. The semicarbazone melted at 192.0–193.2° with dec.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.7; H, 8.1. Found[c]: C, 82.7, 82.9; H, 8.1, 8.3. Calcd. for $C_{13}H_{17}ON_3$: N, 18.2. Found[c]: N, 18.2.

1,2,3,4-Tetrahydro-2-naphthaldehyde, IV.—This aldehyde was prepared in 67% yield by the Rosenmund

(4) All melting points corrected. Microanalyses marked [c] by Oakwold Laboratories, Fairfax, Virginia; [k] by Mrs. E. K. Klotz; [g] by Clark Microanalytical Laboratory, Urbana, Illinois.

(5) Baeyer and Besemfelder, *Ann.*, **266**, 198 (1891).

(6) Newman and Holmes, "Organic Syntheses," **17**, 66 (1937).

(7) A glass centrifugal stirrer was used in concentrated hypochlorite solutions.

(8) Sowinski, *Ber.*, **24**, 2361 (1891).

(9) Derick and Kamm, THIS JOURNAL, **38**, 400 (1916).

(10) A method of reduction described in papers by Papa, Schwenk and Whitman, *J. Org. Chem.*, **7**, 587 (1942), and Schwenk, Papa and Ginsberg, *Ind. Eng. Chem., Anal. Ed.*, **16**, 576 (1943).

(11) van Dorp and Arens, *Rec. trav. chim.*, **65**, 338 (1946).

method,[12] the reaction requiring two hours for evolution of 84% of the theoretical amount of hydrogen chloride gas. Upon vacuum distillation the aldehyde[13] was obtained as a colorless oil, b. p. 90–92° (0.5 mm.), which solidified rapidly at room temperature. This solid product was probably the trimer since it broke down readily at elevated temperatures to yield the oily aldehyde. The semicarbazone melted at 194.8–196.8° with dec.

Anal.[e] Calcd. for $C_{12}H_{15}ON_3$: C, 66.3; H, 7.0; N, 19.3. Found: C, 66.2, 66.3; H, 7.1, 7.1; N, 19.3, 18.9.

2-(1,2,3,4-Tetrahydro-2-naphthyl)-1,3-dioxolane, V.—A mixture of 54.5 g. (0.34 mole) of aldehyde IV, 40 ml. of ethylene glycol, 500 ml. of benzene and a trace of *p*-toluenesulfonic acid was refluxed for three days under a fractionating column with a special take-off head for removing the bottom layer of distillate.[14] After the acid catalyst had been removed by washing with sodium bicarbonate solution, 54.5 g. (78.5%) of the acetal, V, was obtained as a colorless oil, b. p. 126–128° (1 mm.), $n^{20}D$ 1.5423.

Anal.[e] Calcd. for $C_{13}H_{16}O_2$: C, 76.4; H, 7.9. Found: C, 75.9, 76.0; H, 7.8, 7.9.

1,2,3,4-Tetrahydro-2-naphthylcarbinol, II.—During one hour a solution of 194 g. (0.95 mole) of ethyl 1,2,3,4-tetrahydro-2-naphthoate, prepared by esterification of RCOOH with ethanol, in 1 l. of ether was dropped into an ethereal solution of 20 g. (0.52 mole) of lithium aluminum hydride.[15] After the reaction mixture had been decomposed with water and dilute sulfuric acid, 147.2 g. (95.5%) of the desired carbinol, II, was obtained as a colorless oil, b. p. 114–116° (1 mm.), $n^{20}D$ 1.5559. Its 1-naphthylurethan melted at 108.6–109.2°.

Anal.[k] Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 81.4, 81.4; H, 8.8, 9.2. Calcd. for $C_{22}H_{21}O_2N$: C, 79.7; H, 6.4; N, 4.3. Found: C, 79.9, 79.9; H, 6.1, 6.0; N, 4.4, 4.3.

The corresponding acetate, III, was formed in 94% yield by heating the carbinol, II, in benzene with acetic anhydride and a trace of *p*-toluenesulfonic acid. It formed a colorless oil, b. p. 124–126° (1.5 mm.), $n^{20}D$ 1.5238.

Anal.[k] Calcd. for $C_{13}H_{16}O_2$: C, 76.4; H, 7.9. Found: C, 76.8, 76.7; H, 8.2, 8.5.

1-(1,2,3,4-Tetrahydro-2-naphthyl)-2-propanone, VII.—To a cooled solution of 224.0 g. (1.38 moles) of carbinol, II, 109.0 g. (1.38 moles) of dry pyridine and 250 ml. of dry toluene was added slowly 164 g. (1.38 moles) of purified thionyl chloride. After heating the reaction mixture on the steam-bath overnight, the yield of chloride, RCH_2Cl, b. p. 114–118° (1.5 mm.), was 233.8 g. (93.8%). As a structure proof of the product, a portion was refluxed for thirty-six days with potassium acetate and a trace of sodium iodide in anhydrous ethanol. The acetate, thus formed, was readily hydrolyzed by aqueous alkali and the product (68% from the chloride) was shown to be identical with authentic 1,2,3,4-tetrahydro-2-naphthylcarbinol, II, by comparison of the 1-naphthylurethans, m. p. 108.2–108.6 and mixed m. p. 108.5–109.2°.

The Grignard reagent prepared from 54.2 g. (0.3 mole) of the chloride, RCH_2Cl, was added over a period of two hours to a solution of 57.0 g. (0.56 mole) of acetic anhydride in 57 ml. of ether cooled by an external Dry Ice–acetone-bath at −78°.[16] After the reaction mixture has been treated with ammonium chloride solution, 44.3 g. (78.6%) of the ketone, VII, was obtained as a colorless oil, b. p. 114–117° (1 mm.), $n^{20}D$ 1.5362. The semicarbazone melted at 199.8–201.6° with dec.

Anal.[e] Calcd. for $C_{13}H_{16}O$: C, 82.9; H, 8.6. Found: C, 82.4, 82.5; H, 8.5, 8.7. Calcd. for $C_{14}H_{12}ON_3$; N, 17.1. Found: N, 16.9.

1-(1,2,3,4-Tetrahydro-2-naphthyl)-3-butanone, VIII.—The preparation of VIII from RCH_2Cl by way of the acetoacetic ester synthesis failed. The low boiling material obtained probably resulted from dehydrohalogenation of the starting alkyl chloride. Alternately, gaseous formaldehyde was passed into the Grignard reagent[17] made from 161.9 g. (0.895 mole) of RCH_2Cl until the color test[18] for the Grignard reagent was negative (about thirty minutes). After decomposition of the reaction mixture with dilute sulfuric acid, there was obtained 96.4 g. (61%) of 2-(1,2,3,4-tetrahydro-2-naphthyl)-ethanol as a colorless oil, b. p. 123–127° (1 mm.), $n^{20}D$ 1.5490.

Anal.[e] Calcd. for $C_{12}H_{16}O$: C, 81.7; H, 9.2. Found: C, 81.8; H, 9.4.

By a process similar to one above, the alcohol was treated with thionyl chloride to yield the corresponding chloride (93.1%) as a colorless oil, b. p. 104–109° (0.5 mm.). In a reaction similar to one above involving the Grignard reagent from 42.5 g. (0.22 mole) of the chloride, RCH_2CH_2Cl, and 42.4 g. (0.415 mole) of acetic anhydride there was obtained 27.4 g. (62%) of the desired butanone, VIII, as a colorless oil, b. p. 124–126° (1 mm.) $n^{20}D$ 1.5320. The semicarbazone melted at 171.4–173.4° with dec.

Anal.[e] Calcd. for $C_{14}H_{18}O$: C, 83.1; H, 9.0. Found: C, 82.1, 82.4; H, 9.2, 9.0. Calcd. for $C_{15}H_{21}ON_3$: N, 16.3. Found: N, 16.4.

Dehydrogenation Experiments

Palladium-on-Charcoal Catalyst.—The catalyst used in this work was similar to that of the previous investigations.[2,3] A check on the activity of the catalyst was made by dehydrogenation of methyl 1,2,3,4-tetrahydro-6-naphthoate as before.[2] About the same amount of hydrogen was evolved in about the same amount of time.

General Description of Dehydrogenations.—The apparatus made for the dehydrogenations was designed to improve on the two-flask technique in the previous investigations.[2,3] It consisted of a 50-ml. Claisen flask with a condenser and receiver sealed onto its horizontal side arm. In the verticle side-arm was sealed a coil-type condenser through which water was circulated during those dehydrogenations in which water was not liberated. In the dehydrogenation experiments where water was evolved, acetic acid vapor was refluxed through the sealed-in coil. The heated coil served to allow the water to distill from the reaction mixture and prevent excessive splattering and to condense the organic vapors. The remainder of the dehydrogenation procedure was essentially the same as before.

Three duplicate runs were made on each compound, the first served as a pilot run. In the second and third the products were isolated as nearly quantitatively as possible and served as checks on the reproducibility of the results obtained. Since the results of the last two were in substantial agreement, a description is given only for the third run. In each case 0.07 mole ± 0.01 g. of the compound was dehydrogenated. Table I summarizes the experimental details recorded. In working up the products of the reactions, the material was always vacuum distilled from the catalyst prior to further treatment.

$RCOOCH_3$, I.—The distilled dehydrogenated ester was saponified and the acid was recrystallized from ethanol. It melted, alone and mixed with authentic 2-naphthoic acid, at 183.4–185.0°.

RCH_2OH, II.—The product from 11.36 g. of II was fractionated under reduced pressure. The first fraction, 2.47 g. (27.6%), naphthalene, was obtained by careful sublimation into a chilled receiver. A portion, after recrystallization from ethanol, melted at 78.6–80.2°,

(12) Hershberg and Cason, "Organic Syntheses," Vol. XXI, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 84.

(13) Weil and Ostermeier, *Ber.*, **54**, 3218 (1921).

(14) Fieser, Fields and Lieberman, *J. Biol. Chem.*, **156**, 191 (1934).

(15) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

(17) Newman and Booth, *ibid.*, **67**, 154 (1945).

(17) Gilman and Catlin, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 188.

(18) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925); Gilman and Heck, *ibid.*, **52**, 4949 (1930).

mixed m. p. 79.0–80.4°. The second fraction, 5.96 g. (59.8%), b. p. 69–74° (1 mm.), formed a picrate, m. p. 115.8–116.4°, mixed m. p. not depressed with picrate of 2-methylnaphthalene.

A gas analysis[19] showed that the gas evolved was a mixture of carbon monoxide and hydrogen. The amounts of carbon monoxide and naphthalene obtained corresponded rather closely, but a quantitative balance was not undertaken.

RCH_2OCOCH_3, III.—The product obtained from 12.41 g. of III was separated into three fractions by vacuum distillation. Fraction 1, 7.26 g. (73.0%), b. p. 126–131° at 23 mm., formed 2-methylnaphthalene picrate, m. p. and mixed m. p. 116.4–117.4°. Fraction 2, 1.58 g., b. p. 131–177° at 23 mm., was shown by a saponification equivalent determination (assuming the molecular weight of III) to consist of about 40% of ester and 60% of 2-methylnaphthalene. The picrate of 2-methylnaphthalene was isolated and identified. Fraction 3, b. p. 177–180° at 23 mm., weighed 1.06 g. After a portion had been saponified, the carbinol product boiled at 120–125° at 2 mm. The 1-naphthylurethan which was prepared melted at 102–106°, which indicated a mixture of the two 1-naphthylurethans, that of 1,2,3,4-tetrahydro-2-naphthylcarbinol (m. p. 108.6–109.2°) and that of 2-naphthylcarbinol (m. p. 141.2–142.8°). The latter was prepared from 2-naphthylcarbinol,[20] m. p. 81.2–82.0°, obtained by reduction of 2-naphthoic acid with lithium aluminum hydride.[21] Authentic 2-naphthylmethyl acetate,[22] m. p. 57.2–57.8°, was prepared by refluxing 2-naphthylcarbinol with acetic anhydride and a trace of *p*-toluenesulfonic acid in benzene. Mixtures of III and 2-naphthyl acetate were made and their refractive indices determined.

% 2-naphthylmethyl acetate	$n^{20}D$
20	1.5344
40	1.5479
50	1.5530

Since the refractive index of Fraction 3 was $n^{20}D$ 1.5473, it contained about 40% 2-naphthylmethyl acetate and 60% unchanged III. Thus, in all, there was obtained 3.0% of 2-naphthylmethyl acetate, 82.5% of 2-methylnaphthalene and 9.0% of III based on the starting 14.21 g. of III.

RCHO, IV.—Pure naphthalene was obtained by direct sublimation from the catalyst. By analysis[19] the gas collected was shown to contain carbon monoxide, hydrogen and methane. The amounts of carbon monoxide and methane obtained account reasonably well for the amount of naphthalene obtained in the experiment; however, a quantitative balance was not established.

$RCHOCH_2CH_2O$, V.—The product from 14.30 g. of V was separated into two main fractions by vacuum distillation. Fraction 1, 1.58 g. (15.9%), b. p. 104–109° at 6 mm., yielded 2-methylnaphthalene picrate. Since the yield of picrate was somewhat lower (54%) than that from authentic 2-methylnaphthalene prepared in a similar manner (68%), we conclude that Fraction 1 probably contained a small amount of 2-methyltetralin. Fraction 2, b. p. 157–160° at 6 mm., weighed 7.21 g. A portion was hydrolyzed by boiling with dilute aqueous alcoholic hydrochloric acid and the product converted to its semicarbazone in 72% over-all yield. The semicarbazone melted alone and mixed with the semicarbazone of 1,2,3,4-tetrahydro-2-naphthaldehyde at 191–194° with dec. Fraction 2, then, was essentially unchanged V and represents a 50.5% recovery of the starting material. In addition to the two fractions, there remained 3.3 g. of residue.

$RCOCH_3$, VI.—The addition of 0.10 g. of fresh catalyst, after an hour's heating, caused a considerable increase in the pace of the dehydrogenation reaction. The distilled material from 12.20 g. of VI was separated into two main fractions by vacuum distillation. The first fraction, 4.24 g. (38.7%), b. p. 70–77° (0.5 mm.), formed a picrate which melted at 76–78° alone and mixed with the picrate of authentic 2-ethylnaphthalene. The second fraction, 6.58 g. (55.2%), b. p. 95–99° (0.5 mm.), after recrystallization from an alcohol–water mixture, melted alone and mixed with authentic methyl 2-naphthyl ketone at 53–54°. The semicarbazone of the second fraction melted alone and mixed with the semicarbazone of authentic methyl 2-naphthyl ketone at 222.0–223.4°.

RCH_2COCH_3, VII.—The slow rate of evolution of hydrogen from 13.18 g. of VII was not increased by the addition of a fresh portion of catalyst at the end of two hours of heating. After removal of the product from the catalyst by vacuum distillation, there remained 3.4 g. of high boiling residue. The product was separated into two fractions by distillation at reduced pressure. Fraction 1, 1.55 g. (15.6%), b. p. 66–129° (1 mm.), consisted mainly of 2-methylnaphthalene as judged by the ready formation of the picrate. Fraction 2, 7.02 g. (54.5%), b. p. 129–131° (1 mm.), was shown to be 2-naphthyl-2-propanone by comparison with an authentic sample. A portion of Fraction 2, after recrystallization from petroleum ether (b. p. 30–60°), melted alone and mixed at 36.0–37.2°. Its semicarbazone melted at 182.8–184.4° with dec.; a mixed melting point showed no depression.

The previously unknown 2-naphthyl-2-propanone was synthesized in 42% yield from 2-naphthylacetic acid[23] and methyl lithium by a procedure similar to that described in the experimental discussion above. It boiled at 131.5–132.5° at 1.5 mm. and after recrystallization from petroleum ether (b. p. 30–60°) melted at 36.0–37.2°. The semicarbazone melted at 183.0–184.6° with dec.

Anal.[c] Calcd. for $C_{13}H_{12}O$: C, 84.7; H, 6.6. Found: C, 84.9; H, 6.5. Calcd. for $C_{14}H_{15}ON_3$: N, 17.4. Found: N, 17.3.

$RCH_2CH_2COCH_3$, VIII.—With the catalyst remained 2.8 g. of resinous material. The product from 14.16 g. of VIII was fractionated. Fraction 1, 1.71 g. (15.6%), b. p. 76–80° (1 mm.), was shown to be 2-ethylnaphthalene by formation of its picrate which, after one recrystallization from ethanol, melted at 75.2–76.8° alone and mixed with an authentic sample. Fraction 2, 8.73 g. (62.8%), b. p. 139–142° (1 mm.) was shown to be 1-(2-naphthyl)-3-butanone by its melting point, after recrystallization from petroleum ether (b. p. 30–60°), of 48.4–49.0° (lit.[24] 50°), of its semicarbazone, 171.2–172.8° (lit.[24] 173°) and of its oxime, 119.4–120.8° (lit.[24] 115–116°).

Discussion of Results

A number of the compounds in this dehydrogenation study contained the same oxygenated substituents as those of the previous studies.[2,3] *The carbomethoxy group* (*-COOCH₃*) was unharmed in all three cases by the hydrogen which was eliminated from the ring. It is, therefore, concluded that a carboxyl group in a hydroaromatic compound may be protected easily during dehydrogenation over palladium-on-charcoal by conversion to its methyl ester.

In the cases of the compounds containing the *carbinol group* (*-CH₂OH*) the results of the three studies show graded differences. The primary alcohol group on the beta position of the benzenoid ring[2] was hydrogenolyzed to the methyl group, whereas this same group on the alpha position of the saturated ring[3] lost both hydrogen and carbon

(19) Gas analysis through the courtesy of D. J. Demorest, The Ohio State University, Department of Metallurgy.

(20) Sah, *Rec. trav. chim.*, **59**, 461 (1940).

(21) Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

(22) Tarbell, Fukushima and Dam, *ibid.*, **67**, 197 (1945).

(23) Newman, *J. Org. Chem.*, **9**, 518 (1944).

(24) Mayer and Sieglitz, *Ber.*, **55**, 1854 (1922).

monoxide to yield naphthalene almost quantitatively. Hydrogenolysis of the alcohol group to 1-methylnaphthalene occurred only to the extent of 4%. The compound containing the carbinol group on the beta position of the hydrogenated ring lost water in part and carbon monoxide in part, giving 2-methylnaphthalene and naphthalene in the approximate ratio of 2:1. The last results show some similarity to those of each of the others. It seems, therefore, that the fate of the primary alcohol function is dependent both on its position with respect to the point of ring fusion and on the type of ring to which it is bound.

The results of the dehydrogenation of the compounds containing the *ketonic group*, (*-COCH*$_3$) show graded differences. When the compound bearing this group attached to the beta position of the aromatic ring[2] was dehydrogenated, the carbonyl group was reduced to a methylene group; only a small amount of the corresponding naphthyl ketone being obtained. In contrast, the ketone function was not attacked by hydrogen when attached to the alpha position of the hydroaromatic ring.[3] In the latter case, the ring itself was resistant to dehydrogenation and only a small amount of the methyl 1-naphthyl ketone was obtained. The compound bearing the ketonic group at the beta position of the saturated ring, was partially converted to the 2-ethylnaphthalene and partially dehydrogenated to methyl 2-naphthyl ketone. The ratio of the amounts of 2-ethylnaphthalene and methyl 2-naphthyl ketone was approximately 2:3. The results in the last case cited are similar to some extent to those of both of the others. It may be concluded that the behavior of the ketonic group directly bound to the ring depends both upon the type of ring to which it is attached and upon its position relative to the point of ring fusion.

The *aldehyde function* (*-CHO*), when attached to the beta position of the aromatic ring[2] and when attached to the beta position of the hydroaromatic ring, lost carbon monoxide almost quantitatively. However, the decarbonylation reaction is undoubtedly catalyzed by the palladium and is not affected by the removal of hydrogen from the ring.

The two *acetates*, (having the group *-CH*$_2$*OCOCH*$_3$), differing in the position of the ester function on the hydrogenated ring, gave dehydrogenation products that differed in degree but not in kind. The oxygenated function was protected to the extent of 26% in the dehydrogenation of the alpha isomer[3] and only to the extent of 3% in the dehydrogenation of the beta isomer. The other products in each case resulted from hydrogenolysis of the acetate function. It thus appears that it is not feasible to attempt a catalytic dehydrogenation of a compound bearing an alcohol function either free or acetylated.

The two isomeric *propanones*, having the ketone group removed from the saturated ring by a methylene group, yielded somewhat different products. The alpha substituted compound gave a high yield of the corresponding aromatic propanone,[3] whereas the beta substituted compound gave only a fair yield of the corresponding naphthalene derivative. The difference in yields is accounted for by the formation of 2-methylnaphthalene and resinous material in the latter case. Since the beta substituted isomer was heated about 30° higher and about twice as long as the alpha derivative before hydrogen evolution had ceased, the lower yields of aromatic ketone from the former may have been due to pyrolytic decomposition rather than to a dehydrogenation effect.

The differences between the dehydrogenation products of the two butanones, having the ketone group removed from the hydrogenated ring by two methylene groups, are quite a bit greater than those of the propanones described above. The alpha compound[3] in this case was resistant to dehydrogenation and yielded only a small amount (16%) of the corresponding naphthalene ketone, whereas the beta compound dehydrogenated slowly but steadily to give a fair yield (62.8%) of its corresponding naphthalene ketone. The hydrocarbons, isolated from the reaction products, represented the loss of a three carbon fragment (1-methylnaphthalene) from the alpha-butanone and the loss of a two carbon fragment (2-ethylnaphthalene) from the beta-butanone. The hydrocarbon side reaction products presumably resulted from pyrolysis and do not therefore indicate a difference in hydrogenolysis effects resulting from the different relative positions of the parent functional groups on the hydrogenated ring.

Protection of the aldehyde function by formation of its cyclic acetal with ethylene glycol has been tried in only the present case. The only dehydrogenated product isolated, 2-methylnaphthalene, was in low yield. The remainder of the product consisted of high boiling material and unchanged starting material (50.5%). From these results it would appear that this method of protection of aldehydes from decarbonylation during catalytic dehydrogenation has little value.

Summary

The liquid phase catalytic dehydrogenation over a palladium-on-charcoal catalyst of eight oxygenated 2-substituted-1,2,3,4-tetrahydronaphthalenes is described.

The methyl ester, $C_{10}H_{11}COOCH_3$, was converted in high yield into the corresponding naphthalene derivative while the theoretical amount of hydrogen was evolved.

The primary alcohol, $C_{10}H_{11}CH_2OH$, was partially degraded to naphthalene by the loss of hydrogen and carbon monoxide and partially converted to 2-methylnaphthalene by loss of hydrogen and water.

Hydrogenolysis of the acetate function of $C_{11}H_{10}CH_2OCOCH_3$ occurred as the main reaction.

The aldehyde, $C_{10}H_{11}CHO$, readily lost carbon monoxide.

The cyclic acetal, $C_{10}H_{11}\overline{CHOCH_2CH_2O}$, did not dehydrogenate smoothly. The only dehydrogenated product isolated, 2-methylnaphthalene, resulted from hydrogenolysis of the acetal.

The ketones $C_{10}H_{11}COCH_3$, $C_{10}H_{11}CH_2COCH_3$ and $C_{10}H_{11}CH_2CH_2COCH_3$ gave fair yields of the corresponding aromatic ketones. The ketonic group of the first was reduced to a methylene group to a considerable extent. Small amounts of the last two were pyrolyzed to form hydrocarbons, with a resulting loss of a two-carbon fragment in each case.

COLUMBUS 10, OHIO RECEIVED JANUARY 28, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE CATHOLIC UNIVERSITY OF AMERICA]

Pyrolysis of Butadiene[1]

BY MARY THOMAS MURPHY[2a] AND ANN CHARLES DUGGAN[2b]

In the pyrolysis of unsaturated hydrocarbons in this Laboratory, it has been observed that the liquid products are frequently colored yellow. This was noted particularly in the pyrolyses of butadiene, isoprene,[3] and isobutylene,[4] where it appeared in the C_7-C_8 region of products. Similar observations were reported in 1932 by Frey and Hepp[5] in a study of the production of aromatic oils from the pyrolysis of simple paraffins. At 850° and atmospheric pressure, butane gave benzene, toluene, xylenes, and a number of olefins and diolefins, principally butadiene and cyclopentadiene. A few degrees above the boiling point of toluene a bright yellow hydrocarbon was obtained; another yellow hydrocarbon appeared in the xylene fraction. Neither of these was identified because they were present in such small amounts.

The first step in this investigation has been to pyrolyze large quantities of butadiene in order to isolate the yellow fraction in amounts large enough to analyze.

Experimental

The apparatus used for the pyrolysis was a quartz furnace 60 × 3 cm., connected to a series of traps, a manometer, a glycerol-filled vacuum pump and a gas meter. The traps were cooled to −78°. To prevent clogging, the first trap was cooled only to −10°. The furnace was heated by two external resistance heaters, and the temperature at the center was measured with a chromel–alumel thermocouple. The temperature was maintained within 10° during a given run. The pressure did not vary more than 2 mm.

The butadiene obtained from Shell Oil Company was of better than 98% purity; it was used without further purification. The hydrocarbon was introduced to the furnace from a pressure bottle kept in an ice-salt-bath, the input rate, usually a mole an hour, being regulated by a needle valve, and the amount put through determined by the loss in weight of the bottle. The tar, largely naphthalene, collected in the first trap, while the lower aromatic fractions condensed mainly in the second and third traps. Nearly all of the unchanged butadiene condensed in the traps, but 2–5% of the total volume was detected in the effluent gases. The gaseous products (insoluble in glycerol, except acetylene to some extent) passed through the gas meter and escaped into the air. During the course of a run several samples were taken for analysis. At the end of each run the products collected were transferred to weighed bottles and stored at −15° until they were analyzed.

Five runs were made in all. In Table I are given the data for run 3. The analysis of the products was made as follows:

The gases were determined on a modified Hempel apparatus developed in this Laboratory.[6] The reagents for the absorption of the various gases were: acetylene, potassium mercuric iodide; isobutylene, 62.5% sulfuric acid; butenes, 71% sulfuric acid; propylene, 82.5% sulfuric acid; ethylene, fuming sulfuric acid. The different concentrations of acid were those recommended by Hurd and Spence[7] for the detection of the various hydrocarbons. Butadiene was determined by its reaction with maleic anhydride.[8] Since, according to Hurd and Spence, butadiene would be absorbed in both the propylene and isobutylene reagents, the values reported for the C_3 and C_4 hydrocarbons are affected by this amount. The saturated portion of the gas was analyzed for hydrogen by oxidation over copper oxide at 285°. The average value, 25%, checked analyses by combustion data which gave 25.8% for hydrogen and 12% for methane.

The tar in the first trap was collected over several runs and distilled. It was found to contain naphthalene and a small yellow fraction boiling above naphthalene, which we have not yet identified.

An approximate analysis from mass spectrometer data[9] for the liquid samples from the other traps showed, in agreement with Staudinger[10] that the liquids are almost exclusively aromatic. The relative abundance of the compounds was as follows: benzene, > 90%; toluene, ≦ 1%; indene, < 1%; dihydroindene, < 1%; tetralin, < 0.5%; styrene, < 1%; ethylbenzene, ≤ 1%. Other peaks not accounted for occurred at 83, 85, 117 and 119. It will be noticed that the benzene/toluene ratio of 90/1 found by the mass spectrometer differs widely from the ratios reported in Tables I and II (15.4/1.0 and 10.8/1.0, respectively), but no explanation for this deviation is apparent.

(1) Taken from the dissertation presented by Sister Ann Charles Duggan for the degree of Doctor of Philosophy at the Catholic University.

(2) (a) Sister Mary Thomas Murphy, S.S.J., College of Chestnut Hill, Philadelphia, Pa.; (b) Sister Ann Charles Duggan, O.P., Barry College, Miami, Florida.

(3) M. T. Murphy, Ph.D. dissertation, The Johns Hopkins University, 1938, pp. 38, 44.

(4) L. Wall, Ph.D. dissertation, Catholic University of America, 1945, p. 10.

(5) Frey and Hepp, *Ind. Eng. Chem.*, **24**, 282 (1932).

(6) Rev. Aquinas Sweeney, C.P., Master's thesis, Catholic University of America, 1945.

(7) Hurd and Spence, THIS JOURNAL, **51**, 3356 (1929).

(8) Tropsch and Mattox, *Ind. Eng. Chem., Anal. Ed.*, **6**, 104 (1934).

(9) We are indebted to Dr. Leo Wall of the National Bureau of Standards for this analysis.

(10) Staudinger, Endle and Herold, *Ber.*, **46**, 2466 (1913).

TABLE I

PYROLYSIS OF BUTADIENE, RUN 3

Temperature, °C.		838
Pressure, mm.		20
Length of run, min.		392
Contact time, sec.		0.5
Butadiene used, g.		323
Butadiene recovered, g.		153.9
Products recovered, g.	Liquid and solid	74.5
	Gaseous	78.6
Difference in weight balance, g.		16.0
% decomposed, based on recovered products		47.5

Gaseous products	Moles	Moles/mole C_4H_6 decomposed
Hydrogen	0.89	0.313
Methane	.42	.148
Acetylene	.42	.148
Ethylene	1.37	.482
Propylene	0.35	.123
Isobutylene	.09	.033
Liquid and solid products		
Cyclopentane	.038	.013
Benzene	.463	.163
Toluene	.030	.011
Ethylbenzene	.038	.013
Isopropylcyclopentene	.005	.002
Isopropylcyclopentane	.009	.003
Xylenes	.007	.002
Naphthalene	.07	.025
Carbon (tar)	.075	.264
Carbon in furnace	.075	.264

The liquid products were analyzed by distillation at both ordinary and reduced pressures. In run 3, the liquid products were hydrogenated, before distillation on an 11-mm. Podbielniak column.

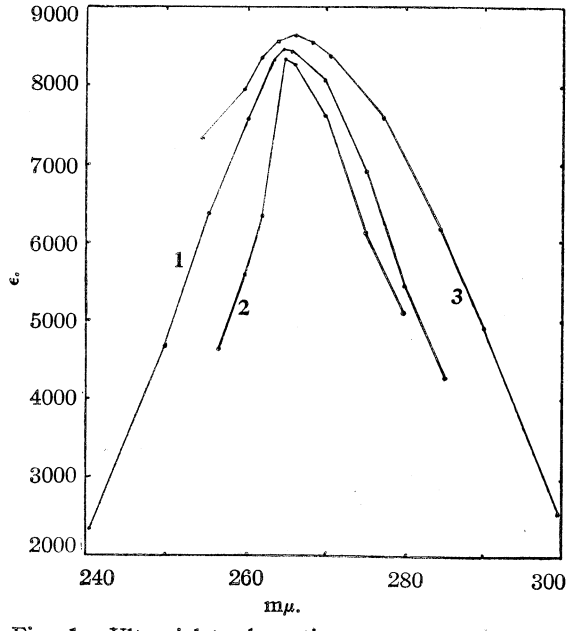


Fig. 1.—Ultraviolet absorption spectra of dimethylfulvene and yellow pyrolysis product: 1, dimethylfulvene in 2,2,4-trimethylpentane; 2, pyrolysis product in *n*-hexane; 3, pyrolysis product in 2,2,4-trimethylpentane.

In Table II are given data for the distillation of the liquid products of run 2. In this case the distillation was carried out on a 35-cm. vacuum-jacketed Vigreux column. The first part of the distillation was run rapidly to prevent polymerization of the dimethylfulvene; 25 cc. of hexadecane was added before the distillation to serve as column hold-up. This distillation showed the presence of cyclopentadiene as well as the aromatic products previously reported in butadiene pyrolysis[10] and indicated that the main yellow product was a C_8 compound. It was subsequently identified as dimethylfulvene by its absorption spectra, hydrogenated products and oxygen derivative.

The sample used for the absorption spectra measurements was obtained by fractional crystallization of the liquid products. After most of the dissolved butadiene had been removed by distillation at room temperature, the remaining liquid was cooled to −80° and filtered through a suction funnel likewise cooled. The process of cooling and filtering was repeated until no more solid could be separated from the yellow liquid. Further separation of the residue was accomplished in a bulb to bulb distillation at 1–2 mm., the receiver being cooled in liquid air. In this way 2.5 cc. of bright yellow liquid was obtained for the absorption spectra measurements.

The absorption in the visible and ultraviolet were measured with a Beckmann Model DU quartz spectrophotometer. Since the work on the spectrum of dimethylfulvene[11] had been done before conventions were established for the reporting of spectral data, it seemed advantageous to repeat the work in this Laboratory in order to facilitate the comparison of the dimethylfulvene spectrum with that of our yellow compound. Accordingly, dimethylfulvene was synthesized by the method of Thiele.[12] Solutions were made from a sample which boiled at 46–48° under 11 mm. pressure and had a freezing point of 0.9°. The 2,2,4-trimethylpentane used as a solvent was distilled over sodium hydroxide and filtered through silica gel. The graphs for the spectra of dimethylfulvene and our yellow compound are shown in comparison in Fig. 1. The absorption maxima, 270 and 365 mμ, are the same as those reported by Stark and his co-workers.

Hydrogenation was carried out under the conditions recommended by Pines and Ipatieff.[13] Three hundred twenty grams of pyrolysis product, including unchanged butadiene, was hydrogenated over Raney nickel at 30 atm. and 25–125°. Distillation was then carried out on a Podbielniak fractionating column. Small amounts of the expected hydrogenation products of dimethylfulvene were obtained: 1.5 cc. isopropylcyclopentene, b. p. 120–122°; 1.8 cc. isopropylcyclopentane, b. p. 126–127.5°, m. p. −113°.

The presence of the fulvene was further substantiated by the formation of its oxide. A dilute solution was allowed to stand in air for a month. At the end of this time a flocculent white precipitate had formed. The solution was centrifuged and the precipitate washed with ether and dried. At 80–90° it reacted in the same way as the oxide of dimethylfulvene[14] which had formed in the same manner. Both oxides exploded when heated to 125°.

The yellow substance also gave a positive color reaction with sulfuric and acetic acids. This test described by Thiele[15] is given by all the simple fulvenes.

The mass spectrometer data indicated the presence of indene, dihydroindene and tetralin, but the small amounts which may have been present were not isolated.

Summary

Butadiene has been pyrolyzed at low pressures in order to study the formation of yellow hydrocarbons produced in the pyrolysis. In addition to

(11) Stark, *et al.*, *Jahrb. Radioakt. Elektronik*, **10**, 139 (1913).
(12) Thiele, *Ber.*, **33**, 666 (1900).
(13) Pines and Ipatieff, THIS JOURNAL, **61**, 1076 (1939).
(14) Engler and Frankenstein, *Ber.*, **34**, 2933 (1901).
(15) Thiele and Balhorn, *Ann.*, **348**, 1 (1906).

TABLE II

LIQUID PRODUCTS FROM BUTADIENE PYROLYSIS, RUN 2

Amount, g.	Description	B. p. °C.	Mm.	F. p., °C.	$n^{20}D$	Probable composition
2.5	Colorless liq.	39–42.5		−90	1.4388	Cyclopentadiene
1.7	Colorless liq.	*ca.* 70		−15	1.4807	
2.6	Colorless liq.	78		0.1	1.4967	Mostly benzene
27.6	Colorless liq.	79.5		3.5	1.5000	Benzene
2.8	Colorless liq.	41–42	60	−96	1.4951	Toluene
1.5	Sl. yellow	50–65	60	−70	1.5037	Ethylbenzene, xylenes and dimethylfulvene
1.0	Yellow	66.6	57	−60	1.5251	Dimethylfulvene
2.7	Sl. yellow	59–62	39	−45	1.5383	Styrene
0.7	Yellow	64–65	40	Glass −82	1.5240	
0.8	Colorless liq.	46.5	10	Glass −80	1.5268	
9.0	White solid			75		Naphthalene

the previously reported products, cyclopentadiene, styrene and dimethylfulvene, a yellow hydrocarbon, have been identified. The presence of two higher boiling yellow fractions is indicated, but they have not been identified.

WASHINGTON, D. C. RECEIVED AUGUST 11, 1948

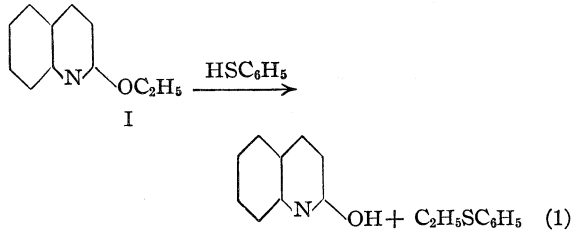
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Reactions of Thiols with Some Alkyl and Aryl Heterocyclic Ethers

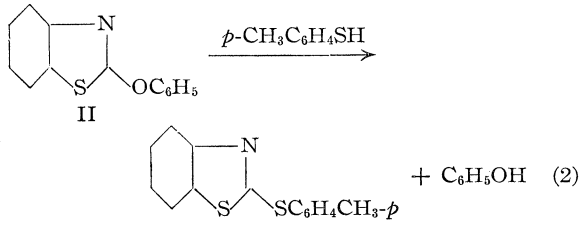
BY GABRIELLO ILLUMINATI AND HENRY GILMAN

Recent work[1] on the action of organolithium compounds on some 2-substituted quinolines has emphasized the special character of the 2-position in quinoline. The present study describes the reactions of aryl thiols on some alkyl and aryl 2- and 4-quinolyl ethers and on corresponding derivatives of 2-benzothiazolyl and 2-benzoxazolyl ethers.

The 2-ethoxy compounds of quinoline (I), benzothiazole and benzoxazole are known to be cleaved by hydrogen chloride[2] to form ethyl chloride and the corresponding 2-hydroxy derivatives. We have now found that a similar cleavage occurs by the action of aryl thiols on these ethoxy compounds at 150–170°, in accordance with the following typical reaction.



This alkylating reaction appears to be general, for 2-benzyloxyquinoline behaves in an analogous manner. However, with aryloxy compounds, the following representative cleavage reaction takes place.



From the results given in Table I it appears that the ease of cleavage of the heterocyclic types varies as follows:

2-Quinolyl > 2-Benzothiazolyl > 2-Benzoxazolyl.—An alkylating reaction appears not to occur with 4-alkoxyquinolines, for 4-ethoxy-7-chloroquinoline (III) reacts in essential accordance with reaction (2).

These reactions generally take place in good yield (see Table I) when aryl thiols like thiophenol, *m*- and *p*-thiocresol and β-thionaphthol are used. An exception in the experiments carried out was *o*-thiocresol, which did not react appreciably with (I), possibly because of steric hindrance. Some reagents containing an acidic hydrogen, other than aryl thiols, have given corresponding exchange reactions with 2-alkoxyquinolines.[3] The fact that benzyl mercaptan cleaved (I) to a small extent (see Table I, Expt. 6) may be accounted for by the lower acidic character of the benzyl mercaptan as compared with that of the aryl thiols.

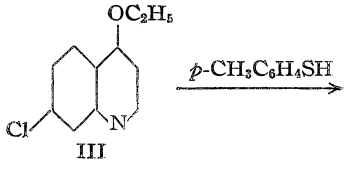
Aryl thiols can also effect a related reaction with the chlorine atom in the activated positions of quinoline and benzothiazole. For example,

(1) Gilman and Beel, unpublished results.

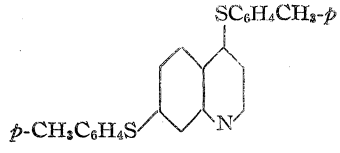
(2) Friedlaender and Ostermaier, *Ber.*, **15**, 335 (1882); Jacobson, *ibid.*, **19**, 1077 (1886); Sandmeyer, *ibid.*, **19**, 2655 (1886); MacCoy, *Am. Chem. J.*, **21**, 122 (1899).

(3) Unpublished studies; see, also, ref. 2.

2-chloroquinoline was converted by thiophenol to phenyl 2-quinolyl sulfide in 79% yield. Surprisingly, this type of reaction was also observed in (III), in which the supposedly stable 7-chlorine in the benzenoid ring was replaced by a *p*-thiocresoxy group to form 4,7-di-(*p*-thiocresoxy)-quinoline.



III



Compound (III) was obtained quantitatively from 4,7-dichloroquinoline and sodium ethoxide, even when the latter reagent was used in excess.[3a]

A discussion of the course of cleavage of the ethers examined warrants a consideration of an intermediate addition product to the azomethine linkage, in view of the tendency of the ring system of quinoline to form isolable 1,2-dihydro-2-substituted derivatives with some organometallic reagents.[4] However, in our work, no experimental evidence has been found to support such an hypothesis. Also, the conditions in which reactions with organometallic reagents are carried out are different from those used in our experiments, in which we used higher temperatures and no solvent. We have observed that a mixture of thiophenol and 2-ethoxyquinoline, stirred for three days at room temperature, underwent no reaction and no change in color; the starting materials were recovered at low temperature by high vacuum distillation.

Because of a possible relationship between extent of cleavage of the ether and acidity of reagent used and by comparison with other related observations, it appears rather likely that thiols act as nucleophilic cleavage reagents on ethers containing an especially weakened carbon–oxygen bond. Thus ethyl benzyl ether was cleaved to an extent of 2.5% by *p*-thiocresol to give benzyl *p*-tolyl sulfide. This reaction was promoted, as expected, by either sulfuric acid or anhydrous aluminum chloride to give 50 and 75% yields, respectively, of the same sulfide. In an analogous manner thiols react with compounds like ethylene oxide[5] to yield sulfides of the type $HOCH_2CH_2SR$. In addition, ether linkages are cleaved in lignin by mercaptoacetic acid, in presence of hydrogen chloride, to form sulfides of the type $RSCH_2COOH$.[6]

Depending on the firmness of attachment of the groups to the oxygen of the ether, the bond may be cleaved on either side, as we have observed with the alkyl and aryl ethers reported in Table I. It is interesting to note that ethyl β-naphthyl ether, unlike 2-ethoxyquinoline, does not react with thiophenol, even after prolonged treatment. From this point of view the weakening effect of the aromatic ring nitrogen on the carbon–oxygen bond resembles that of the nitro groups in polynitro aromatic ethers.[7] However, a weak ether bond has also been found in piperidinomethyl ethyl ether,[8] in which the tertiary nitrogen bears no double bond.

Experimental

Cleavage by Thiols.—A mixture of the compound to be cleaved and the thiol, in a molar ratio 1:2 to 1:3, was stirred for twenty-four to forty-eight hours, at 150–170°, in a dry nitrogen atmosphere. In the experiments 1 to 9 (see Table I), the 2-hydroxy derivative crystallized at the end of the reaction after cooling and was isolated by filtration. The crystals were washed with a little diethyl ether or petroleum ether (b. p. 32–35°) to give a practically pure compound.

The reaction mixture, or the filtrate, was diluted with diethyl ether or petroleum ether (b. p. 32–35°) and extracted with a 5% sodium hydroxide solution. This alkaline extract contained the unreacted thiol and, for the experiments 10 and 11, the phenol formed as one of the cleavage products. In some cases, as, for instance, in the experiments 1 to 6, it was possible to extract completely the unreacted heterocyclic compounds with hydrochloric acid, so the ether-soluble fraction consisted of cleavage products only (sulfides). Usually, however, the ether-soluble fraction contained more or less large amounts of the disulfide corresponding to the thiol used.

2-Benzyloxyquinoline.—To a solution of 0.16 mole of sodium benzyloxide in benzyl alcohol, 24.4 g. (0.15 mole) of 2-chloroquinoline was added, and the mixture was stirred at 120° overnight. After cooling, the reaction product was diluted with ether and washed with water. After removal of the ether, the excess benzyl alcohol was removed by distillation at reduced pressure. The residue was distilled at 170° at 0.8 mm. to give 28 g. (80%) of a solid melting at 46–48°, which was purified by crystallization from ethanol to form white crystals (m. p. 48.5–49.5°).[9]

Anal. Calcd. for $C_{16}H_{13}ON$: N, 5.95. Found: N, 5.87.

2-Phenoxybenzothiazole.—To a solution of 0.3 mole of sodium phenoxide in hot phenol, 33.8 g. (0.2 mole) of 2-chlorobenzothiazole was added, and the mixture was stirred at 120° overnight. After cooling, the reaction product was taken up in ether and the excess phenol was extracted with 5% sodium hydroxide solution. The residue obtained from the ether layer was distilled at 147° at 1 mm. to give 42 g. (94.6%) of a solid (m. p. 51–52.5°), which was purified by crystallization from ethanol as white crystals (m. p. 51.5–52.5°).

(3a) However, see Bradford, Elliott and Rowe, *J. Chem. Soc.*, 437 (1947), for a reaction at elevated temperature in a sealed tube in which a 7-halogen is replaced by a dimethylamino and a methoxy group, respectively.

(4) See, for example, Ziegler and Zeiser, *Ber.*, **63B**, 1847 (1930); *Ann.*, **488**, 174 (1931); Gilman and Gainer, THIS JOURNAL, **69**, 1946 (1947).

(5) Nenitzescu and Scarlatescu, *Ber.*, **68B**, 587 (1935).

(6) Richtzenhain, *ibid.*, **72B**, 2152 (1939).

(7) See, for example, Le Fèvre, *et al.*, *J. Chem. Soc.*, 1168 (1927). For a comparison of the structural effects of ring nitrogen and nitro groups, see, for example, Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 243.

(8) Yang, *J. Org. Chem.*, **10**, 67 (1945).

(9) This compound has just been reported by Lott and Shaw, THIS JOURNAL, **71**, 73 (1949). The m. p. reported by them is 46–47°.

TABLE I

REACTIONS WITH THIOLS

Expt.	Compound examined	Thiol	Time, hr.[a]	Products (yield, %)[b]	
1	2-Ethoxyquinoline (I)	Thiophenol	22, 44	2-Hydroxyquinoline (62–67)	Ethyl phenyl sulfide (51)
2	2-Ethoxyquinoline (I)	*o*-Thiocresol	48	No reaction	
3	2-Ethoxyquinoline (I)	*m*-Thiocresol	44	2-Hydroxyquinoline (55)	Ethyl *m*-tolyl sulfide (40)[c]
4	2-Ethoxyquinoline (I)	*p*-Thiocresol	48	2-Hydroxyquinoline (71)	Ethyl *p*-tolyl sulfide (60)
5	2-Ethoxyquinoline (I)	β-Thionaphthol	48	2-Hydroxyquinoline (92)	Ethyl β-naphthyl sulfide (71)
6	2-Ethoxyquinoline (I)	Benzyl mercaptan	12–48	2-Hydroxyquinoline (6–7)	...
7	2-Benzyloxyquinoline	Thiophenol	52	2-Hydroxyquinoline (96)	Benzyl phenyl sulfide (75)
8	2-Ethoxybenzothiazole	Thiophenol	48	2-Hydroxybenzothiazole (74)	Ethyl phenyl sulfide (50)
9	2-Ethoxybenzoxazole	Thiophenol	48	2-Hydroxybenzoxazole (87)	Ethyl phenyl sulfide (67)
10	2-Phenoxyquinoline	Thiophenol	48	Phenol	Phenyl 2-quinolyl sulfide (21)[d]
11	2-Phenoxybenzothiazole (II)	*p*-Thiocresol	26	Phenol	*p*-Tolyl 2-benzothiazolyl sulfide (21)[d]
12	2-Chloroquinoline	Thiophenol	53	...	Phenyl 2-quinolyl sulfide (79)[d]
13	4,7-Dichloroquinoline	*p*-Thiocresol	24	...	4,7-Di-(*p*-thiocresoxy)-quinoline (87)[e]
14	4-Ethoxy-7-chloroquinoline (III)	*p*-Thiocresol	24	...	4,7-Di-(*p*-thiocresoxy)-quinoline (34)[e]
15	Ethyl β-naphthyl ether	Thiophenol	48	No reaction	
16	Ethyl benzyl ether	*p*-Thiocresol	48	...	Benzyl *p*-tolyl sulfide (2.5)
17	Ethyl benzoate	Thiophenol	22	No reaction	
18	Benzyl benzoate	Thiophenol	48	No reaction	

[a] The times selected for many of these reactions were arbitrary. [b] The solid cleavage products were identified by the method of mixed m. p.; the liquids by determining the b. p., density and refractive index. The compounds without corresponding yields were only identified qualitatively. [c] Not reported in literature; b. p. 216–219° (735 mm.); d^{25} 0.9947; $n^{15}D$ 1.5610. *Anal.* Calcd. for $C_9H_{12}S$: S, 21.05. Found: S, 20.63. [d] The authentic specimen was prepared according to the directions given in the Experimental. [e] Not reported in literature; b. p. 250° (0.5 mm.); m. p. 101–101.5°. *Anal.* Calcd. for $C_{23}H_{19}S_2N$: S, 17.17; N, 3.75. Found: S, 17.14; N, 3.77.

Anal. Calcd. for $C_{13}H_9ONS$: S, 14.08. Found: S, 13.95.

4-Ethoxy-7-chloroquinoline.—To a solution of 0.22 mole of sodium ethoxide in hot ethanol, an alcoholic solution of 39.8 g. (0.20 mole) of 4,7-dichloroquinoline was added and the mixture was refluxed and stirred for four hours. After cooling, the reaction product was diluted with ether and washed with a large volume of water. The residue from the ether layer was a white solid melting at 100–102° (95%) which by recrystallization from petroleum ether (b. p. 65–67°) gave bright colorless prisms (m. p. 103°). The same results were obtained when 0.22 mole of sodium ethoxide was allowed to react with 0.10 mole of the dichloro compound over a period of twenty-four hours.

Anal. Calcd. for $C_{17}H_{16}ONCl$: Cl, 17.07. Found: Cl, 16.91.

Phenyl 2-Quinolyl Sulfide.—This compound was prepared from 8.1 g. (0.050 mole) of 2-chloroquinoline and 0.055 mole of sodium thiophenoxide in ethanol solution by refluxing and stirring the mixture for four hours. The crude product was obtained in 80% yield by vacuum distillation (b. p. 164–166° at 0.6 mm.). Recrystallization from ethanol gave colorless crystals melting at 48–49°.

Anal. Calcd. for $C_{15}H_{11}NS$: S, 13.49. Found: S, 13.28.

***p*-Tolyl 2-Benzothiazolyl Sulfide.**—To a solution of 0.22 mole of sodium *p*-thiocresoxide in ethanol, 32.8 g. (0.20 mole) of 2-chlorobenzothiazole was added, and the mixture was refluxed and stirred for four hours; 48.4 g. (94%) of crude product (m. p. 69–71°) was obtained. The pure compound crystallizes from ethanol and melts at 71–72°.

Anal. Calcd. for $C_{14}H_{11}NS_2$: S, 24.94. Found: S, 24.71.

Summary

Some alkyl and aryl 2-quinolyl, 2-benzothiazolyl and 2-(benzoxazolyl) ethers are cleaved extensively by aryl thiols. The alkyl ethers have an alkylating action; for example, 2-ethoxyquinoline and thiophenol give ethyl phenyl sulfide and 2-hydroxyquinoline. The aryl ethers yield heterocyclic aryl sulfides.

Aryl thiols react with the 2-chloro compounds to form the aryl heterocyclic sulfides.

Both 4,7-dichloroquinoline and 4-ethoxy-7-chloroquinoline react with *p*-thiocresol to give 4,7-di-(*p*-thiocresoxy)-quinoline.

An interpretation of the course of some of these reactions has been considered.

AMES, IOWA RECEIVED MARCH 28, 1949

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Quaternary Carbon Compounds. III. Trialkylcarbinyl Isocyanates and Trialkylcarbinamines

BY NATHAN SPERBER AND ROSEMARIE FRICANO

It has been reported that trialkylacetamides[1] (I), trialkylethylamines[2] (II) and trialkylacetic acids[3] (III), in which R is a 3, 4 or 5 carbon atom alkyl group and R_3 totals 12–18 carbon atoms, possess musculotropic antispasmodic activity equal to or greater than papaverine. In order to establish whether the structural requirements for antispasmodic activity observed for I, II and III are generally applicable to highly branched, aliphatic compounds, we prepared a series of trialkylcarbinamines (IV) for pharmacological testing: $R_3C—R'$, I, R′—$CONH_2$; II, R′—CH_2NH_2; III, R′—COOH; IV, R′—NH_2.

Low molecular weight trialkylcarbinamines[4] have been prepared by the Hofmann degradation of the corresponding acetamides (VI) and subsequent acidic hydrolysis of the resulting isocyanates (VII). Trialkylcarbinamines having one long chain alkyl and two methyl groups and aralkyldialkylcarbinamines[5] have been reported. Tertiary alkyl primary amines have also been prepared[6] by the abnormal reaction of one molar equivalent of a nitrile with two molar equivalents of allylmagnesium bromide. This method results in carbinamines containing at least one allyl or propyl group. Recently Ritter and Kalish[7] have described several *t*-carbinamines prepared by the hydrolysis of N-*t*-alkyl formamides.

In this study, the carbinamines (IV) were synthesized by a series of transformations

$$\underset{\text{V}}{R_3C—CN} \xrightarrow{H_2SO_4} \underset{\text{VI}}{R_3C—CONH_2} \xrightarrow{NaOBr} \underset{\text{VII}}{R_3C—NCO} \xrightarrow{HCl} \text{IV}$$

The trialkylacetonitriles[8] (V) were hydrolyzed to the corresponding acetamides[2] (VI) with hot 80% sulfuric acid and the amides converted to the corresponding isocyanates[4] (VII) in 80–90% yields. The isocyanates (VII) were hydrolyzed to the carbinamines[9] (IV) when heated with 20% hydrochloric acid. The trialkyl isocyanates (Table I) form ureas upon reaction with various amines. In Table II are listed the amines prepared in this investigation.

In general, the trialkylcarbinamines were less spasmolytic and more toxic than the corresponding trialkylethylamines. N,N′-bis-(1,1-Dibutylamyl)-urea was inactive, whereas N-1,1-dibutylamylurea and N-1,1-dibutylamylacetamide possess musculotropic antispasmodic activity in the range of papaverine.

Experimental

The preparation of 1,1-dibutylamylamine will illustrate the general procedures.

Trialkylcarbinyl Isocyanates.[4]—In a 500 cc., three-necked flask cooled in an ice–salt-bath and fitted with an efficient stirrer, condenser and dropping funnel, was placed an ice cold solution of 24 g. of sodium hydroxide in 200 cc. of water. To the rapidly stirred solution, 8 cc. of bromine was added slowly. When the bromine color had disappeared, 22.7 g. (0.1 mole) of finely powdered tributylacetamide was added in one portion and the suspension was stirred vigorously for four hours at 0°. Within one hour, the solid was transformed into an oil. The oil was extracted with ether, the ether layer washed with water, dried over sodium sulfate, the solvent removed *in vacuo* and the residue fractionated. The isocyanate was then redistilled for analysis.

The isocyanate was fairly stable at room temperature, but slowly deposited N,N′-bis-(1,1-dibutylamyl)-urea. The latter was formed by the reaction of 1,1-dibutylamyl isocyanate and 1,1-dibutylamylamine and melted at 127–128°. This urea was also prepared by warming a mixture of 1,1-dibutylamyl isocyanate and 1,1-dibutylamylamine and melted at 127–127.5° after recrystallization from ethanol–water. A mixed melting point of the two samples showed no depression.

Anal. Calcd. for $C_{27}H_{56}N_2O$: N, 6.60. Found: N, 6.43.

The following derivatives of 1,1-dibutylamyl isocyanate were prepared.

N-1,1-Dibutylamylurea.—A mixture of 12 g. of 1,1-dibutylamyl isocyanate and 55 cc. of concentrated ammonia water (28%) was stirred for six hours and stored for four days in a refrigerator. The oily precipitate was filtered, washed with cold, dilute ethanol and recrystallized from a mixture of ethanol–water; weight 4 g.; m. p. 153–153.5°.

Anal. Calcd. for $C_{14}H_{30}N_2O$: N, 11.56. Found: N, 11.75.

N-(β-Diethylaminoethyl)-N′-(1,1-dibutylamyl)-urea hydrochloride: A cold solution of 11.3 g. (0.05 mole) of 1,1-dibutylamyl isocyanate in 25 cc. of benzene was added to a cold solution of 5.8 g. (0.05 mole) of β-diethylaminoethylamine in 25 cc. of benzene. The resulting warm solution was cooled in an ice-bath until the reaction subsided. After standing overnight at room temperature,

(1) Junkmann and Allardt, U. S. Patent 2,186,976 (1940).

(2) Allardt and Junkmann, U. S. Patent 2,361,524 (1944).

(3) Sperber, Papa and Schwenk, THIS JOURNAL, **70**, 3091 (1948).

(4) Montagne and Casteran, *Compt. rend.*, **191**, 139 (1930).

(5) Mentzer, Buu-Hoï and Cagniant, *Bull. soc. chim.*, **9**, 813 (1942); **10**, 141 (1943); Cagniant, Mentzer and Buu-Hoï, *ibid.*, **10**, 145 (1943).

(6) Allen and Henze, THIS JOURNAL, **61**, 1790 (1939); Henze, Allen and Leslie, *ibid.*, **65**, 87 (1943).

(7) Ritter and Kalish, *ibid.*, **70**, 4048 (1948).

(8) Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932); see ref. 3.

(9) Buu-Hoï (*Nature*, **156**, 392 (1945)) found that the primary amines prepared from a series of fatty acids isolated from dead tubercle bacilli were active against tubercle bacilli, although the parent acids and amides were inactive. In addition, a series of fatty acid amines were also bacteriostatic against acid-fast bacteria. Borrows, Hargreaves, Page, Resugg and Robinson (*J. Chem. Soc.*, 197 (1947)) prepared a series of primary, secondary and tertiary amines containing 8–30 carbon atoms and found that amines containing 17–20 carbon atoms were highly active *in vitro* against *Strep. haemolyticus* and *Staph. aureus*. *Mycobacterium tuberculosis* was inhibited by some of these amines.

TABLE I

TRIALKYLCARBINYL ISOCYANATES, RR'R"C—NCO

R	R'	R"	B. p., °C.	Mm.	Yield, %		N Analyses, % Calcd.	Found
n-C_3H_7	*n*-C_3H_7	*n*-C_3H_7	65–66	2	90	$C_{11}H_{21}NO$	7.65	7.23
n-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	103–105	1	90	$C_{14}H_{27}NO$	6.22	6.22
n-C_4H_9	*n*-C_5H_{11}	*n*-C_5H_{11}	120–121	2	92	$C_{16}H_{31}NO$	5.53	5.54
n-C_5H_{11}	*n*-C_5H_{11}	*n*-C_5H_{11}	126–127	1	94	$C_{17}H_{33}NO$	5.24	5.17
CH_3	*n*-C_7H_{15}	*n*-C_7H_{15}	130–132	2	68	$C_{17}H_{33}NO$	5.24	5.40
n-C_4H_9	*n*-C_7H_{15}	*n*-C_7H_{15}	176–177	6.5	79	$C_{20}H_{39}NO$	4.53	5.00
n-$(C_2H_5)_2NCH_2$—	*n*-C_4H_9	*n*-C_4H_9	126	4	70	$C_{15}H_{30}N_2O$	11.02	10.45
	*n*-C_4H_9	*n*-C_4H_9	146–148	6	65	$C_{16}H_{30}N_2O$	10.53	10.63

TABLE II

TRIALKYLCARBINAMINES—RR'R"C—NH_2

R	R'	R"	B. p., °C.	Mm.	Yield,[a] %		N Analyses, % Calcd.	Found
n-C_3H_7	*n*-C_3H_7	*n*-C_3H_7	78	13	71	$C_{10}H_{23}N$[b]	8.91	9.04
n-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	78–80	1	72	$C_{13}H_{29}N$	7.30	6.82
n-C_4H_9	*n*-C_5H_{11}	*n*-C_5H_{11}	119	3	80	$C_{15}H_{33}N$	6.16	6.01
n-C_5H_{11}	*n*-C_5H_{11}	*n*-C_5H_{11}	121–122	2	81	$C_{16}H_{35}N$	5.80	5.55
CH_3	*n*-C_7H_{15}	*n*-C_7H_{15}	130–131	2.5	79	$C_{16}H_{35}N$	5.80	5.20
n-C_4H_9	*n*-C_7H_{15}	*n*-C_7H_{15}	147–149	2	89	$C_{19}H_{41}N$	C, 80.48	C, 80.56
							H, 14.57	H, 14.43

[a] Yields are based on distilled products. [b] $n^{21}D$ 1.4349; literature,[6] b. p. 47–48° (5 mm.); $n^{20}D$ 1.4353.

the solution was refluxed for two hours and the solvent was removed *in vacuo*, leaving a gummy sirup. The latter was dissolved in ether and saturated with hydrogen chloride and upon removal of the ether, a gum remained, which was crystallized from ligroin; yield 11 g. (58%), m. p. 91–91.5°.

Anal. Calcd. for $C_{20}H_{44}N_3OCl$: N, 11.13. Found: N, 10.91.

N-Benzyl-N'-1,1-dibutylamylurea.—Upon mixing equivalent quantities of benzylamine and 1,1-dibutylamyl isocyanate the urea crystallized immediately. The solid was recrystallized from a mixture of alcohol and water and appeared as white needles, m. p. 127–128°.

Anal. Calcd. for $C_{21}H_{36}N_2O$: N, 8.40. Found: N, 8.30.

N-(2-Pyridyl)-N'-(1,1-dibutylamyl)-urea.—A solution of 4.7 g. (0.05 mole) of 2-aminopyridine and 12.7 g. (0.05 mole) of 1,1-dibutylamyl isocyanate in 50 cc. of benzene was refluxed for twenty-four hours. The benzene was removed and the residual oil crystallized slowly. The solid was recrystallized twice from a mixture of ethanol and water, m. p. 138–138.5°.

Anal. Calcd. for $C_{19}H_{33}N_3$: N, 13.85. Found: N, 13.53.

Trialkylcarbinamines.—A mixture of 20 g. (0.089 mole) of 1,1-dibutylamyl isocyanate and 70 cc. of 20% hydrochloric acid was heated and stirred for five hours on a steam-bath. Upon cooling 1,1-dibutylamylamine hydrochloride precipitated, yield 16.7 g.; m. p. 68–69°. To an aqueous suspension of the hydrochloride, there was added sodium hydroxide pellets, the liberated amine ether extracted and the ether extracts washed with water. After drying over anhydrous potassium carbonate, the solvent was removed and the residue distilled. A colorless, free-flowing liquid was obtained. In other experiments, the amine hydrochloride was not isolated. After completion of the hydrolysis of the isocyanate to the carbinamine, the mixture was neutralized with sodium hydroxide pellets and the free base taken up in ether and distilled.

The time required for the hydrolysis varied with the molecular weight of the isocyanate. 1,1-Dipropylamyl isocyanate hydrolyzed immediately upon contact with hydrochloric acid, whereas 1-heptyl-1-butyloctyl isocyanate required seven hours to complete the hydrolysis.

N-1,1-Dibutylamylacetamide.—To a solution of 1 cc. of 1,1-dibutylamylamine dissolved in 5 cc. of dry pyridine was added dropwise 2 cc. of acetic anhydride. The warm solution was allowed to stand one hour and then decomposed on ice and water. The white solid was recrystallized from a mixture of ethanol and water, m. p. 80.5–81.5°.

Anal. Calcd. for $C_{15}H_{31}NO$: N, 5.81. Found: N, 5.79.

Acknowledgment.—The authors wish to express their appreciation to Dr. Richard Tislow and Mrs. Annette LaBelle for the pharmacological examination of these compounds.

Summary

The preparation of a series of trialkylcarbinyl isocyanates and trialkylcarbinamines by the Hofmann degradation of the corresponding acetamides is described.

The trialkylcarbinamines exhibit weaker antispasmodic activity than the corresponding trialkylethylamines.

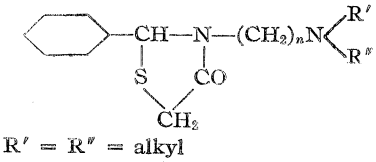
BLOOMFIELD, N. J. RECEIVED MAY 10, 1949

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

4-Thiazolidones. IV. The Preparation of Some 3-Alkylaminoalkyl-2-aryl Derivatives

BY ALEXANDER R. SURREY

The observation[1] that several of the 2-aryl-3-dialkylaminoalkyl-4-thiazolidones (I) showed promising local anesthetic activity suggested that



I, R′ = R″ = alkyl
II, R′ = H, R″ = alkyl, cycloalkyl, aralkyl

it would be of interest to study the activity of some 2-aryl-3-alkylaminoalkyl derivatives (II). A series of these compounds has been synthesized and is reported in the present communication.

TABLE I

ALKYLAMINOPROPIONITRILES,[2] $RNHCH_2CH_2CN$

R	Yield %	B. p. °C.	mm.	$n^{25}D$	Analyses, % Nitrogen Calcd.	Found
n-Hexyl	91	130–134	12	1.4410	18.15	18.02
n-Octyl	91	117–120	1	1.4452	7.67	7.65[a]
Benzyl	92	119–124	0.7–0.8	1.5296	8.75	8.69[a]
Cyclopentyl	82	115–116	7	1.4685	10.01	10.10[a]

[a] Titration of basic nitrogen.

TABLE II

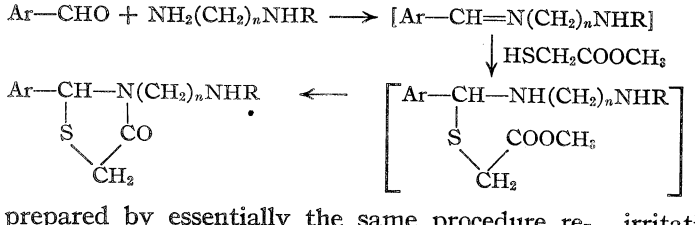
N-ALKYL PROPANEDIAMINES-1,3[2] $RNHCH_2CH_2CH_2NH_2$

R	Yield, %	B. p. °C.	mm.	$n^{25}D$	Analyses, % Nitrogen Calcd.	Found
n-Amyl	70	106–109[a]	18	1.4470	19.43	19.22
n-Hexyl	70	110	9	1.4481	17.72	17.69
n-Octyl	70	143–146	12	1.4512	15.00	14.86
Benzyl	77	98–102	1	1.5321	17.08	17.05
Cyclopentyl	73	90–95	8	1.4757	19.70	19.58

[a] Reference 2. The boiling point 102–103° at 15 mm. and analysis for picrate are reported.

The compounds described in Table III were prepared by essentially the same procedure reported for the tertiary aminoalkyl derivatives.[1] The appropriate benzaldehyde and secondary–primary diamine (see Tables I and II) were condensed to form the corresponding Schiff base which in turn was allowed to react with methyl thioglycolate (see flow sheet). With the exception of benzylidene-*n*-propyl-(and *n*-butyl)-aminopropylamine, none of the Schiff bases was isolated. Attempts to purify several of them by vacuum distillation resulted in considerable decomposition.

FLOW SHEET



It has been reported that trimethylene-1,3-diamines[3] and 1,3-dianilinopropane[4] react with aldehydes to yield hexahydropyrimidines. In these instances, both amino groups were either primary or secondary. With a primary–secondary diamine, as is the case in the present series, the reaction with aldehydes does not give the heterocyclic compound but rather a Schiff base as shown by the ultraviolet absorption spectrum[5] (see Fig. 1) and molecular refraction of benzylidene-*n*-propylaminopropylamine.

In order to determine the effect of substitution in the 5-position of the thiazolidone nucleus, 3-(3-butylaminopropyl)-5-ethyl-2-phenyl-4-thiazolidone hydrochloride was prepared according to the above described procedure by the reaction of benzylidene-*n*-propylaminopropylamine with methyl α-mercapto-*n*-butyrate. In addition, two of the thiazolidones, 2-(4-chlorophenyl)-3-(3-pentylaminopropyl)-4-thiazolidone and 3-(3-butylaminopropyl)-2-phenyl-4-thiazolidone were oxidized to the corresponding 1-dioxides with potassium permanganate. Good yields of the desired products were obtained when the reaction was carried out in acetic acid solution at 5–10°.

Pharmacology.—The anesthetic activity of the present series of 2-aryl-3-alkylaminoalkyl-4-thiazolidones was investigated by the Pharmacology Division of this Institute.[6] The results of this study showed that most of the compounds possessed a high degree of activity in producing sciatic nerve block in guinea pigs and spinal anesthesia in rabbits. Good results were also obtained in intracutaneous wheal tests in man. It was observed that increasing the length of the terminal N-alkyl group increased the local anesthetic activity. The optimum was reached at 5–6 carbon atoms after which the solubility decreased rather sharply. Substitution of the 4-butoxy for the 3,4-methylenedioxy group in the benzene ring increased the tissue irritation properties of the compound.

(1) Surrey, THIS JOURNAL, 71, 3015 (1949).

(2) Prepared according to the procedure of Tarbell, Shakespeare, Claus and Bunnett, THIS JOURNAL, 68, 1217 (1946).

(3) Bergmann, Herman and Zimkin, *J. Org. Chem.*, **13**, 353 (1948).

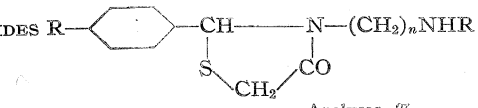
(4) (a) Veer, *Rec. trav. chim.*, **57**, 989 (1938); (b) Scholtz, *Ber.*, **32**, 2251 (1899).

(5) The author wishes to thank Dr. F. C. Nachod for the data on the absorption spectra reported.

(6) The author is indebted to Dr. F. P. Luduena and Dr. J. O. Hoppe under whose supervision the pharmacological investigation was carried out. The details of this study will be published elsewhere.

TABLE III

3-ALKYLAMINOALKYL-2-ARYL-4-THIAZOLIDONE HYDROCHLORIDES



R	R′	Yield,[a] %	M. p., °C.	Formula[b]	Analyses, % Sulfur Calcd.	Sulfur Found	Chlorine[c] Calcd.	Chlorine[c] Found
			$n = 2$					
3,4-O_2CH_2	2-Hydroxyethyl	16	152.2–155.4	$C_{14}H_{18}N_2O_4S$	9.24	9.38	10.22	10.02
3,4-O_2CH_2	Cyclohexyl	77	186.3–187[d]	$C_{18}H_{24}N_2O_3S$	8.32	8.28	9.20	8.99
			$n = 3$					
3,4-O_2CH_2	2-Hydroxyethyl	57	140.1–141.3	$C_{15}H_{20}N_2O_4S$	8.88	8.98	9.82	9.75
4-OC_4H_9-*n*	*n*-Propyl	81	84.2–85.4	$C_{19}H_{30}N_2O_2S$	7.92	8.00	8.77	8.46
3,4-O_2CH_2	*n*-Propyl	80	173.3–174.5	$C_{16}H_{22}N_2O_3S$	8.94	8.64	9.89	9.80
3,4-O_2CH_2	*i*-Propyl	57	169.3–171.4	$C_{16}H_{22}N_2O_3S$	8.94	8.90	9.89	9.72
H	*n*-Butyl	85[e]	168–170	$C_{16}H_{24}N_2OS$	9.75	9.72	10.78	10.59
3,4-O_2CH_2	*n*-Butyl	49	189.4–190.8	$C_{17}H_{24}N_2O_3S$	8.60	8.49	9.50	9.33
3-OCH_3-4-OC_2H_5	*n*-Butyl	54	96–99	$C_{19}H_{30}N_2O_3S$	7.96	7.87	8.80	8.65
4-NO_2	*n*-Butyl	80	205–205.6	$C_{16}H_{23}N_3O_3S$	8.57	8.67	9.48	9.45
4-NH_2	*n*-Butyl	78	192.6–193.2	$C_{16}H_{25}N_3OS$	9.32	9.23	10.31	10.26
3,4-O_2CH_2	*i*-Butyl	57	149.9–150.3[f]	$C_{17}H_{24}N_2O_3S$	8.60	8.65	9.51	9.36
3,4-O_2CH_2	*n*-Amyl	90	179.8–181.1	$C_{18}H_{26}N_2O_3S$	8.29	8.10	9.19	9.16
3,4-O_2CH_2	*n*-Hexyl	60	172.7–173	$C_{19}H_{28}N_2O_3S$	8.00	8.09	8.84	8.67
3,4-O_2CH_2	*n*-Octyl	42	132.3–134	$C_{21}H_{32}N_2O_3S$	7.47	7.25	8.27	8.24
3,4-O_2CH_2	Cyclopentyl	25	170.4–171.8	$C_{18}H_{24}N_2O_3S$	8.33	8.14	9.21	8.98
4-OCH_3	Cyclohexyl	22	152–153.8	$C_{19}H_{28}N_2O_2S$	8.33	8.33	9.21	9.09
3,4-O_2CH_2	Cyclohexyl	95	146–148	$C_{19}H_{26}N_2O_3S$	8.06	8.00	8.92	8.81
3,4-O_2CH_2	Benzyl	10	176.7–178.2	$C_{20}H_{22}N_2O_3S$	7.87	7.99	8.73	8.46
			$n = 6$					
3,4-O_2CH_2	Cyclohexyl	30	128.7–130.2[g]	$C_{22}H_{32}N_2O_3S$	7.27	7.38	8.04	7.90

[a] The majority of the yields reported are based on single experimental runs. [b] The formulas of the bases are listed. [c] Ionic chlorine. [d] Melting point of base, 99–100°. *Anal.* Calcd.: N (basic nitrogen), 4.02. Found: N, 4.02. [e] Based on purified Schiff base. [f] Melting point of base, 81.3–82.4°. *Anal.* Calcd.: S, 9.53. Found: S, 9.51. [g] Melting point of base, 98.4–100.2°. *Anal.* Calcd.: S, 7.92. Found: S, 7.55 (dry basis); H_2O, 1.86.

Experimental[7]

N-Cyclohexylhexamethylenediamine-1,6.—The procedure employed was that described by Pearson, Jones and Cope[8] for the preparation of N-cyclohexylethylenediamine. The product distilled at 115–118° (0.7–0.8 mm.); $n^{25}D$ 1.4756.

Anal. Calcd. for $C_{12}H_{26}N_2$: N, 14.13. Found: N, 14.35.

3-(6-Cyclohexylaminohexyl)-2-(3,4-methylenedioxyphenyl)-4-thiazolidone.—The following is an example of the general procedure employed for the preparation of most of the compounds listed in Table III.

A mixture of 18.5 g. of N-cyclohexylhexamethylenediamine-1,6 and 14 g. of piperonal in 100 ml. of Skellysolve E was refluxed until no more water was collected in a separator connected to the apparatus. Methyl thioglycolate (10 g.) was then added and refluxing was continued at a gentle rate until no more methanol was collected in the separator. After cooling, the solvent[9] was decanted from the oil which separated and the latter was dissolved in ether and extracted with 1 *N* hydrochloric acid. The acid extracts were combined, basified, and the oil extracted with ether. The ether was dried over Drierite and removed by distillation. The residue (24 g.) was dissolved in 120 ml. of acetone, filtered with Norite and to the filtrate was added alcoholic hydrogen chloride solution. The solid (1 g.) which separated melted at 223–226° (uncor.) and did not depress the melting point of a sample of dihydrochloride prepared from N-cyclohexylhexamethylenediamine-1,6.

Ether was added to the acetone filtrate and a crystalline solid separated on standing (9 g.). It was recrystallized once from isopropyl alcohol, dissolved in hot water and the solution basified. The solid base was collected, washed with water and then recrystallized from a mixture of ethanol and ether.[10]

2-(4-Butoxyphenyl)-3-(3-propylaminopropyl)-4-thiazolidone Hydrochloride.—A mixture of 26.7 g. of 4-butoxybenzaldehyde and 17.4 g. of N-propylpropanediamine-1,3 in 100 ml. of dry benzene was refluxed until no more water separated. After removing the solvent *in vacuo*, the crude Schiff base was dissolved in 100 ml. of Skellysolve E and the reaction was continued according to the general procedure described above.

3-(3-Butylaminopropyl)-2-(4-nitrophenyl)-4-thiazolidone Hydrochloride.—Fifteen grams of 4-nitrobenzaldehyde and 13 g. of N-butylpropanediamine-1,3 in 100 ml. of dry benzene[11] were refluxed for one and one-half hours while removing the water as it formed. Methyl thioglycolate (11 g.) was added and refluxing was continued for three and one-half hours. After standing overnight some tarry material had separated. Additional benzene was added to the reaction mixture and the benzene solu-

(7) All melting points are corrected unless otherwise indicated.

(8) Pearson, Jones and Cope, THIS JOURNAL, **68**, 1225 (1946).

(9) In most instances the solvent was distilled off under reduced pressure.

(10) Where the preparation of a particular compound was repeated, the isolation of the product could be simplified considerably by seeding the reaction mixture with the solid base where available or with the hydrochloride after the addition of alcoholic hydrogen chloride and acetone. The solid base or hydrochloride was obtained in this manner directly from the reaction mixture.

(11) When Skellysolve E was used as a solvent excessive decomposition occurred.

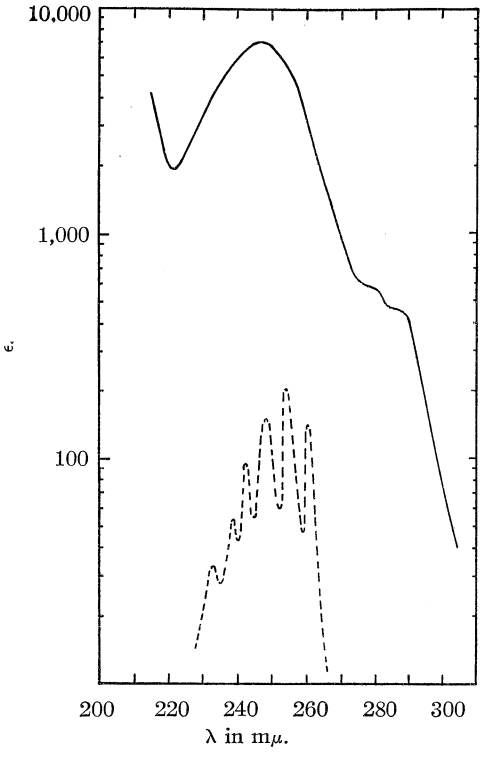


Fig. 1.—Absorption curves of benzylidene-*n*-propylminopropylamine in 95% ethanol: —, benzene in 95% ethanol: ---, as constructed from data of Campbell, Linden, Godshalk and Young, THIS JOURNAL, **69**, 881 (1947).

tion was extracted with 1 *N* hydrochloric acid. The solid hydrochloride which separated from the combined acid extracts was recrystallized from isopropyl alcohol and triturated with acetone; yield, 14 g.

2-(4-Aminophenyl)-3-(3-butylaminopropyl)-4-thiazolidone Hydrochloride.—A mixture of 7 g. of 3-(3-butylaminopropyl)-2-(4-nitrophenyl)-4-thiazolidone, 28 g. of iron filings, 50 ml. of ethanol, 25 ml. of water and 1 ml. of glacial acetic acid was refluxed with efficient stirring for three hours. The solution was made alkaline with sodium carbonate, more ethanol added, and the resulting solution was filtered hot. After removing the ethanol by distillation, the amino compound was extracted with chloroform. The crude base, after removal of the solvent, was converted to the hydrochloride.

Benzylidene-3-propylaminopropylamine.—This compound was prepared from benzaldehyde and N-propylpropanediamine-1,3 by refluxing the reactants in benzene and removing the water as it formed. After washing the benzene solution with sodium bicarbonate solution and then water, the product distilled at 107° (0.3 mm.); $n^{27}D$ 1.5272, d^{27} 0.9697.

Anal. Calcd. for $C_{13}H_{26}N_2$: N, 13.72; mol. ref., 65.24. Found: N, 13.70; mol. ref., 64.80.[12]

(12) The molecular refraction calculated for the isomeric hexahydropyrimidine is 63.65.[3]

Benzylidene-3-butylaminopropylamine.—The compound distilled at 113–117° (0.4–0.5 mm.).

Anal. Calcd. for $C_{14}H_{22}N_2$: N, 12.85. Found: N, 12.97.

3-(3-Butylaminopropyl)-5-ethyl-2-phenyl-4-thiazolidone Hydrochloride.—A mixture of 13.4 g. of methyl α-mercaptobutyrate[13] and 21.8 g. of benzylidene-3-butylaminopropylamine in 100 ml. of Skellysolve E was treated according to the general procedure described above. The crude base (26 g.) was dissolved in 250 ml. of acetone, filtered with Norite and the calculated amount of alcoholic hydrogen chloride was added. After adding dry ether to the solution, 12 g. (34%) of solid hydrochloride separated. Two recrystallizations from ethyl acetate followed by drying at 95° for two hours gave a product melting at 125.2–126.5°.

Anal. Calcd. for $C_{18}H_{28}N_2OS\cdot HCl$: S, 8.98; Cl^-, 9.93. Found: S, 9.07; Cl^-, 10.21.

2-(4-Chlorophenyl)-3-(3-pentylaminopropyl)-4-thiazolidone-1-dioxide Hydrochloride.—A solution of 8.6 g. of potassium permanganate in 300 ml. of water was added dropwise with stirring at 5–10° to a solution of 8.5 g. of 2-(4-chlorophenyl)-3-(3-pentylaminopropyl)-4-thiazolidone in 30 ml. of glacial acetic acid. The addition required thirty minutes. Sodium bisulfite solution was added to the reaction mixture and the colorless solution treated with an excess of ammonium hydroxide. The solution was extracted with chloroform, dried, and the solvent was removed by distillation. The residue (7 g.) was converted to the hydrochloride, which after recrystallization from ethanol melted at 198.5–200°.

Anal. Calcd. for $C_{17}H_{25}ClN_2O_3S\cdot HCl$: S, 7.83; Cl^-, 8.66. Found: S, 7.93; Cl^-, 8.60.

3-(3-Butylaminopropyl)-2-phenyl-4-thiazolidone-1-dioxide Hydrochloride.—This compound was recrystallized from ethanol; m. p. 158.8–160.4°.

Anal. Calcd. for $C_{16}H_{24}N_2O_3S\cdot HCl$: S, 8.88; Cl^-, 9.82. Found: S, 9.15; Cl^-, 9.55.

Summary

A series of 3-alkylaminoalkyl-2-aryl-4-thiazolidones has been prepared by the reaction of methyl thioglycolate with several benzylidene-alkylaminoalkylamines. Methyl α-mercaptobutyrate has been employed for the preparation of 3-(3-butylaminopropyl)-5-ethyl-2-phenyl-4-thiazolidone. Two of the thiazolidones were oxidized with potassium permanganate to yield the 1-dioxides.

Most of the compounds reported showed high local anesthetic activity in the production of sciatic nerve block in guinea pigs and spinal anesthesia in rabbits.

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(13) The ester was obtained by refluxing the corresponding acid in methanol with concentrated sulfuric acid. The product was taken up in ether and the ether solution was washed with water, sodium bicarbonate solution and again with water. After drying, the ether was distilled off. Calcd. for $C_5H_{10}O_2S$: SH, 24.6. Found: SH, 23.6.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Maltotriose and its Crystalline β-D-Hendecaacetate

BY J. M. SUGIHARA[1] AND M. L. WOLFROM

In previous communications[2] there was described the isolation of a crystalline trisaccharide hendecaacetate (m. p. 134–136°, $[\alpha]^{25}D$ + 86° in chloroform) from the acetylated enzymic (malt amylases) hydrolyzate of waxy maize starch (amylopectin). The acetate chromatographic technics[3] developed in this Laboratory made the separation of the pure compound from the complex mixture possible, although it was present only in small quantities.

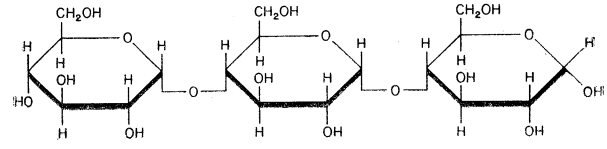
Herein evidence is presented to demonstrate that this trisaccharide hendecaacetate is β-maltotriose hendecaacetate (a trisaccharide with two α-D 1,4 linkages). The acetate was first converted into the corresponding amorphous hendecamethyl ether of unknown and probably mixed anomeric form, by employing three different technics in succession. The general procedure (dimethyl sulfate and alkali) of Haworth, Hirst and Webb[4] was employed initially and this was followed by that of Purdie and Irvine[5] using silver oxide and methyl iodide. Essentially the theoretical methoxyl content was then attained by a final treatment using sodium in liquid ammonia followed by reaction with methyl iodide as described by Muskat[6] and modified by Hendricks and Rundle.[7] The sirupy methyl ether exhibited $[\alpha]^{25}D$ + 122° and $[\alpha]^{25}$ 578 + 128° in chloroform, the latter value being in agreement with that cited by Freudenberg and co-workers[8] for a similar product (of unknown anomeric constitution) prepared by the methylation of a starch acetolyzate.

Acid hydrolysis of the methyl ether gave a sirup which was chromatographically separated into two crystalline compounds, 2,3,6-trimethyl-D-glucose and 2,3,4,6-tetramethyl-D-glucose, characterized by melting point, mixed melting point, rotation and the crystalline derivatives 2,3,6-trimethyl-β-D-glucose 1,4-diacetate and 2,3,4,6-tetramethyl-D-glucose anilide. The chromatographic technic employed[3] allowed this separation to be effected utilizing only 1 g. of the crystalline acetate. The molar ratio of the 2,3,6-trimethyl-D-glucose to 2,3,4,6-tetramethyl-D-glucose was 2 to 1 with the recovery of the chromatographed, crystalline substances of good purity being approximately 90%. This demonstrates that there are two 1,4-D-glucosidic linkages per molecule, assuming the normal pyranoid rings in each D-glucose unit.

The deacetylation of the crystalline hendecaacetate yielded the free sugar, obtained as an amorphous solid, which to date has resisted crystallization; $[\alpha]^{23}D$ + 160° (water). This sugar was not fermented by a commercial bakers' yeast that did not ferment maltose. Myrbäck and co-workers[9,10] have stated that sirupy products assumed by them to be or to contain maltotriose were fermented by a maltose-fermenting yeast.

One mole of the free sugar was partially hydrolyzed by a commercial maltase preparation at 26–27° in forty-four hours into 1.7 moles of D-glucose and 0.2 mole of maltose with recovery of 0.1 mole of the original trisaccharide, as determined by weights of the products isolated. The products of hydrolysis as well as the unchanged sugar were isolated as acetates using a chromatographic technic.[3] The free sugar was not hydrolyzed by emulsin. The fact that the sugar was hydrolyzed by maltase but not by emulsin establishes the two 1,4-D-glucosidic linkages as being α-D. The conversion to maltose gives final support to the assignment of the maltotriose structure to the trisaccharide. The experiments further illustrate the value of chromatographic technics in the analysis and separation of sugar mixtures.

Since the acetate of maltotriose was prepared[2] by the hot sodium acetate acetylation procedure and since it exhibits a specific rotation of $[\alpha]^{25}D$ +86° in chloroform, we have considered the compound to be the β-D-anomer of 4-[4-(α-D-glucopyranosyl)-α-D-glucopyranosyl]-β-D-glucopyranose hendecaacetate.



Experimental[11]

Methyl Decamethylmaltotrioside.[12]—Following the general procedure of Haworth, Hirst and Webb,[4] 1.000 g. of maltotriose hendecaacetate (m. p. 134–136°, $[\alpha]^{25}D$ +86° in chloroform)[2] was dissolved in 3 ml. of acetone in a conical, four-necked flask fitted with a mechanical stirrer, a condenser, two dropping funnels and a capillary to introduce nitrogen. While maintaining an atmosphere of ni-

(1) Corn Industries Research Foundation Associate of The Ohio State University Research Foundation (Project 203).

(2) M. L. Wolfrom, L. W. Georges, Alva Thompson and I. L. Miller, THIS JOURNAL, **71**, 2873 (1949); L. W. Georges, I. L. Miller and M. L. Wolfrom, *ibid.*, **69**, 473 (1947).

(3) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, *ibid.*, **67**, 527 (1945).

(4) W. N. Haworth, E. L. Hirst and J. I. Webb, *J. Chem. Soc.*, 2681 (1928).

(5) T. Purdie and J. C. Irvine, *ibid.*, **83**, 1021 (1903); **85**, 1049 (1904).

(6) I. E. Muskat, THIS JOURNAL, **56**, 693, 2449 (1934).

(7) B. C. Hendricks and R. E. Rundle, *ibid.*, **60**, 2563 (1938).

(8) K. Freudenberg, K. Friedrich, Ilse Bumann and K. Soff, *Ann.*, **494**, 41 (1932).

(9) K. Myrbäck and Elsa Leissner, *Arkiv. Kemi, Mineral. Geol.*, **17A**, No. 18 (1944).

(10) K. Myrbäck and W. Thorsell, *Svensk Kem. Tid.*, **55**, 178 (1943).

(11) All melting points are uncorrected.

(12) Anomeric composition unknown.

trogen and an external bath at 30–35° and vigorously stirring, 3 ml. of 30% sodium hydroxide and 2 ml. of dimethyl sulfate were added through the dropping funnels in small quantities over a period of two hours. The bath temperature was raised to 35–40° and vigorous stirring was continued until a small aliquot of the reaction mixture did not reduce Fehling solution (about four hours after adding the methylating reagents). The temperature of the bath was then increased to 55° and 5 ml. of dimethyl sulfate and 9 ml. of 30% sodium hydroxide were added in portions over a period of one and one-half hours with continued stirring. The bath temperature was then raised to 100° for one-half hour. The reaction flask was cooled and the solution was neutralized with 6 *N* sulfuric acid, sufficient water being added to dissolve any precipitated sulfate. This aqueous solution was extracted four times with 5-ml. portions of chloroform. Solvent removal from the combined, dried chloroform extracts left a sirup which was dried to constant weight in a vacuum desiccator containing Dehydrite (anhydrous magnesium perchlorate); yield 414 mg.

The aqueous solution remaining after chloroform extraction was evaporated to a thick slurry. Absolute ethanol (25 ml.) was added and the precipitated sodium sulfate was removed by filtration. The filtrate was again evaporated to a slurry, and a second portion of 25 ml. of absolute ethanol was added. Filtration and concentration of the filtrate to 3 ml. was followed by remethylation with 3 ml. of dimethyl sulfate and 5 ml. of 30% sodium hydroxide at 55°. This treatment was followed by reaction at 100° for one-half hour. The aqueous solution obtained was treated as previously described; yield of dried sirup 81 mg.

The sirups obtained were combined (495 mg.) and subjected to the general methylation procedure described by Purdie and Irvine.[5] The combined material was dissolved in 10 ml. of methyl iodide and placed in a flask fitted with a mechanical stirrer and a reflux condenser. An amount of 2 g. of silver oxide was added under gentle refluxing maintained subsequently for four hours. Excess methyl iodide was allowed to evaporate and the residue was repeatedly extracted with anhydrous ether (total volume 50 ml.). Evaporation of the ether left a sirup which was dried to constant weight over Dehydrite under reduced pressure; yield 490 mg.

This sirup (490 mg.) was dissolved in 5 ml. of liquid ammonia in an unsilvered Dewar flask and subjected to the Muskat[6] methylation procedure as modified by Hendricks and Rundle.[7] A solution of 60 mg. of sodium in 20 ml. of liquid ammonia was added in portions such that the blue color of the liquid ammonia solution persisted for one hour after the last addition (total volume 10 ml.). Excess methyl iodide (5 ml.) was added in portions and the ammonia was allowed to evaporate. The reaction mixture was transferred to a 25-ml. round-bottomed flask fitted with a reflux condenser. A further amount of 5 ml. of methyl iodide was added under gentle refluxing maintained for four hours. The mixture was then held overnight at room temperature. Excess methyl iodide was allowed to evaporate and the residue was extracted repeatedly with anhydrous ether. The combined ether solution (50 ml.) was treated with activated charcoal. Solvent removal left a sirup which was dried to constant weight at 78°, under reduced pressure, over phosphorus pentoxide; yield 488 mg. (72%), $[\alpha]^{25}D$ +122° (*c* 1.91, chloroform), $[\alpha]^{25}578$ +128° (*c* 1.91, chloroform). Freudenberg and co-workers[8] report: $[\alpha]^{18}_{578}$ +129.9° (*c* 1.57, chloroform) for a preparation of methyl decamethylmaltotrioside of undetermined anomeric admixture.

Anal. Calcd. for $C_{18}H_{21}O_5(OCH_3)_{11}$: C, 52.87; H, 8.26; OCH_3, 51.8. Found: C, 53.05; H, 8.30; OCH_3, 51.0.

Hydrolysis of Methyl Decamethylmaltotrioside.—The general procedure described by West and Holden[13] was applied. An amount of 98.5 mg. of methyl decamethylmaltotrioside was dissolved in 1 ml. of chloroform and 2.5 ml. of 2 *N* hydrochloric acid was added. Steam, generated at atmospheric pressure, was bubbled into the mixture. The chloroform was rapidly distilled leaving the methylated trisaccharide in a state of fine suspension. The reaction vessel was submerged in a bath, maintained at 104–106° and the current of steam was passed through for two and one-half hours at such a rate as to maintain the volume constant at 3–5 ml. The cooled solution was neutralized with silver carbonate and residual silver ion was removed with hydrogen sulfide. Distillation of the solution under reduced pressure left a sirup which was dried to constant weight in a vacuum desiccator over Dehydrite; yield 99 mg. This sirup (99 mg.) was dissolved in 25 ml. of chloroform containing 0.5% ethanol and the solution was placed on a chromatographic column packed with acid-washed[14] Magnesol[15]–Celite[16] (5:1 by wt.) (200 × 35 mm. diam.[17]) and developed with 350 ml. (5 column lengths) of benzene–ethanol (100:1 by vol.). Extrusion of the column and streaking with a permanganate indicator (1 part of potassium permanganate, 10 parts of sodium hydroxide and 100 parts of water) located two zones, the first about one-fifth of a column length from the top and the second near the middle of the column. These zones were sectioned and each section was eluted with 50 ml. of acetone. From the eluate of the top zone, solvent removal left 61 mg. (92%) of crystalline material; m. p. 112–114°, $[\alpha]^{24}D$ +65° (*c* 1.78, methanol, equilibrium). This substance was recrystallized from ether; yield 45.3 mg., melting point and mixed melting point with authentic 2,3,6-trimethyl-D-glucose 117.5–118°, $[\alpha]^{27}D$ +67.5° (*c* 1.69, methanol, equilibrium).[18]

An amount of 17.0 mg. of this material was acetylated by heating at 98° with acetic anhydride (5 ml.) and anhydrous sodium acetate (25 mg.). The product obtained on pouring the cooled reaction mixture into an excess (150 g.) of ice and water was extracted with chloroform and the washed (with aqueous sodium bicarbonate) and dried extract was concentrated to a sirup; yield 50.2 mg. This sirup was dissolved in 25 ml. of benzene and placed on a chromatographic column packed with acid-washed[14] Magnesol[15]–Celite[16] (5:1 by wt.) (200 × 35 mm. diam.[17]) and developed with two column lengths (130 ml.) of benzene–ethanol (100:1 by vol.). A zone near the middle of the extruded column was located by means of the permanganate streak indicator. This was sectioned and eluted with 50 ml. of acetone. Evaporation of the solvent left 36.9 mg. of a sirup, which when dissolved in a minimum of petroleum naphtha (b. p. 90–100°)-ether (4:1 by vol.) and allowed to stand overnight in the cold gave crystals; yield 15 mg., m. p. 57–61°. Pure material was obtained on further crystallization from the same solvent; m. p. 66–66.5°. Micheel and Hess[19] reported for 2,3,6-trimethyl-β-D-glucose 1,4-diacetate, m. p. 67–68°. A mixed melting point with an authentic sample showed no depression.

Solvent removal from the acetone eluate of the second zone of the above-described chromatogram left 30.6 mg. (87%) of crystals; m. p. 81–86°, $[\alpha]^{22}D$ +89.5° (*c* 2.24, ethanol, equilibrium). Recrystallization from petroleum naphtha (b. p. 90–100°)-ether (3:1 by vol.) left 22.3 mg.

(13) E. S. West and R. F. Holden, THIS JOURNAL, **56**, 930 (1934).

(14) A mixture of 5 parts (by wt.) of Magnesol and 1 part of Celite was suspended with efficient stirring in a solution composed of 1 part (by vol.) of concentrated hydrochloric acid and 3 parts of water. The amount of Magnesol–Celite added to the diluted acid was regulated so that a very thin paste resulted. After stirring for sixty minutes the slurry was filtered and washed free of chloride ion and the water was displaced with acetone. The material was dried at room temperature overnight and then for two hours at 110°. The adsorbent was cooled, and only that portion which passed a 200-mesh (per linear inch) sieve was used in the chromatographic procedures.

(15) A product of Westvaco Chlorine Products Co., South Charleston, West Virginia.

(16) No. 535, a product of Johns-Manville Co., New York, N. Y.

(17) Dimensions of the adsorbent.

(18) M. L. Wolfrom and L. W. Georges, THIS JOURNAL, **59**, 602 (1937).

(19) F. Micheel and K. Hess, *Ber.*, **66**, 1898 (1927).

of material, melting point and mixed melting point with authentic 2,3,4,6-tetramethyl-D-glucose 91–92°, $[\alpha]^{26}D$ +84.3° (*c* 1.62, ethanol, equilibrium).[5] An amount of 17 mg. of this material was converted to the anilide according to the procedure of Irvine and Moodie[20]; m. p. 134–135°, unchanged on admixture with an authentic specimen of like melting point.

Evaporation of the effluent from the above-described chromatogram left 4.0 mg. of an unidentified sirup.

Maltotriose.—Two grams of β-maltotriose hendecaacetate was dissolved in 40 ml. of absolute methanol and cooled to 0°. A solution of 2.4 ml. of 0.4 *N* barium methoxide was added, and the whole was kept at 0° for twenty-four hours. Then to the solution 200 ml. of cold water was added and the ionic material was removed by passage through Amberlite[21] resins IR-100 and IR-4. The effluent was concentrated to a sirup under reduced pressure. The residual water was removed by repeatedly stirring with absolute ethanol and evaporating to dryness at room temperature in a vacuum desiccator containing anhydrous calcium chloride. All attempts to crystallize the amorphous solid have failed; $[\alpha]^{23}D$ +160° (*c* 2.36, water).

Anal. Calcd. for $C_{18}H_{32}O_{16}$: C, 42.86; H, 6.39. Found: C, 42.32; H, 6.39.

The free sugar was not hydrolyzed by emulsin and was not fermented by bakers' yeast,[22] which also failed to ferment maltose but fermented D-glucose rapidly.

Hydrolysis of Maltotriose by Maltase.—An amount of 98.0 mg. (1 mole) of maltotriose was dissolved in 0.5 ml. of 0.1 *N* acetate buffer (*p*H 4.7) and 0.5 ml. of an aqueous solution containing 1 mg. of a commercial purified maltase (Maltase 20[23]) preparation. The resultant solution was diluted to a volume of 2.52 ml. The enzymic reaction was followed polarimetrically. After twenty-six hours at 26–27°, hydrolysis to D-glucose was 71% complete; after forty-four hours, 82% complete (as determined polarimetrically). At the end of the latter period, the solution was evaporated to a sirup under reduced pressure. Residual water was removed by azeotropic distillation with absolute ethanol at reduced pressure. To the solids remaining were added 5 ml. of acetic anhydride and 50 mg. of anhydrous sodium acetate. Acetylation was conducted at 110–120° for one hour. The solution was then cooled and poured into 100 g. of ice and water. After hydrolysis of the excess acetic anhydride was complete, the aqueous solution containing suspended material was extracted with three 5-ml. portions of chloroform. The combined chloroform solution was repeatedly washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and evaporated to a solid; yield 196 mg. This crude product was dissolved in 25 ml. of benzene and placed on a chromatographic column packed with Magnesol[15]–Celite[16] (5:1 by wt.) (200 × 35 mm. diam.[17]) and developed with 200 ml. of benzene–ethanol (100:1 by vol.). A zone about one-third of a column length from the bottom of the extruded column was located by means of the permanganate streak indicator. This was sectioned and eluted with 50 ml. of acetone. Evaporation of the solvent left 140 mg. of crystals which were recrystallized from methanol; yield 128 mg. (1.7 moles), melting point and mixed melting point with β-D-glucopyranose pentaacetate 129–130°, $[\alpha]^{25}D$ +5° (*c* 3.58, chloroform).

A second zone about one-third of a column length from the top was sectioned and eluted with 50 ml. of acetone. Solvent removal left 30 mg. (0.2 mole) of material which crystallized from 95% ethanol; melting point and mixed melting point with β-maltose octaacetate 152–153.5°, mixed melting point with β-D-glycopyranose pentaacetate 114–119°, mixed melting point with β-maltotriose hendecaacetate 121–129°. A third zone at the top of the column was treated in the same fashion to yield 21 mg. (0.1 mole) of material which crystallized from 95% ethanol; melting point with β-maltotriose hendecaacetate 131–133°, mixed melting point with β-D-glucopyranose pentaacetate 105–109°, mixed melting point with β-maltose octaacetate 123–130°.

Acknowledgment.—The assistance of Dr. Alva Thompson and of Mr. I. L. Miller in the preparation of material is acknowledged, as is also the assistance of Mr. T. T. Galkowski in some of the enzyme experiments.

Summary

A crystalline trisaccharide hendecaacetate isolated from the acetylated enzymic hydrolyzate of amylopectin in the form of waxy maize starch[2] was shown to be β-maltotriose hendecaacetate. The methylation and acid hydrolysis of the acetate yielded crystalline 2,3,6-trimethyl-D-glucose and crystalline 2,3,4,6-tetramethyl-D-glucose, separated by chromatographic technics, and further characterized as the crystalline 2,3,6-trimethyl-β-D-glucose 1,4-diacetate and 2,3,4,6-tetramethyl-D-glucose anilide. The molar ratio of 2,3,6-trimethyl-D-glucose to 2,3,4,6-tetramethyl-D-glucose was 2:1.

Amorphous maltotriose, prepared through its crystalline β-hendecaacetate, was not fermented by bakers' yeast, was not hydrolyzed by emulsin, and was partially hydrolyzed by a maltase preparation into D-glucose and maltose (identified as the crystalline β-D-acetates separated chromatographically).

COLUMBUS, OHIO RECEIVED MAY 12, 1949

(20) J. C. Irvine and Agnes M. Moodie, *J. Chem. Soc.*, **93**, 95 (1908).

(21) A product of the Resinous Products Division of the Rohm and Haas Co., Philadelphia, Pennsylvania.

(22) Manufactured by Standard Brands, Inc., New York, N. Y.

(23) A product of Rohm and Haas Co., Philadelphia, Pennsylvania.

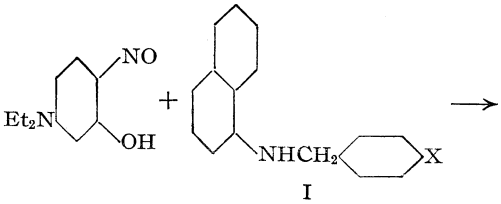
[CONTRIBUTION FROM THE HARRISON DEPARTMENT OF SURGICAL RESEARCH, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, AND THE DEPARTMENT OF NEUROSURGERY, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA]

Halogenated Benzophenoxazine Dyes[1,2]

BY HENRY A. SLOVITER

The discovery[3] that certain oxazine dyes stain and inhibit the growth of cancer cells when administered to living animals stimulated the investigation of related compounds. Since these oxazine dyes showed some selective affinity for tumor tissue, the present work was undertaken to prepare derivatives which might ultimately be used as "carriers" of radioactivity when radioactive isotopes were incorporated in the molecule. The halogens were selected as the intended radioactive isotopes because of their availability and because their emission characteristics are suitable for the intended biological studies.

Since one of these dyes, 5-benzylamino-9-diethylaminobenzo[a]phenoxazine[4] (II, X = H) was found to have optimal physiologic activity, its halogen derivatives (II, X = Cl, Br, I) were prepared by the reaction



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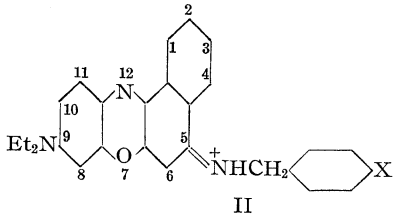
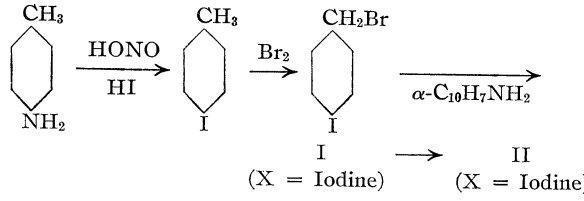


II

The N-(*p*-halobenzyl)-α-naphthylamines (I) have not been described previously. They were prepared by treating the proper *p*-halobenzyl halide with a large excess of α-naphthylamine in a manner similar to that described[5] for the preparation of the N-(nitrobenzyl)-α-naphthylamines.

The preparation of *p*-iodobenzyl bromide[6,7] by the bromination of *p*-iodotoluene without a solvent was found to give the product in poor yield and accompanied by considerable tarry matter. Good yields of pure *p*-iodobenzyl bromide were obtained by the modification of a procedure[8] used for the study of the photochemical bromination of *p*-iodotoluene in carbon tetrachloride.

In a complete synthesis of II where X is radioactive iodine, the sequence of reactions is



This synthesis has been successfully carried out and has yielded a product whose radioactivity is of the order of 0.5 millicurie per gram. The details of this preparation will be described in a subsequent report.

Since this synthesis involves carrying the radioactive iodine through four steps, an attempt was made to develop a shorter method of preparation. Accordingly, the preparation of I (X = Iodine) was attempted, without success, by replacement with iodine of the amino group of N-(*p*-aminobenzyl)-α-naphthylamine. The hydrochloride of the latter compound was prepared as described previously[5] by reduction of N-(*p*-nitrobenzyl)-α-naphthylamine. The product of this reduction on treatment with nitrous acid and iodide did not yield the desired N-(*p*-iodobenzyl)-α-naphthylamine.

An attempt was also made to prepare a benzo[a]phenoxazine dye containing a halogen atom in the ring structure. The reaction of 5-bromo-1-naphthylamine with 2-nitroso-5-diethylaminophenol which might have been expected to yield 1-bromo-5-amino-9-diethylaminobenzo[a]phenoxazine resulted in a substance which was apparently not a benzophenoxazine compound.

N-Allyl-α-naphthylamine was prepared with the intent of adding two atoms of iodine to obtain N-(2,3-diiodopropyl)-α-naphthylamine, from which the corresponding benzophenoxazine dye containing two atoms of iodine per molecule could be prepared. Thus far, N-(2,3-diiodopropyl)-α-naphthylamine has not been successfully isolated. However, 5-allyl-9-diethylaminobenzo[a]phenoxazine has been prepared.

Experimental

***p*-Iodobenzyl Bromide.**—Sixteen grams (5.4 ml.) of bromine in 50 ml. of pure carbon tetrachloride was added to 19 g. of freshly distilled *p*-iodotoluene (m. p. 35.0–35.3°) in 50 ml. of carbon tetrachloride. The flask was attached to an efficient reflux condenser and then illumi-

(1) Presented at the Meeting-in-Miniature of the Philadelphia Section, American Chemical Society, January 20, 1949.

(2) Aided in part by a grant to Doctor Margaret Lewis from the National Cancer Institute.

(3) Lewis, Sloviter and Goland, *Anatomical Record*, **95**, 89 (1946).

(4) The nomenclature is that of the Ring Index. This dye is known commercially as Nile blue 2B; number 914 in the Colour Index, Society of Dyers and Colourists, Great Britain, 1924.

(5) Darier and Mannassewitch, *Bull. soc. chim.*, [3] **27**, 1055 (1902).

(6) Wheeler and Clapp, *Am. Chem. J.*, **40**, 460 (1908).

(7) Jackson and Mabery, *ibid.*, **2**, 250 (1880).

(8) Sampey, Fawcett and Morehead, THIS JOURNAL, **62**, 1839 (1940).

TABLE I

N-SUBSTITUTED-α-NAPHTHYLAMINES

N-Substituent	Halide used	Formula	Yield, %	M. p., °C.	B. p., 4 mm., °C.	Halogen, % Calcd.	Found
p-Chlorobenzyl	Chloride	$C_{17}H_{14}NCl$	56	76.0–76.5	184–188	13.26	13.39[b]
p-Bromobenzyl	Bromide	$C_{17}H_{14}NBr$	62	88.5–89.0	190–195	25.62	25.69[b]
p-Iodobenzyl	Bromide	$C_{17}H_{14}NI$	70	84.5–85.0	200–205	35.36	35.73[c]
Allyl[a]	Chloride	$C_{13}H_{13}N$	95		110–120	[d]	[d]

[a] Distills as colorless liquid, rapidly becomes light amber. [b] Parr bomb method. [c] Chromic–sulfuric acid digestion, gravimetric. [d] Calcd.: iodine no., 139; N, 7.65. Found: iodine no. (two minutes contact with Wijs soln.), 144; N, 7.74.

nated by two 200-watt clear Mazda lamps placed almost in contact with the flask. Heat was applied to maintain the mixture at gentle reflux whereupon copious evolution of hydrogen bromide took place. After two hours the evolution of hydrogen bromide had almost ceased, and no vapors of bromine were visible in the reaction flask. The heat and light were continued for thirty minutes more. The flask was cooled, and 5 g. of potassium iodide in 50 ml. of water was added. Sodium thiosulfate solution (approximately 0.1 *N*) was added in slight excess (about 80 ml.). The carbon tetrachloride layer was separated and washed with water. After removal of the carbon tetrachloride by distillation, the residue solidified rapidly on cooling to a clean white crystalline mass. Recrystallization from ethanol yielded 15 g. (60% yield) of clean white crystals, m. p. 78.5–79.5°. The *p*-bromobenzyl bromide was similarly prepared.

N-(*p*-Halobenzyl)-α-naphthylamines.—To a solution of 14.3 g. (0.1 mole) of α-naphthylamine in 50 ml. of ethanol was added a solution of 0.03 mole of *p*-halobenzyl halide in 50 ml. of ethanol. The solution was refluxed for two hours and the alcohol was removed by distillation. About 100 ml. of hot water was added to the viscous residue and, after swirling the mixture, 1:1 hydrochloric acid was added dropwise until the aqueous phase became clear. The supernatant liquid was removed by siphon. This procedure was repeated two times, and the residue was then washed with hot water. This procedure served to remove most of the excess α-naphthylamine. The residue was then cooled in an ice-bath, whereupon it hardened sufficiently so that remaining water could be drained off. It was then washed with about 10 ml. of cold ethanol to remove water adhering to the flask and residue. The residue was then recrystallized from ethanol. The product tended to separate as an oil but very slow cooling and seeding gave clean, almost white crystalline products. The amines could be distilled under reduced pressure prior to recrystallization. The yields thus obtained were somewhat lower and the products were white, but the melting points were the same in both cases.

The yields, properties and analyses of these amines are listed in Table I. The melting points shown are corrected values.

N-Allyl-α-naphthylamine.—This was prepared in the same manner as the *p*-halobenzyl-α-naphthylamines using 25 g. of α-naphthylamine and 5 ml. of allyl chloride. After removal of the excess α-naphthylamine, the crude product was dissolved in ether and washed with water. After removal of the ether, the product was distilled under reduced pressure.

5-(N-Substituted Amino)-9-diethylaminobenzo[a]phenoxazine Chloride.—A mixture of 0.02 mole of N-substituted-α-naphthylamine, 5 ml. of concentrated hydrochloric acid and 30 ml. of ethanol was warmed gently until a clear solution was obtained. To this was added a solution of 5.8 g. (0.03 mole) of 2-nitroso-5-diethylaminophenol[9] in 15 ml. of ethanol, and the mixture was boiled under reflux for three hours. After standing overnight, the mixture was cooled in ice, and the crystalline dye was filtered, washed with a small quantity of cold ethanol and finally with ether. The products were pure as shown by analysis (Table II) and adsorption chromatograms on paper. The dyes could be recrystallized in small batches from ethanol containing a trace of hydrochloric acid.

TABLE II

5-R-9-DIETHYLAMINOBENZO[a]PHENOXAZINE CHLORIDES

R	Formula	Yield, %	Analyses, % Calcd.		Found
p-Chlorobenzylamino	$C_{27}H_{25}ON_3Cl_2$	75	Cl	14.84	14.77[a]
p-Bromobenzylamino	$C_{27}H_{25}ON_3ClBr$	80	Br	15.30	15.08[b]
p-Iodobenzylamino	$C_{27}H_{25}ON_3ClI$	88	I	22.29	22.43[c]
Allylamino	$C_{23}H_{24}ON_3Cl$	40			

[a] Parr bomb method. [b] Robertson method followed by weighing of mixed silver halides and after conversion of silver bromide to silver chloride. [c] Chromic–sulfuric acid digestion, gravimetric.

Attempts to prepare the sulfates of these dyes always yielded a resinous product which could not be crystallized.

Reaction of N-(*p*-Aminobenzyl)-α-naphthylamine with Nitrous Acid and Iodide.—A suspension of 5 g. of N-(*p*-aminobenzyl)-α-naphthylamine dihydrochloride[5] in a mixture of 40 ml. of water and 5 ml. of 1:1 hydrochloric acid was kept below 5°, and a solution of 0.75 g. of sodium nitrite in 10 ml. of water was added dropwise until a slight excess was present (starch–iodide paper). A clear solution resulted. To this was added slowly a solution of 1.75 g. of potassium iodide in 10 ml. of water. A dark brown precipitate formed slowly which floated to the surface. The mixture was kept below 5° for two hours and allowed to warm to room temperature overnight. The mixture was filtered and washed with water. The very dark brown powdery product was not appreciably soluble in water, dilute hydrochloric acid, alcohol or acetone.

Attempted Preparation of 1-Bromo-5-amino-9-diethylaminobenzo[a]phenoxazine Chloride.—To a boiling solution of 2 g. of 5-bromo-1-naphthylamine[10] in a mixture of 15 ml. of glacial acetic acid, 10 ml. of water and 3 ml. of 1:1 hydrochloric acid was added 2.2 g. of 2-nitroso-5-diethylaminophenol in small portions. The mixture was kept near boiling for one hour during which time it became almost black in color. After standing overnight, it was filtered, washed with water until the washings were only faintly colored and allowed to dry. This almost black, granular product gave a blue solution in glacial acetic acid and a cherry red solution in xylene. It was insoluble in water and dilute hydrochloric acid.

Acknowledgment.—The author is indebted to Mr. Louis Goldberg for the preparation of several batches of 2-nitroso-5-diethylaminophenol and for assistance with the analyses, and to Dr. Milton H. Paul and Mr. Bernard Shapiro for assistance in the preparation of adsorption chromatograms.

(9) Mohlau, *Ber.*, **25**, 1060 (1892), reports m. p. 84°; we consistently obtained m. p. 89–90°.

(10) Ullmann and Consonno, *ibid.*, **35**, 2804 (1902).

Summary

1. The 5-(*p*-halobenzylamino)-9-diethylaminobenzo[a]phenoxazine chlorides and corresponding 5-allylamino compound have been prepared. The intermediates, N-(*p*-halobenzyl)-α-naphthylamines and N-(allyl)-α-naphthylamine, have been prepared.

2. The attempted preparation of N-(*p*-iodobenzyl)-α-naphthylamine by treatment of N-(*p*-aminobenzyl)-α-naphthylamine with nitrous acid and iodide was unsuccessful.

3. The reaction of 5-bromo-1-naphthylamine with 2-nitroso-5-diethylaminophenol does not yield a benzophenoxazine dye.

PHILADELPHIA, PENNSYLVANIA RECEIVED APRIL 8, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Reduction of Terminal Epoxides[1]

BY MELVIN S. NEWMAN, GERALD UNDERWOOD AND MARY RENOLL

Although the reduction of the epoxide function has been studied,[2] little systematic work has been done on the production of primary alcohols from terminal epoxides. The formation of *n*-propyl, *n*-butyl[3,4] and β-phenylethyl alcohols by catalytic reduction of the corresponding epoxide by hydrogen has been mentioned in the patent literature.

In this paper we report the successful reduction of 1,2-epoxydecane and of styrene oxide to the corresponding primary alcohols by catalytic methods. Reductions involving sodium amalgam and lithium aluminum hydride[5] gave mainly secondary alcohols and hence were not studied in detail.

TABLE I

REDUCTION OF 1,2-EPOXYDECANE AND STYRENE OXIDE

	Reaction conditions	T, °C.	Pr (p. s. i.)	$n^{20}D$[a]	Epoxide	Analyses,[b] % Sec. alc.	Pri. alc.
			1,2-Epoxydecane				
1	Raney nickel[c]	20	37	1.4292	+[d]		
2	Raney nickel[c] (large amount)[e]	20	15	1.4355			+[d]
3	Platinic oxide (Adams)	20	37	1.4289	+[d]		
4	Raney nickel[c]	150	900	1.4362	5	10	83[g]
5	Raney nickel[f]	150	900	1.4360	<5	<10	90
6	Raney nickel[c] + 0.01 g. NaOH	150	900	1.4353	5	10	85
7	Raney nickel[c] + 0.1 g. NaOH	150	900	1.4347	5	85	7.5[g]
8	Raney nickel[f] + 0.1 g. NaOH	150	900	1.4343	<5	95	<5
9	Raney nickel[c] + 0.1 g. H_3PO_4[h]	150	900	1.4359	<5	50	50[g]
10	Raney nickel[f] + 0.1 g. H_3PO_4[h]	150	1100[i]	1.4354	<5	50	50
11	Raney nickel[f]	25	1000	1.4298	+[d]		
12	Ni-on-kieselguhr (UOP)	200	1450	1.4358	5	10	85
13	Sodium amalgam				60	35	5
14	Lithium aluminum hydride				10	90	
	Standards 1,2-Epoxydecane			1.4289			
	2-Decanol			1.4340			
	1-Decanol			1.4373			
			Styrene Oxide				
15	Raney nickel[c] and [f]	25	700	1.5309	0	0	100[g]
16	Raney nickel[c] and [f] + 0.1 g. NaOH	25	700	1.5317	0	0	100[g]
17	Raney nickel[c] + 0.1 g. H_3PO_4	25	700	1.5299	41[j]	0	75[k]
18	Raney nickel[f] + 0.1 g. H_3PO_4	25	700	1.5295	40	0	60[k]
19	Raney nickel[c]	150	700	1.4770[k]			

[a] The indices of refraction are those of the crude distillate obtained directly from the hydrogenation experiments. [b] The analytical results reported were carried out by Dr. J. J. Shipman of the B. F. Goodrich Co. using an infrared spectrophotometer. Calibration curves for pure 1-decanol, 2-decanol and 1,2-epoxydecane were obtained and synthetic

Our results are summarized in Table I. Of particular interest is the effect of small amounts of acidic or basic substances on the course of the reduction of 1,2-epoxydecane but *not* of styrene oxide. In the absence of such additives reduction

(1) The work herein reported was carried out during 1946 and 1947 on research project 162 of the Ohio State University Research Foundation and was sponsored by the B. F. Goodrich Company of Akron, Ohio.

(2) Grignard, "Trâité de chime organique," Vol. VI, Masson et Cie, Paris, 1940, p. 286.

(3) Usines de Melle and H. M. E. Guinot, British Patent 496,264 (1938).

(4) I. G., German Patent 573,535 (1933).

(5) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947); Finholt, Bond and Schlesinger, *ibid.*, **69**, 1199 (1947).

mixtures analyzed by comparison with the standard curves at suitable wave lengths. The values cited are approximate only. We have checked several results qualitatively by formation of the phenyl urethans. Our qualitative results checked the infrared results about as well as could be expected. [c] Raney nickel prepared as described in "Organic Syntheses," Vol. XXI, John Wiley & Sons, Inc., New York, N. Y., 1941, p. 15. [d] Presence of this component judged qualitatively either by $n^{20}D$ and b. p. or by formation of phenyl urethan. [e] Attempted hydrogenolysis by adsorbed hydrogen as in desulfurization reactions. [f] Raney nickel prepared as by Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946). [g] Average of two identical runs, per cent. calculated from infrared analysis; see *b*. [h] Reductions with added phosphoric acid much more sluggish. [i] Higher pressure to attempt speedier reduction, however, still sluggish. [j] Some compound other than styrene oxide was also present. [k] At the higher temperature the ring reduced yielding cyclohexane derivatives.

gave mainly primary alcohol but in the presence of as little as 0.1 g. of acid or base in over 100 cc. of solution primary alcohol formation was markedly decreased.

Experimental

1-Decene was converted to 1,2-epoxydecane, b. p. 82–83.5° at 10 mm., by reaction with peracetic acid.[6] 1-Decanol, b. p. 111.5–113.5° at 11 mm., and 2-decanol, b. p. 104.5–106.0° at 13 mm., were prepared by treating *n*-octylmagnesium bromide with ethylene oxide and acetaldehyde. The corresponding phenylurethans melted at 58.5–59.5 and 37–38°.

A commercial sample of styrene oxide (Dow) was rectified to yield pure styrene oxide, b. p. 81.5° at 15 mm., $n^{20}D$ 1.5350. Pure rectified α-phenylethyl alcohol, $n^{20}D$ 1.5272, formed a phenylurethan which melted at 93–94° and pure rectified β-phenylethyl alcohol, $n^{20}D$ 1.5325, formed a phenylurethan which melted at 78–79°.

General Procedure for Catalytic Reduction.—A mixture of 10 g. of 1,2-epoxydecane, 2.5 g. of wet catalyst (wet with absolute alcohol but containing 1 g. dry weight of catalyst), and 115 cc. of absolute alcohol was reduced in standard high pressure equipment. After reduction the catalyst was removed by filtration and washed well with solvent. The solvent was stripped and the residue was vacuum distilled without attempting fractionation. The entire distillate which usually amounted to 8.5 g. was weighed and its index of refraction determined. Part of the sample was then sealed in a glass ampoule and sent to the Goodrich Company for infrared analysis. In several cases the reaction mixture was treated with excess phenyl isocyanate and the melting point of the mixed phenylurethans taken. For runs which analysis indicated to consist of mainly primary alcohol there was no difficulty in isolating fairly good yields of the phenylurethan of the primary alcohol. The same was true for the phenylurethan of the secondary alcohol in mixtures rich in this compound. From reaction mixtures which analysis indicated a mixture of about equal parts, no pure urethan was isolated.

In the catalytic reductions involving styrene oxide conditions were the same as above except that only 100 cc. of alcohol was used.

Chemical Reduction of 1,2-Epoxydecane.—To a solution of 10 g. of epoxide in 100 cc. of water and 200 cc. of ethyl alcohol was added 500 g. of 3% sodium amalgam. After standing at room temperature for sixteen hours with occasional shaking and neutralization of excess alkali with carbon dioxide the product was isolated as above. The reduction, incomplete under these conditions, yielded mainly 2-decanol.

When 1,2-epoxydecane was treated with an equivalent amount of lithium aluminum hydride[5] in dry ether the product consisted exclusively of 2-decanol except for some unreacted epoxide.

(6) Swern, Billen and Scanlan, THIS JOURNAL, **68**, 1504 (1946).

Summary

On catalytic hydrogenation over Raney nickel 1,2-epoxydecane yields mainly 1-decanol. In the presence of small amounts of sodium hydroxide, however, mainly 2-decanol results. With sodium amalgam and lithium aluminum hydride 2-decanol is the main product.

Styrene oxide yields β-phenylethyl alcohol exclusively on catalytic reduction over Raney nickel either with or without added sodium hydroxide. The addition of phosphoric acid retards the reduction markedly and causes complications but primary alcohol is still the main product.

COLUMBUS 10, OHIO RECEIVED MARCH 25, 1949

[CONTRIBUTION FROM THE CHEMICAL DIVISION OF THE PROCTER & GAMBLE CO.]

The Polymorphism of Saturated 1,3-Diglycerides

BY F. J. BAUR, F. L. JACKSON, D. G. KOLP AND E. S. LUTTON

Introduction

Malkin, Shurbagy and Meara[1] have described the polymorphism of both even and uneven monacid saturated 1,3-diglycerides of the series dicaprin through distearin. They have reported two sets of long spacings which give two straight lines if spacings are plotted against chain length. For the lower members, including dilaurin (LL) and dimyristin (MM), the greater long spacings were reported to be associated with short spacings of a type specified as "a"; the lesser long spacings were associated with short spacings of type "b." In the case of dipalmitin (PP) and distearin (SS) only the lesser long spacings were observed and these were associated, oddly, with "a" instead of "b" short spacings.

In the present paper are reported results of a reexamination of the even diglycerides, dilaurin through distearin, in the course of which two long spacing values were found uniformly for each compound, and the lesser and greater long spacings were respectively associated with "a" and with "b" type short spacings.

Experimental

The dipalmitin used in this study was prepared according to the directed rearrangement procedure described by Eckey and Formo.[2] Cottonseed oil stearin containing approximately 35% of saturated fatty acids was rearranged

(1) Malkin, Shurbagy and and Meara, *J. Chem. Soc.*, 1409 (1937).

(2) Eckey and Formo, *J. Am. Oil Chem. Soc.*, **26**, 207 (1949).

TABLE I

CONSTANTS FOR 1,3-DIGLYCERIDES

	M. p., °C.	Hydroxyl value Found	Hydroxyl value Calcd.	Saponification value Found	Saponification value Calcd.	% monoglyceride[4] Found	% monoglyceride[4] Calcd.
Distearin	78.2, 78[1]	89	90	179.4	179.7	0.1	0.0
Dipalmitin	72.9, 72.5[1]	98	99	197.3	197.2	.2	.0
Dimyristin	66.5, 65.5[1]	109	109	216.8	218.5	<.1	.0
Dilaurin	56.8, 56.5[1]	119	123	245.7	245.7	<.1	.0

with 8% glycerol, representing a slight excess over the theoretical quantity required to convert all triglycerides to diglycerides. The crude diglyceride was purified by 6 recrystallizations from hexane and hexane–alcohol. The distearin, dimyristin, and dilaurin were prepared by a modification of this procedure.[3] Constants for the diglycerides are given in Table I.

Thermal examination was carried out in the manner of previous investigations in this Laboratory[5] but with one additional procedure to register a "cloud point." For this observation sealed 1-mm. capillary tubes containing the diglyceride were lowered in temperature about 2° per minute until the temperature of clouding was observed. This value is reproducible within about 0.5°. The test was run to see whether diglycerides like mono- and triglycerides show a supercooling limit near their lowest m. p. level. Such behavior would indicate the occurrence of alpha-type forms. "Rapid c. m. p." was determined on a freshly chilled sample by a "thrust-in" technique and "regular c. m. p." by raising the bath temperature 0.2° per minute.

X-Ray diffraction patterns were obtained as previously described[5] on chilled, aged and solvent crystallized samples.

Thermal and diffraction data are recorded in Tables II and III.

TABLE II

THERMAL DATA FOR 1,3-DIGLYCERIDES

Thermal point	Distearin	Dipalmitin	Dimyristin	Dilaurin
Cloud point (beta-a?)	73.5	67.0	60.5	50.0
Rapid c. m. p. (beta-a)	77.2	71.8	64.3	54.0
Regular c. m. p. (beta-a and beta-b)	78.2	72.9	66.5	56.8
Time required for transformation (beta-a to beta-b) at reg. c. m. p. −2°	5 hr.	2 hr.	1 min.	1–5 min.

Discussion

The reëxamination of this glyceride series reveals a close resemblance of the members to each other in polymorphic behavior as would be expected from their homologous molecular structures. Previously reported discontinuities between dimyristin and dipalmitin[1] were not confirmed.

Two forms were obtained for each diglyceride, each form having a strong 4.6 Å. short spacing line. A nomenclature has been adopted which is consistent on one hand with that established for triglycerides[6] (and stemming originally from the work of Malkin) and on the other hand with Malkin's distinction between "a" and "b" short spacing types for diglycerides.[1] Both forms are labeled "beta" on the basis of their strong 4.6 spacings, and distinguished as "a" or "b" on the basis of other important short spacings. Thus the two different forms here reported are named as follows—beta-a with characteristic short spacings 4.6 Å. VS, 3.9 M, 3.7 S; beta-b with characteristic short spacings 4.6 Å. VS, 3.75 S^+. This corresponds to the nomenclature of Sidhu and Daubert[7] for mixed diglycerides.

A feature of significance in clarifying the polymorphism of these compounds is illustrated in Fig. 1. In contrast to the data of Malkin, *et al.*,[1] it is shown that the beta-a short spacings are uniformly associated with the lesser long spacing for each of the four homologs; similarly beta-b is associated with the greater long spacing.

Beta-a is invariably obtained on cooling a melt. It is extremely stable at room temperature, in no case having been observed to transform at that level. It transforms to beta-b at a temperature within 2° of the melting point at rates which are, in general, inversely related to chain length. Rate of transformation is controlled by purity of sample, increasing with purity of constituent saturated acids and with increasing number of crystallizations. The corresponding monoglyceride, however, actually promotes transformation while triglyceride exerts a negligible retarding effect. It would seem that mixed diglycerides might be responsible for the slowing down of conversion in less pure samples. Such mixed glycerides are thought to account for the slower transformation rate of dilaurin relative to dimyristin, indicated in Table II. Beta-a is frequently obtained by solvent crystallization, being favored by lower temperatures, by more polar solvents and by presence of impurities (not monoglycerides), but the conditions are not clearly established.

Beta-b, as has been said, may be obtained from beta-a. Since the tranformation has not been observed to be reversible, beta-b appears to be the only thermodynamically stable form. It is favored in solvent crystallization by higher temperatures and less polar solvents. (Beta-b was not reported for dipalmitin and distearin by Malkin, *et al.*[1])

Beta-a, when formed from the melt by chilling, gives a "rapid c. m. p." (by "thrust-in" technique) about 2° below the solvent crystallized m. p. This signifies a certain degree of imperfection of the rapidly formed crystallites. A "regular c. m. p." on a chilled sample is within 0.5° of the maximum m. p. value and solvent crystallized beta-a appears

(3) To be reported.

(4) Handschumacher and Linteris, *J. Am. Oil Chem. Soc.*, **24**, 143 (1947).

(5) Lutton, Jackson and Quimby, THIS JOURNAL, **70**, 2441 (1948).

(6) Lutton, THIS JOURNAL, **70**, 248 (1948).

(7) Sidhu and Daubert, *ibid.*, **68**, 2603 (1946).

TABLE III

X-RAY DIFFRACTION DATA FOR 1,3-DIGLYCERIDES IN Å.

hkl	Beta-a Distearin	Beta-a Dipalmitin	Beta-a Dimyristin	Beta-a Dilaurin	Beta-b Distearin	Beta-b Dipalmitin	Beta-b Dimyristin	Beta-b Dilaurin
				Long spacings				
001	50 VS	44 VS	40.5 VS	35 VS	51.3 VS	47.0 VS	42.7 S	36.7 VS
002	25.1 M	22.2 M	20.3 M	17.7 W	26.2 M	23.8 M	21.2 W	18.8 S
003	16.7 S+	14.9 S	13.5 S	11.8 M	17.5 S	15.9 S	14.2 M	12.6 VS
004			10.2 W	8.89 W			10.49 W	9.41 M
005	10.0 VW	8.9 W			10.6 W	9.48 VW		
006	8.37 VW+	7.5 W+	6.88 M	5.89 W	8.5 W	7.86 M	7.02 W	6.23 W
007								5.30 W
008	6.28 VW	5.6 W+			6.6 W	5.97 W		
Av. d	50.2	44.7	40.6	35.4	52.8	47.4	42.4	37.5
				Short spacings				
					5.38 VW		5.68 W	
	4.61 VS	4.60 VS	4.58 S	4.58 S	4.59 VS−	4.58 VS	4.55 S	4.55 M
	4.21 VW	4.06 VW	4.15 VW	4.11 VW	4.14 W		4.13 VW	
	3.90 S	3.88 M	3.91 M	3.89 M	3.74 VS	3.75 VS	3.74 S	3.70 S
	3.71 S+	3.72 S+	3.73 S	3.68 S	2.52 W	2.69 W	3.44 VW	3.42 VW
	3.39 VW	3.31 VW	2.79 VW	3.39 W	2.44 W	2.62 W	3.31 VW	2.42 W
	2.80 VW	2.77 VW	2.53 W	2.75 W	2.31 VW	2.45 M	3.11 VW	2.20 VW
	2.55 W+	2.50 M	2.44 VW	2.50 W	2.18 W	2.40 W	2.91 VW	2.13 VW
	2.44 VW	2.29 W	2.38 VW	2.41 W		2.33 W−	2.64 VW	
	2.30 VW	2.23 W	2.24 W	2.30 W		2.26 W	2.48 VW	
				2.25 W		2.17 W+		

to melt as high as beta-b. (Of course, it may be that beta-a transforms to beta-b very rapidly near the m. p.)

It is a matter of speculative interest, at least, that certain analogies exist between the diffraction patterns of saturated di- and triglycerides. Thus, as pointed out by Malkin, *et al.*,[1] both beta-a diglyceride forms and beta-2 triglyceride forms show 4.6, 3.9, and 3.7 Å. short spacings (4.6 strongest). Likewise, beta-b (diglyceride) and beta-3 (triglyceride) have 4.6 and 3.75 Å. short spacings (3.75 strongest) in common. Moreover, just as beta-b forms exceed corresponding beta-a forms by about 2 Å. in long spacings, so beta-3 long spacings (when compared on a double-chain length basis) are 2 Å. greater than beta-2 values.[8] It should be noted, however, that beta-a long spacings exceed corresponding beta-2 long spacings by 5 Å.

A notable feature of these diglycerides is their apparent lack of alpha forms (single strong spacing near 4.2 Å.). While each compound shows approximately 5° of supercooling, in no case is a m. p. observable in the neighborhood of the supercooling limit. Therefore one characteristic common to the alpha forms of 1-mono- and triglycerides, namely, the close agreement of supercooling limit and lowest melting point, is here lacking. This fact and failure to obtain alpha patterns show that if alpha forms do occur at all for these diglycerides, they are extremely fleeting.

Acknowledgment.—The authors wish to express their appreciation to those of this laboratory who have assisted in the experimental work.

(8) In the terms of a previous publication,[6] $2/3\ (L\beta)_T' = (L\beta)_D + 2$.

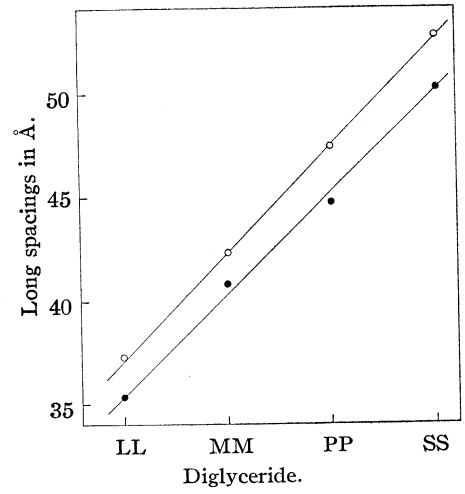


Fig. 1.—Diglyceride long spacings: ●, beta-a (metastable); ○, beta-b (stable).

Summary

A reëxamination of the polymorphism of the even, saturated 1,3-diglycerides, dilaurin through distearin, has revealed a uniformity of behavior which does not confirm the discontinuities reported by Malkin, *et al.*[1]

Each diglyceride has two forms, both classified as beta-like on the basis of strong 4.6 Å. spacings. After a suggestion of Malkin, the two forms are called beta-a and beta-b and are readily distinguishable by differences in short spacings in the

3.8 Å. region. For a given glyceride the beta-b long spacing exceeds that of beta-a by about 2 Å.

Beta-a is invariably obtained from the melt and may sometimes be obtained by solvent crystallization. Highly stable at room temperature, it transforms to beta-b near the m. p. Beta-b, apparently the only thermodynamically stable form, is obtained by transformation of beta-a and commonly by solvent crystallization.

It is notable that no alpha-like patterns were observed, although they are readily obtained with 1-mono- and triglycerides.

Purely on the basis of similarity in X-ray diffraction patterns, it is suggested that a structural similarity may exist between beta-a diglyceride forms and beta-2 triglyceride forms and between beta-b (diglyceride) and beta-3 (triglyceride).

IVORYDALE, OHIO RECEIVED APRIL 29, 1949

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Sulfur-Containing Amines. VIII.[1] Local Anesthetics. III

BY R. O. CLINTON, U. J. SALVADOR AND S. C. LASKOWSKI

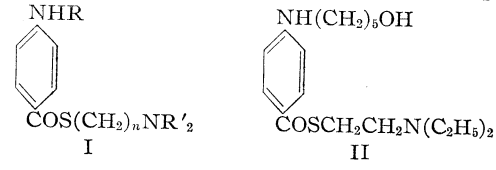
In extending previous investigations[2,3] there have been prepared a number of dialkylaminoalkyl thiol esters derived from various nuclei, for testing as local anesthetics.

In comparison to the oxygen analogs, very few local anesthetics of the dialkylaminoalkyl thiol ester type have appeared in the literature. Karjala and McElvain[4] have recorded the preparation of 3-(2-methylpiperidyl-1)-propyl thiolbenzoate hydrochloride, the thiol analog of Metycaine, by a four step synthesis *via* 3-bromopropyl thiolbenzoate. Lischer and Jordan[5] prepared a short series of 3-dialkylaminopropyl 4-aminothiolbenzoate hydrochlorides *via* 3-chloropropyl 4-nitrothiolbenzoate, in which the terminal tertiary amino group varied from diethylamino to diamylamino. Sergievskaya and Kropacheva[6] investigated a series of diethylamino-ethyl, -propyl and -butyl naphthalene-1-thiolcarboxylates and 4-aminonaphthalene-1-thiolcarboxylates. These compounds were reported by the authors to possess high anesthetic potency without irritation or other untoward effects. Further, a patent[7] reported the properties of three diethylaminoethyl 4-alkoxythiolbenzoate hydrochlorides, prepared by the action of a 4-alkoxybenzoyl chloride on 2-bromoethanethiol and subsequent reaction with a secondary amine.

An important advantage of simple local anesthetics of the types of Apothesine and Metycaine is the lack of PABA interference in clinical usage. It was felt in the present work that simple thiolbenzoates and thiolcinnamates might, while satisfying this condition, in addition possess lowered toxicity while retaining activity. Certain examples of these types have been prepared.

A few additional examples of diphenylthiolacetates[3,8] were prepared, since pharmacological screening has indicated that these compounds are strong local anesthetics, in analogy with other antispasmodics of related type.

A further interesting type of thiol ester is that related to Thiocaine.[2,9] This ester possesses a high therapeutic index in relation to Procaine[9]; similar high activity in analogous types is reported by Lischer and Jordan.[5] This series has therefore been widely extended, through variation of the dialkylaminoalkyl grouping. Of greater interest, insofar as activity is concerned, are the dialkylaminoalkyl thiol esters, (I), related to Tetracaine. A series of these compounds was prepared,



either by reductive alkylation of the parent 4-aminothiolbenzoate, or by the reaction between a dialkylaminoalkanethiol and a 4-alkylaminobenzoyl chloride hydrochloride. A new example of this type was prepared by using 5-hydroxypentanal as the alkylating agent, to yield the compound II. The effect on activity of the inclusion of a hydroxyl group in this position of the nucleus has not been previously determined.

Several thiol esters derived from 2-butyloxyquinoline-4-carboxylic acid were also prepared, to determine whether the high toxicity and irritation associated with the Nupercaine series could be decreased through inclusion of a sulfur linkage in the ester group. Further, two examples of the 4-alkoxythiolbenzoate type[7] were prepared from the acid chloride and a thiol, to enable evaluation in comparison with the 4-aminothiolbenzoate analogs.

(1) Paper VII, Clinton, Salvador and Laskowski, THIS JOURNAL, **71**, 1300 (1949).

(2) Albertson and Clinton, *ibid.*, **67**, 1222 (1945).

(3) Clinton and Salvador, *ibid.*, **68**, 2076 (1946).

(4) Karjala and McElvain, *ibid.*, **55**, 2966 (1933).

(5) Lischer and Jordan, *ibid.*, **59**, 1623 (1937).

(6) Sergievskaya and Kropacheva, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1737 (1940) (*C. A.*, **35**, 4003 (1941)).

(7) Harris and Braker, U. S. Patent 2,342,142.

(8) Richardson, U. S. Patent 2,390,555 (1945); Dupré, Lévy and Tchoubar, *Compt. rend. soc. biol.*, **140**, 477 (1946); Tchoubar and Letellier-Dupré, *Bull. soc. chim.*, 792 (1947).

(9) Hansen and Fosdick, THIS JOURNAL, **55**, 2872 (1933); *J. Pharmacol.*, **50**, 323 (1934); Nolle, *Farm. i. Farmacol.* (*U. S. S. R.*), (1937) No. 2, 1 [*C. A.*, **34**, 3820 (1940)].

TABLE I

DIALKYLAMINOALKYL INTERMEDIATES $R_2N(CH_2)_nX$

Compound							Analyses, %		Picrate	Analyses, % Nitrogen[a]	
R_2	n	X	M. p. or b. p., °C.	Mm.	$n^{25}D$	Yield, %	Formula	Calcd. Found	M. p., °C.	Calcd.	Found
C_6H_{12}[b]	2	OH	87.0	8	1.4788	86	$C_8H_{17}NO$[c]	N, 9.85 9.80	109–111[d]	3.76	3.75
C_6H_{12}[b]	2	Cl.HCl	184–185		....	98	$C_8H_{17}Cl_2N$[e]	N, 7.07 7.00	.....	...	...
C_6H_{12}[b]	2	Cl	88.0	16	1.4721	65	$C_8H_{16}ClN$[f]	N, 8.66 8.62	136.1–136.7	3.58	3.62
C_6H_{12}[b]	2	SCH_4ClN_2[g]	226–227		....	94	$C_9H_{21}Cl_2N_3S$	S, 11.69 11.84	.....	...	...
C_6H_{12}[b]	2	SH	96.5–97	14	1.4974	57	$C_8H_{17}NS$	N, 8.79 8.87	117–118	3.61	3.62
C_5H_{10}[h]	2	OH	72	8	1.4683	56	$C_7H_{15}NO$[i]	N, 10.84 10.67	103–104[j]	11.72	11.79
C_5H_{10}[h]	2	SCH_4ClN_2[g,l]	205–208		....	96	$C_8H_{19}Cl_2N_3S$	S, 12.32 12.52	.....	...	...
C_5H_{10}[h]	2	SH	74.0–74.5	11	1.4898	44	$C_7H_{15}NS$	N, 9.64 9.63	.....	...	...
C_4H_8O[m]	3	SCH_4ClN_2[g,n]	218–220		....	95	$C_8H_{19}Cl_2N_3S$	S, 11.61 11.70	.....	...	...
C_4H_8O[m]	3	SH	110–112	11–12	1.4962	42	$C_7H_{15}NOS$	N, 8.69 8.72	129–130	3.59	3.59
C_6H_{12}[b]	3	Cl.HCl[o]	177.2–178.2		....	97	$C_9H_{19}Cl_2N$[p]	N, 6.60 6.85	.....	...	...
C_6H_{12}[b]	3	SCH_4ClN_2[g]	186–188		....	97	$C_{19}H_{23}Cl_2N_3S$	S, 11.12 11.16	.....	...	...
C_6H_{12}[b]	3	SH	95.5	6	1.4950	53	$C_9H_{19}NS$	N, 8.08 8.13	116–118	3.48	3.48

[a] See ref. 22. [b] 2-Methylpiperidyl-1. [c] Calcd.: OH, 11.96. Found: OH, 12.18. [d] The picrolonate, yellow plates from absolute alcohol, melted at 185–186°. *Anal.* Calcd. for $C_{18}H_{25}N_5O_6$: N,[a] 3.44. Found: N,[a] 3.46. [e] Calcd.: Cl, 35.79. Found: Cl, 35.86. [f] Calcd.: Cl, 21.93. Found: Cl, 21.60. [g] Isothiouronium chloride hydrochloride. [h] 2-Methylpyrrolidyl-1. [i] Calcd.: OH, 13.16. Found: OH, 13.37. [j] The picrolonate, canary yellow needles from absolute alcohol, melted at 168–169°. *Anal.* Calcd. for $C_{17}H_{23}N_5O_6$: N,[k] 7.12. Found: N,[k] 6.93. [k] Nitro nitrogen, determined by titration with titanous chloride in glacial acetic acid solution. [l] From the chloride hydrochloride, m. p. 187–188°; unpublished work by Dr. A. W. Ruddy of these Laboratories. [m] 4-Morpholinyl. [n] From the chloride hydrochloride, described by Adams and Whitmore, THIS JOURNAL, **67**, 735 (1945). [o] The free base has been described by McElvain, ref. 14. [p] Calcd.: Cl, 33.42. Found: Cl, 33.20.

In most of the above series an attempt has been made to vary the basic ester portion of the molecule sufficiently to ascertain variations of toxicity and activity accompanying such changes.

Complete pharmacological data will be published at a later date by Dr. F. P. Luduena and Dr. T. J. Becker of these laboratories.

Experimental[10]

3-Dialkylaminopropanols.—Substantial improvements in yield were made in the synthesis of certain 3-dialkylaminopropanols, through modification of the conventional secondary amine-trimethylene chlorohydrin procedure of Adams, *et al.*[11,12] This synthesis is illustrated by the description in detail of the preparation of **3-(2-methylpiperidyl-1)-propanol**. A mixture of 770 g. (7.78 moles) of 2-methylpiperidine,[13] 368 g. (3.89 moles) of trimethylene chlorohydrin, 800 ml. of absolute alcohol and 30 g. of sodium iodide or potassium iodide, was refluxed with stirring for twenty-four hours. The stirred reaction mixture, after cooling, was treated with a solution of 90 g. (3.9 moles) of sodium in 1500 ml. of absolute alcohol, filtered, and the filtercake was washed well with ether. The filtrate was distilled at atmospheric pressure, with mechanical stirring, through a twelve-inch Vigreux column to a head temperature of 122°, reserving the fraction of b. p. 105–122° for recovery of 2-methylpiperidine. The still residue was diluted with three volumes of ether, filtered, and distilled, first at atmospheric pressure and then *in vacuo*. Redistillation gave 582 g. (95% yield based on trimethylene chlorohydrin or 92% yield based on recovered 2-methylpiperidine) of colorless product, b. p. 105–108° at 10–11 mm., $n^{25}D$ 1.4769 (lit.,[14] 60% yield, b. p. 112° at 15 mm., $n^{20}D$ 1.4780).

In a similar manner **3-(4-morpholinyl)-propanol** was prepared in 92% yield (twice distilled), b. p. 109–111° at 7–8 mm., $n^{25}D$ 1.4745 (lit.[15] 75% yield, b. p. 147–149° at 21 mm., $n^{25}D$ 1.4743), and **3-(1-piperidyl)-propanol** was prepared in 93% yield (twice distilled), b. p. 93.5–95° at 9 mm., $n^{25}D$ 1.4755 (lit.[12], 82% yield, b. p. 149° at 68 mm.; see also Brill[16]).

Dialkylaminoalkanethiols.—The two new dialkylaminoethanols used in the present work were prepared by the reaction between a secondary amine and ethylene oxide in boiling methanol, by a method similar to that of Pollard.[17] The alcohols were converted to the chloride hydrochlorides by treatment with thionyl chloride in chloroform solution. The thiols were then prepared by methods previously outlined.[18] The new compounds are listed in Table I.

Dialkylaminoalkyl Thiolbenzoates, Thiolcinnamates and Diphenylthiolacetates.—These compounds were prepared with little difficulty by the usual method. The thiol ester hydrochlorides were usually obtained crystalline directly from the reaction; however, in certain cases (*e. g.*, 2-(2-methylpiperidyl-1)-ethyl diphenylthiolactate) it was necessary to purify the isolated base by transference from acid to base twice, with appropriate washings. The hydrochlorides were crystallized from absolute alcohol–ethyl acetate or acetone–ethyl acetate. These compounds are listed in Table II.

2-(2-Methylpiperidyl-1)-ethyl 4-butyloxythiolbenzoate hydrochloride was prepared in quantitative yield by the reaction between 2-(2-methylpiperidyl-1)-ethanethiol and 4-butyloxybenzoyl chloride[19] in dry benzene. The compound crystallized from absolute alcohol in rosets of white needles, m. p. 171.4–173.0°.

Anal. Calcd. for $C_{19}H_{30}ClNO_2S$: Cl, 9.53; S, 8.61. Found: Cl, 9.32; S, 8.74.

In a similar manner there was obtained **2-diethylaminoethyl 4-hexyloxythiolbenzoate hydrochloride**, as white needles from ethyl acetate, m. p. 125.0–126.3°.

Anal. Calcd. for $C_{19}H_{32}ClNO_2S$: C, 61.02; H, 8.62; S, 8.57. Found: C, 61.13; H, 8.58; S, 8.65.

(10) All melting and boiling points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

(11) Adams, *et al.*, THIS JOURNAL, **59**, 2249 (1937).

(12) *Cf.* also the novel synthesis of these compounds by Hromatka, *Ber.*, **75**, 131 (1942).

(13) Prepared in 90% yield by the reduction of 2-methylpyridine (4 moles) with Raney nickel (40 g.) at 1000 lb. and 190°. The reduction required three hours. *Cf.* Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, pp. 64–67.

(14) McElvain and Carney, THIS JOURNAL, **68**, 2592 (1946).

(15) Cheney and Bywater, *ibid.*, **64**, 970 (1942); *cf.* Gardner and Haenni, *ibid.*, **53**, 2763 (1931), and ref. 12.

(16) Brill, *ibid.*, **47**, 1134 (1925).

(17) Pollard, *ibid.*, **57**, 1988 (1935).

(18) Clinton, Salvador, Laskowski and Suter, *ibid.*, **70**, 950 (1948).

(19) Rohmann, U. S. Patent 2,081,712 (1937).

TABLE II

THIOL ESTERS

R_2	n	Derivative	M. p., °C.	Formula	Analyses, % Calcd.	Found	Calcd.	Found
			Thiolbenzoates, $C_6H_5COS(CH_2)_nNR_2$					
$(C_2H_5)_2$	2	Hydrochloride	137–138.5	$C_{13}H_{20}ClNOS$	N, 5.12	5.41	S, 11.72	11.97
$(C_2H_5)_2$	3	Hydrochloride	93.6–96.2	$C_{14}H_{22}ClNOS$	Cl, 12.32	12.32	S, 11.14	11.32
$(C_2H_5)_2$	4	Hydrochloride	115.5–116.5	$C_{15}H_{24}ClNOS$	Cl, 11.76	11.98	N, 4.64	4.50
C_5H_{10}[a]	3	Hydrochloride	171–172.5	$C_{15}H_{22}ClNOS$	Cl, 11.82	11.90	N, 4.67	4.64
C_6H_{12}[b]	2	Hydrochloride	200.5–201.5	$C_{15}H_{22}ClNOS$	Cl, 11.82	11.72	S, 10.69	10.68
C_6H_{12}[b,c]	3	Hydrochloride	138.2–139.4	$C_{16}H_{24}ClNOS$	Cl, 11.30	11.10	S, 10.22	10.12
			Diphenylthiolacetates, $(C_6H_5)_2CHCOS(CH_2)_nNR_2$					
C_4H_8O[d]	2	Hydrochloride	205.4–206.5	$C_{20}H_{24}ClNO_2S$	Cl, 9.38	9.19	S, 8.48	8.38
C_6H_{12}[b]	2	Phosphate	170.5–171.0	$C_{22}H_{30}NO_5PS$	N, 3.10	2.96	S, 7.10	7.12
C_6H_{12}[b]	3	Hydrochloride	162–163.5	$C_{23}H_{30}ClNOS$	Cl, 8.77	8.55	S, 7.93	7.98
			Thiolcinnamates, $C_6H_5CH{=}CHCOS(CH_2)_nNR_2$					
$(CH_3)_2$	2	Hydrochloride	178.5–179.4	$C_{13}H_{18}ClNOS$	N, 5.15	5.15	S, 11.79	11.97
$(C_2H_5)_2$	2	Hydrochloride	156.5–158	$C_{15}H_{22}ClNOS$	Cl, 11.82	11.91	N, 4.67	4.65
$(C_2H_5)_2$	3	Hydrochloride	110–113.8	$C_{16}H_{24}ClNOS$	Cl, 11.30	11.41	S, 10.22	10.45
$(C_2H_5)_2$	4	Hydrochloride	131.8–133	$C_{17}H_{26}ClNOS$	Cl, 10.82	10.85	N, 4.27	4.21
C_5H_{10}[a]	3	Hydrochloride	177–179.5	$C_{17}H_{24}ClNOS$	N, 4.29	4.35	S, 9.83	9.98
C_6H_{12}[b]	2	Hydrochloride	193.3–194.6	$C_{17}H_{24}ClNOS$	Cl, 10.88	10.63	S, 9.83	9.82
C_6H_{12}[b]	3	Hydrochloride	163–165	$C_{18}H_{26}ClNOS$	Cl, 10.43	10.18	S, 9.43	9.54
			p-Nitrothiolbenzoates, $NO_2C_6H_4COS(CH_2)_nNR_2$					
$(CH_3)_2$	2	Hydrochloride[e]	191.6–194.2	$C_{11}H_{15}ClN_2O_3S$	Cl, 12.19	11.99	S, 11.03	10.99
$(C_2H_5)_2$	3	Hydrochloride	125–127	$C_{14}H_{21}ClN_2O_3S$	Cl, 10.65	10.35	S, 9.63	9.68
$(C_2H_5)_2$	4	Hydrochloride	160.5–162	$C_{15}H_{23}ClN_2O_3S$	Cl, 10.22	10.10	S, 9.24	9.32
C_4H_8O[d]	2	Hydrochloride	209.6–211	$C_{13}H_{17}ClN_2O_4S$	Cl, 10.65	10.62	S, 9.63	9.83
C_4H_8O[d]	3	Hydrochloride[f]	201–202	$C_{14}H_{19}ClN_2O_4S$	Cl, 10.23	10.08	S, 9.24	8.99
C_5H_{10}[a]	2	Hydrochloride	175–176.6	$C_{14}H_{19}ClN_2O_3S$	Cl, 10.72	10.73	S, 9.69	9.94
C_5H_{10}[a]	3	Hydrochloride	206–207.5	$C_{15}H_{21}ClN_2O_3S$	Cl, 10.28	10.07	S, 9.30	9.30
C_6H_{12}[b]	2	Hydrochloride	163.5–165.9	$C_{15}H_{21}ClN_2O_3S$	Cl, 10.28	10.00	S, 9.30	9.29
C_6H_{12}[b]	3	Hydrochloride	184–186	$C_{16}H_{23}ClN_2O_3S$	S, 8.93	8.72	...	...
C_5H_{10}[g]	2	Hydrochloride[h]	171.4–172	$C_{14}H_{19}ClN_2O_3S$	Cl, 10.72	10.45	S, 9.69	9.92
C_5H_{10}[g]	2	Picrate	194.5–196.0	$C_{20}H_{21}N_5O_{10}S$	N,[i] 2.67	2.67	...	...
			p-Aminothiolbenzoates, $NH_2C_6H_4COS(CH_2)_nNR_2$					
$(CH_3)_2$	2	Phosphate	187–189.2	$C_{11}H_{19}N_2O_5PS$	N, 8.64	8.41	S, 9.94	9.98
$(C_2H_5)_2$	3	Phosphate[j]	209.8–210.6	$C_{14}H_{25}N_2O_5PS$	N, 7.68	7.38	S, 8.79	8.82
$(C_2H_5)_2$	4	Phosphate	199.2–200.8	$C_{15}H_{27}N_2O_5PS$	N, 7.40	7.22	S, 8.47	8.32
C_4H_8O[d]	2	Phosphate	207–208	$C_{13}H_{21}N_2O_6PS$	S, 8.80	8.84	[k]	[k]
C_4H_8O[d]	2	Base	161–162	$C_{13}H_{18}N_2O_2S$	N, 10.52	10.30	...	...
C_4H_8O[a]	3	Phosphate	129–135.6	$C_{14}H_{23}N_2O_6PS$	N, 7.40	7.21	S, 8.47	8.50
C_5H_{10}[a]	2	Phosphate	204–206	$C_{14}H_{23}N_2O_5PS$	S, 8.85	8.79	[l]	[l]
C_5H_{10}[a]	2	Base	122.5–123.5	$C_{14}H_{20}N_2OS$	N, 10.60	10.32	S, 12.13	12.04
C_5H_{10}[a]	3	Phosphate[m]	210–211.2	$C_{15}H_{25}N_2O_5PS$	N, 7.44	7.22	S, 8.52	8.62
C_6H_{12}[b]	2	Phosphate	196.7–197.8	$C_{15}H_{25}N_2O_5PS$	S, 8.52	8.64	[n]	[n]
C_6H_{12}[b]	2	Base	98.5–99.5	$C_{15}H_{22}N_2OS$	S, 11.52	11.81	...	...
C_6H_{12}[b]	3	Flavianate[o]	223.4–224.0	$C_{68}H_{84}N_{10}O_{19}S_5$	S, 10.65	10.79	N, 3.72[p]	3.89
$(C_2H_5)_2$[q]	[r]	Phosphate	147–151	$C_{16}H_{29}N_2O_5PS$	N, 7.14	7.03	[s]	[s]
			p-Butylaminothiolbenzoates, $C_4H_9NHC_6H_4COS(CH_2)_nNR_2$					
$(CH_3)_2$	2	Dihydrochloride	157–161.5	$C_{15}H_{26}Cl_2N_2OS$	Cl, 20.07	20.07	S, 9.07	8.96
$(C_2H_5)_2$	2	Dihydrochloride	142.6–145.6	$C_{17}H_{30}Cl_2N_2OS$	Cl, 18.59	18.65	S, 8.40	8.52
$(C_2H_5)_2$	2	Citrate	154.6–156	$C_{23}H_{36}N_2O_8S$	N, 5.60	5.42	S, 6.40	6.22
$(C_2H_5)_2$	3	Dihydrochloride	138–139.8	$C_{18}H_{32}Cl_2N_2OS$	N, 7.08	7.34	S, 8.10	7.95
$(C_2H_5)_2$	4	Dihydrochloride	103.2–107	$C_{19}H_{34}Cl_2N_2OS$	Cl, 17.32	17.03	S, 7.83	7.72
C_4H_8O[d]	2	Dihydrochloride	196.4–199.2	$C_{17}H_{28}C_2N_2O_2S$	Cl, 17.93	17.65	S, 8.11	8.08
C_4H_8O[d]	2	Base	67–68	$C_{17}H_{26}N_2O_2S$	N, 8.68	8.40	....	...

TABLE II (*Continued*)

R_2	n	Derivative	M. p., °C.	Formula	Analyses, % Calcd.	Found	Calcd.	Found
C_4H_8O[d]	3	Dihydrochloride[t]	192.6–197.2	$C_{17}H_{30}Cl_2N_2O_2S$	Cl, 17.32	17.36	S, 7.83	7.66
C_5H_{10}[a]	2	Dihydrochloride	200.4–203.4	$C_{18}H_{30}Cl_2N_2OS$	Cl, 18.02	17.75	S, 8.15	7.92
C_5H_{10}[a]	2	Base	65.5–67.0	$C_{18}H_{28}N_2OS$	N, 8.74	8.64	....	...
C_5H_{10}[a]	3	Dihydrochloride	186–188.4	$C_{19}H_{32}Cl_2N_2OS$	Cl, 17.40	17.35	S, 7.87	7.68
C_6H_{12}[b]	2	Sesquiphosphate[u]	112.5–124.5	$C_{38}H_{69}N_4O_{14}P_3S_2$	S, 6.66	6.79	N, 5.82	5.78
C_6H_{12}[b]	3	Dihydrochloride	170.8–173.4	$C_{20}H_{34}Cl_2N_2OS$	Cl, 16.82	16.51	S, 7.60	7.69
C_6H_{12}[b]	3	Picrolonate	134–137	$C_{30}H_{40}N_6O_6S$	N,[i] 4.57	4.32	...	...

[a] 1-Piperidyl. [b] 2-Methylpiperidyl-1. [c] Reported (ref. 4) m. p. 137–138°. [d] 4-Morpholinyl. [e] Reported m. p. 187° (dec.) [Renshaw, Dreisbach, Ziff and Green, THIS JOURNAL, **60**, 1765 (1938)]. [f] The crude base crystallized in pale yellow plates from dilute alcohol, m. p. 62.5–64.0°. [g] 2-Methylpyrrolidyl-1. [h] The crude base had m. p. 53–55° (from Skellysolve B). [i] Ref. 22. [j] *Cf.* ref. 5. [k] Calcd.: H_3PO_4, 26.90. Found: H_3PO_4, 26.70. [l] Calcd.: H_3PO_4, 27.05. Found: H_3PO_4, 26.80. [m] The base crystallized from dilute alcohol as an unstable hydrate, m. p. 78–80°, and from benzene–Skellysolve B in the anhydrous form, m. p. 60–61°. [n] Calcd.: H_3PO_4, 26.05. Found: H_3PO_4, 25.96. [o] The compound formed a flavianate with a base to flavianic acid ratio of 3:2. [p] Nitro nitrogen, by titration with titanous chloride in glacial acetic acid solution. [q] For the 4-nitrothiolbenzoate see ref. 3. [r] 4-Diethylamino-1-methylbutyl-. [s] Calcd.: C, 48.96; H, 7.44. Found: C, 49.01; H, 7.22. [t] The crude base had m. p. 50–52° (from benzene–Skellysolve B). [u] Calcd.: H_3PO_4, 30.54. Found: H_3PO_4, 31.00.

2-Diethylaminoethyl 2-butyloxyquinoline-4-thiolcarboxylate hydrochloride, from the cinchonyl chloride[20] and the thiol, formed pale yellow cottony needles from absolute alcohol–ethyl acetate–ether, m. p. 161–162°. The compound was difficultly soluble in water.

Anal. Calcd. for $C_{20}H_{29}ClN_2O_2S$: S, 8.08; Cl, 8.93. Found: S, 8.00; Cl, 8.70.

3-(Piperidyl-1)-propyl 2-butyloxyquinoline-4-thiolcarboxylate hydrochloride crystallized from absolute alcohol–ethyl acetate in slender white needles, m. p. 149–150°.

Anal. Calcd. for $C_{22}H_{31}ClN_2O_2S$: S, 7.58; Cl, 8.38. Found: S, 7.47; Cl, 8.36.

Dialkylaminoalkyl 4-Alkylaminothiolbenzoates.—The preparation of the intermediate dialkylaminoalkyl 4-nitrothiolbenzoates was effected by the reaction between 4-nitrobenzoyl chloride and the thiol in cold benzene, or in a chloroform–water–sodium bicarbonate admixture.[18] These compounds are listed in Table II. Reduction to the 4-aminothiolbenzoates was preferably carried out by a method similar to that of West,[21] since the ferrous sulfate–ammonia method used with similar types[18] offered no evident advantages in this case. Certain of the resulting dialkylaminoalkyl 4-aminothiolbenzoates (see Table II) were obtained crystalline. In the case of 2-(2-methylpyrrolidyl-1)-ethyl 4-nitrothiolbenzoate, a pure 4-amino base could not be isolated, nor were pure salts obtained from this compound.

The dialkylaminoalkyl 4-alkylaminothiolbenzoates were prepared either by reductive alkylation of the 4-amino compounds with an aldehyde in the presence of zinc dust and acetic acid, or directly from a 4-alkylaminobenzoyl chloride hydrochloride and a dialkylaminoalkanethiol. The former method was found preferable, since purification was more easily effected. The bases thus obtained were in most cases mobile, pale yellow oils, which readily yielded crystalline salts. The dialkylaminoalkyl 4-butylaminothiolbenzoates are listed in Table II; other homologs and a representative example of the reductive alkylation procedure appear below.

2-Diethylaminoethyl 4-Butylaminothiolbenzoate.—A stirred mixture of 20.0 g. (0.079 mole) of 2-diethylaminoethyl 4-aminothiolbenzoate,[2] 20.6 g. (0.32 mole) of zinc dust, 19.5 g. (0.33 mole) of glacial acetic acid and 100 ml. of benzene was brought to reflux on the steam-bath. During the course of twenty minutes there was added dropwise a solution of 6.9 g. (0.096 mole) of *n*-butyraldehyde in 20 ml. of benzene. After the addition was complete, refluxing and stirring were continued for an additional hour. The resulting mixture was filtered and the zinc–zinc acetate precipitate was washed thoroughly with warm dilute acetic acid and with benzene. The cooled filtrate, after being made basic to litmus with 35% sodium hydroxide solution, was filtered if necessary and the benzene layer separated. A further extraction of the aqueous layer with benzene, followed by concentration of the dried benzene extract *in vacuo*, gave 23.0 g. of residual mobile, pale yellow oil.

2-Diethylaminoethyl 4-propylaminothiolbenzoate, from the 4-amino compound[2] and propionaldehyde; the **picrate** crystallized from alcohol in canary-yellow needles, m. p. 129.5–131.3°.

Anal. Calcd. for $C_{22}H_{29}N_5O_8S$: N,[22] 5.35. Found: N,[22] 5.22.

The **dihydrochloride** crystallized from absolute alcohol–acetone–ethyl acetate in massive, pale yellow prisms, m. p. 152.4–153.5°.

Anal. Calcd. for $C_{16}H_{28}Cl_2N_2OS$: Cl, 19.30; S, 8.73. Found: Cl, 19.30; S, 8.77.

2-Diethylaminoethyl 4-Amylaminothiolbenzoate, Method A.—Reductive alkylation of ethyl 4-aminobenzoate with *n*-valeraldehyde gave a 95% yield of **ethyl 4-amylaminobenzoate**, white prisms from Skellysolve B, m. p. 54.0–55.0°.

Anal. Calcd. for $C_{14}H_{21}NO_2$: N, 5.95. Found: N, 6.05.

Saponification of the ester with aqueous-alcoholic sodium hydroxide solution gave a 99% yield of **4-amylaminobenzoic acid**, white needles from dilute alcohol, m. p. 135.5–136.5°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.65.

The acid was converted to the chloride hydrochloride either by the phosphorus pentachloride procedure of Graf and Langer[23] or the thionyl chloride procedure of Mndzhoyan[24]; the resulting 4-amylaminobenzoyl chloride hydrochloride was used without purification because of instability. Condensation with 2-diethylaminoethanethiol in benzene gave, after several purifications by crystallization and conversion to the base, a 45% yield of 2-diethylaminoethyl 4-amylaminothiolbenzoate as a pale yellow oil.

Method B.—The reductive alkylation of 2-diethylaminoethyl 4-aminothiolbenzoate[2] with *n*-valeraldehyde gave a 90% yield of an easily purified base.

The **picrate** formed pale orange needles from alcohol, m. p. 120.2–121.2°.

Anal. Calcd. for $C_{24}H_{33}N_5O_8S$: N,[22] 5.08. Found: N,[22] 4.83.

(20) Gardner and Hammel, THIS JOURNAL, **58**, 1360 (1936); see also ref. 1.

(21) West, *J. Chem. Soc.*, **127**, 494 (1925).

(22) Basic amino nitrogen, by titration with perchloric acid in acetic acid solution.

(23) Graf and Langer, *J. prakt. Chem.*, **148**, 161 (1937).

(24) Mndzhoyan, *J. Gen. Chem.* (*U. S. S. R.*), **16**, 1033 (1946); [*C. A.*, **41**, 2737 (1947)].

A crystalline dihydrochloride was also isolated, but its extreme hygroscopicity prevented purification for analysis.

2-Diethylaminoethyl 4-heptylaminothiolbenzoate citrate, prepared from the base (reductive alkylation with *n*-heptaldehyde) and citric acid monohydrate in acetone, crystallized in rosets of tiny white needles from absolute alcohol–ethyl acetate, m. p. 123–124° (dec.).

Anal. Calcd. for $C_{26}H_{42}N_2O_8S$: N, 5.16; S, 5.91. Found: N, 4.70; S, 6.04.

2-Diethylaminoethyl 4-(5-hydroxyamylamino)-thiolbenzoate, from the 4-amino base[2] and 5-hydroxypentanal,[25,26] crystallized from benzene–Skellysolve B in large white prisms, m. p. 72.3–73.6°.

Anal. Calcd. for $C_{18}H_{30}N_2O_2S$: N, 8.28; S, 9.47. Found: N, 8.15; S, 9.53.

(25) Woods and Sanders, THIS JOURNAL, **68**, 2111 (1946); *Org. Syn.*, **27**, 43 (1947). Comparable yields were obtained when the preparation was modified by saturation of the neutralized hydrolysis mixture with ammonium sulfate, followed by a single ether extraction. This obviates the continuous ether extraction.

(26) The final reflux period, after the addition of the hydroxyaldehyde, was extended to two hours.

The **picrate** formed tiny orange-yellow needles from alcohol, m. p. 96.6–98.2°.

Anal. Calcd. for $C_{24}H_{33}N_5O_9S$: N,[22] 4.94. Found: N,[22] 4.79.

The **phosphate** crystallized from alcohol–acetone in rosets of white cottony needles, m. p. 163.6–164.4°.

Anal. Calcd. for $C_{18}H_{33}N_2O_6PS$: S, 7.35; H_3PO_4, 22.46. Found: S, 7.34; H_3PO_4, 22.51.

Summary

There has been described the preparation of a series of dialkylaminoalkyl thiol esters derived from the benzoyl, cinnamoyl, 4-aminobenzoyl, 4-alkylaminobenzoyl, 4-alkoxybenzoyl and 2-butyloxyquinoline-4-carbonyl nuclei. Modifications in the preparation of certain intermediates, leading to increased yields, have also been described.

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On an Alkaloid of *Kopsia Fruticosa.* I

BY A. BHATTACHARYA, A. CHATTERJEE[1] AND P. K. BOSE

Kopsia fruticosa, A.D. (*Apocynaceae*) is a large, evergreen shrub of the East Indies, which has been now naturalized in India. It was used as an arrow poison. All *Kopsia* species so far investigated have been found to contain alkaloids. Thus, a crystalline alkaloid has been isolated from the seeds of *K. flavida* Bl.[2]; the presence of three other alkaloids has been reported in *K. arborea* Bl., *K. albiflorum*, Bl., and *K. Roxburghii*[2] Bl. From *K. fruticosa* we have obtained a new alkaloid, kopsine, $C_{22}H_{26}N_2O_4$, m. p. 217–218° (dec.), $[\alpha]^{20}D$ +16.4° (in ethyl alcohol), and we wish to report its isolation and properties. Our mature leaves contained 0.12% kopsine and in the bark 0.06% was found (on the basis of dry weight). Thus, for large scale extraction, the leaves were preferred. Kopsine (in alcohol) is neutral to litmus. The solution shows green fluorescence. Its molecular extinction curve is represented in Fig. 1. The curve shows the maxima at 240 and 283 mμ and minima at 264, 279 and 286 mμ. The absorption spectra of kopsine are similar to those of indole alkaloids.[3,4] Kopsine does not show a coloration with ferric chloride but it gives the following reactions: concentrated sulfuric acid, colorless in the cold, pinkish upon heating; Erdmann reagent, gradual appearance of apple-green color; Fröhde reagent, solution slowly turns pink; Mandelin reagent, dissolves the alkaloid with permanganate-like color which gradually turns olive-green.

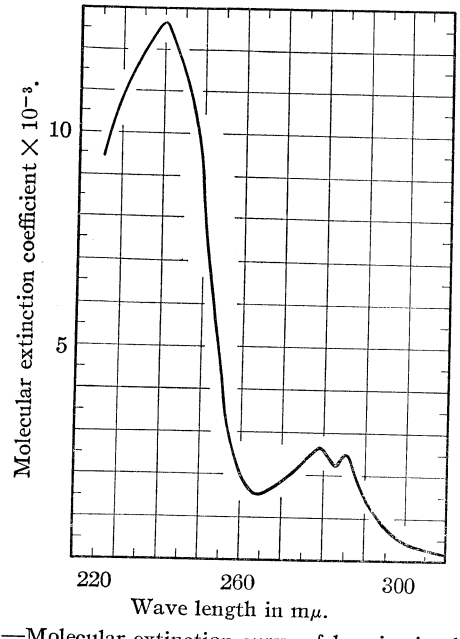

Fig. 1.—Molecular extinction curve of kopsine in alcohol.

A solution of kopsine in hydrochloric or sulfuric acid produces an orange precipitate with potassium bismuth iodide, a yellow precipitate with picric acid and a white precipitate with potassium mercuric iodide. (So far it has not been possible to prepare kopsine salts with some common mineral acids (HCl, HNO_3 and H_2SO_4, etc.) because of resinification). It forms, however, well defined

(1) Née Mookerjee.

(2) M. Greshoff, *Ber.*, **23**, 3537 (1890).

(3) M. S. Kharasch, D. W. Stanger, M. A. Bloodgood and R. R. Legault, *Science*, **83**, 36 (1936).

(4) W. A. Jacobs, L. C. Craig and A. Rothen, *ibid.*, **83**, 166 (1937).

salts with perchloric, picric, oxalic, chloroauric and chloroplatinic acids and then behaves as a monoacidic base. Both the base and its salts taste bitter. Kopsine contains one methoxyl. Dioxymethylene, carbonyl, hydroxyl and N-methyl groups are absent. The presence of two active hydrogens has been observed. On catalytic hydrogenation dihydrokopsine is formed. Kopsine readily yields a methiodide and gives negative tests for primary and secondary amino groups which suggests that the basic nitrogen atom is tertiary.

Kopsine is insoluble in cold alkali but is decomposed by hot ammonia to give a new base, kopsidine, $C_{20}H_{24}N_2O_3$, m. p. 142°, $[\alpha]^{25}D$ +30.2° (in alcohol), which yields a well crystallized picrate, m. p. 190° (dec.). Kopsidine dissolves in concentrated sulfuric acid and shows the following reactions: Erdmann reagent, olive-green; Fröhde reagent, the colorless solution slowly turns pink; Mandelin reagent, the purple solution gradually turns bottle-green.

Kopsidine contains the O-methyl group. On the basis of the empirical formulas kopsidine might be a deacetylation product of kopsine; however, kopsidine cannot be acetylated to kopsine.

Experimental

Isolation of Kopsine.—The coarsely powdered leaves (5 kg.) were extracted in a percolator with alcohol (10 liters, acidified with 10 ml. of glacial acetic acid) for four weeks. The deep green extract was concentrated to 100 ml. *in vacuo*. The viscous residue was poured into 0.5 liter of iced water. Overnight a thick, dark, tarry mass separated. The clear supernatant liquid was decanted and the tarry mass digested with 5 × 50 ml. of water (shaking). The filtrate was combined with the bulk of the decanted liquid, cooled in ice-water and basified with sodium bicarbonate. The separated kopsine was taken up in 200 ml. of chloroform; the extract was washed with water, dried over sodium sulfate and concentrated to 25 ml. This solution was diluted with 1 vol. of alcohol and kept overnight. Pale-yellow, glistening crystals of kopsine (6 g.), coated with a slimy mass, were thus obtained. On several crystallizations from acetone, alcohol, benzene and ethyl acetate, the m. p. increased from 198–220° to 208–210° (dec.). The base was dissolved in 100 ml. of 1% hydrochloric acid, filtered from the slimy mass and basified with sodium bicarbonate. The alkaloid crystallized from alcohol in colorless plates, m. p. 213–214° (dec.). By repeating this procedure thrice, it was obtained in the pure state, m. p. 217–218° (dec.). Samples regenerated from the picrate or oxalate showed the same m. p. Kopsine is freely soluble in chloroform, sparingly in methanol, ethanol, ethyl acetate, benzene and ether; it is insoluble in petroleum ether or water.

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.10; H, 6.80; N, 7.30; OCH_3, 8.11. Found: C, 69.35, 69.56; H, 6.43, 6.25; N, 7.47, 7.44; OCH_3, 8.28, 8.32.

Kopsine picrate was prepared by adding an ethereal solution of kopsine to picric acid (in ether). The yellow precipitate crystallized from alcohol in glistening yellow rods, m. p. 230° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot C_6H_3O_7N_3 \cdot 2C_2H_5OH$: N, 9.96. Found: N, 10.2.

Kopsine Oxalate.—An ethereal solution of anhydrous oxalic acid (0.2 g.) was added to 0.2 g. of kopsine (in ether). The colorless precipitate (0.15 g.) was washed acid-free and recrystallized from alcohol and acetone; prisms, m. p. 154° (dec.). It is highly soluble in water, acidic to litmus and liberates iodine from potassium iodide and potassium iodate.

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot C_2H_2O_4$: N, 5.93; Found: N, 6.1.

Kopsine Perchlorate.—One-quarter gram of powdered alkaloid was added slowly to perchloric acid (5 ml., 70%) diluted with 1 vol. of water. The colorless precipitate (0.27 g.) crystallized from water containing a little perchloric acid in needles, m. p. 284° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot HClO_4 \cdot 5H_2O$: Cl, 6.19. Found: Cl, 5.9.

Kopsine chloroplatinate was prepared by adding an aqueous solution of platinic chloride (5%) to a faintly acidic solution (HCl) of kopsine. Upon crystallization from water containing a little hydrochloric acid, glistening orange colored rods separated, which did not melt but decomposed above 150°.

Anal. Calcd. for $(C_{22}H_{26}N_2O_4)_2 \cdot H_2PtCl_6$: Pt, 16.6. Found: Pt, 16.12.

Kopsine Chloroaurate.—One-half gram of kopsine was dissolved in hydrochloric acid (2 *N*, 5 ml.) and an aqueous solution of auric chloride was added until precipitation was complete. The golden yellow rods were recrystallized from water containing a little hydrochloric acid; m. p. 203–205° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot HAuCl_4$: Au, 27.30. Found: Au, 27.30.

Kopsine Methiodide.—0.15 g. of kopsine was dissolved in dry acetone (8 ml.). Freshly distilled methyl iodide (1 ml.) was added and the mixture was kept overnight. The solution was concentrated *in vacuo* to a viscous residue which crystallized from alcohol; colorless plates, m. p. 200° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot MeI$: NMe, 5.54. Found: NMe, 4.83.

Determination of Active Hydrogen in Kopsine (Zerewitinoff).—0.05 g. of kopsine in 5 ml. of dry pyridine yielded 6 ml. of methane (0°, 760 mm.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: H, 0.526. Found: H, 0.53.

Catalytic Hydrogenation of Kopsine.—Kopsine (0.2736 g.), dissolved in glacial acetic acid (10 ml.), was treated with hydrogen and Adams platinum oxide catalyst (0.15 g.) which had been previously saturated with hydrogen. The absorption of hydrogen (17 ml. at 30°, 760 mm.) corresponded to two atoms of hydrogen per mole. The solution was filtered, diluted with water and basified with sodium bicarbonate. The base was taken up in 100 ml. of ether. The colorless ethereal digest was washed with water, dried over sodium sulfate and distilled. The residue was successively crystallized from acetone, ethanol, ethyl acetate and benzene; colorless crystals, m. p. 218° (dec.). Dihydrokopsine showed a m.p. depression of 26° when mixed with kopsine.

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.75; H, 7.29; N, 7.29. Found: C, 68.32; H, 7.50; N, 7.62.

Hydrolysis of Kopsine and Isolation of Kopsidine.—A half gram of kopsine in alcohol (5 ml.) was refluxed with 10% ammonia (2 ml.) for six hours. The clear solution deposited overnight colorless prisms, m. p. 140–142°. After recrystallizations from ethanol, ethyl acetate and acetone, the m. p. was found to be 142°. Kopsidine is soluble in methanol, ethanol, ether, ethyl acetate or benzene and is insoluble in petroleum ether and water; $[\alpha]^{25}D$ +30.2° (in alcohol).

Anal. Calcd. for $C_{20}H_{24}N_2O_3$: C, 70.59; H, 7.05; N, 8.26; OMe, 9.12. Found: C, 70.28; H, 6.75; N, 7.92; OMe, 8.82.

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Summary

From *Kopsia fruticosa* a new alkaloid, termed kopsine, $C_{22}H_{26}N_2O_4$, m. p. 217–218° (dec.), has

been obtained. The isolation and properties of this alkaloid have been studied. On hydrolysis, it yields a base, kopsidine, $C_{20}H_{24}N_2O_3$, m. p. 142°; and on hydrogenation, a dihydro derivative, m. p. 218° (dec.).

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A New Series of Testosterone Esters

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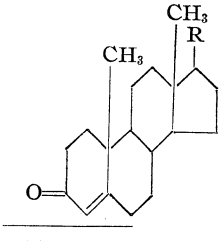
The literature is replete with attempts by workers in the field to prepare esters of testosterone which would show both more intensive and more prolonged androgenic action than testosterone itself. It was shown in early studies[2] that the lower aliphatic acid esters are most effective; as one increases the length of the carbon chain in the fatty acid residue, the effect becomes more prolonged but the intensity decreases rapidly. Ruzicka,[3] by his preparation and testing of the acetate and benzoate esters, initiated work which resulted in the general adoption of testosterone propionate as an activated form of testosterone. These workers[4] prepared a long series of aliphatic acid esters. Miescher's group[5] made a study of halogenated, aminated, and unsaturated aliphatic esters as well as carbonate esters. This latter group of workers[6] also studied the enol diesters of testosterone. Rabold and Dietrich[7] have made a study of the glucoside and tetraacetyl glucoside. The patent literature[8] describes a sulfonic acid and a phosphoric acid ester.

However, since it was felt that the field had not been combed thoroughly enough in view of the importance of the problem, there has been prepared a new series of esters several of which show activities surpassing testosterone propionate in rat tests where the weight increase of the seminal vesicles and the prostate was studied. A preliminary summary of the results obtained is shown in Table III. More complete biological results will be published[9] at a later date.

Esters of the general types



I, R = —OCOR′
II, R = —OCOR″—Y—R‴
III, R = —OCOR″OCOR‴

have been prepared (Table III) where R′ is of the carbocyclic or heterocyclic type, R″ and R‴ are various aliphatic or aromatic radicals and Y is oxygen or sulfur. Types I and III have been prepared from the acid chlorides and type II from the acid chlorides and anhydrides.

The acids shown in Table I were prepared by three methods. Method A involves the reaction of the appropriate sodium alkoxide or mercaptide with a halogenated acid. The second method, B, was used only to make ethyl or methylmercapto acids by the alkylation of the appropriate mercapto acid with ethyl or methyl sulfates. Method C involves hydrolysis of the corresponding nitrile.

In preparing the acid chlorides shown in Table II, both thionyl chloride (D) and phosphorus trichloride (E) were used. Phosphorus trichloride possesses the advantage that a colorless product almost always results. This is of decided advantage in the preparation of a color-free ester. Furthermore, in some instances in which thionyl chloride results in tar formation, phosphorus trichloride gives a fair yield of product. From the viewpoint of yield, however, thionyl chloride is usually to be preferred.

Some of the acids and acid chlorides described are old compounds but are included where the characterization is somewhat more complete than that described in the literature. Those acids which were obviously used but not described may be found elsewhere in the literature.

Experimental

***n*-Butylmercaptoacetic Acid (Method A).**—To 21.6 g. of *n*-butylmercaptan (0.24 mole) dissolved in 200 cc. of 18% sodium hydroxide solution was added 20.8 g. of chloroacetic acid (0.22 mole) dissolved in 100 cc. of 18% sodium hydroxide. The mixed solutions were heated for two hours on a steam-bath. The solution was then cooled and acidified and the product extracted with ether and distilled. Distillation gave 29 g. of product, b. p., 136–137° at 10 mm.

2-Ethylmercaptopropanoic Acid (Method B).—A solution of 43.5 g. (0.41 mole) of 2-mercaptopropanoic acid was prepared by dissolving it in a solution containing 36 g. (0.9 mole) of sodium hydroxide in 45 cc. of water. While this solution was being stirred and heated on a steam-bath 63.2 g. (0.41 mole) of diethyl sulfate was added dropwise. Heating was continued until a single phase resulted. The solution was cooled, acidified with dilute sulfuric acid, and extracted with ether three times. The ether was evaporated and the residue distilled, yielding 24.5 g. of product, b. p. 111–113° at 8 mm.

4-Methylmercaptobutanoic Acid (Method C).—Eighteen grams of methyl mercaptan (0.37 mole) was dissolved

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(2) Miescher, Wettstein and Tschopp, *Biochem. J.*, **30**, 1970 (1936).
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(4) Ruzicka and Wettstein, *Helv. Chim. Acta*, **19**, 1141 (1936).
(5) Miescher, *et al.*, *Biochem. Z.*, **294**, 39 (1937).
(6) Miescher, Fischer and Tschopp, *Biochem. Z.*, **300**, 14 (1938).
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(8) Hartmann, Wettstein, U. S. Patent 2,182,920.
(9) By A. J. Bergman.

TABLE I

ACIDS

	B. p. °C.	Mm.	$n^{25}D$	Yield, %	Method	Molecular formula	Analyses, % sulfur Calcd.	Found
n-$C_3H_7SCH_2COOH$	126–128	11	1.4805	83	A	$C_5H_{10}O_2S$	23.89	23.78
i-$C_3H_7SCH_2COOH$	118–119	10	1.4788	65	A	$C_5H_{10}O_2S$	23.89	24.19
				39	B			
n-$C_4H_9SCH_2COOH$	136–137	10	1.4780	89	A	$C_6H_{12}O_2S$	21.63	21.13, 21.18
$CH_3SCH_2CH_2COOH$	119–123	12	1.4884	88	B	$C_4H_8O_2S$	26.68	26.86
$CH_3CH(SCH_3)COOH$	105–106	8	1.4815	27	B	$C_4H_8O_2S$	26.68	26.94
$CH_3CH(SC_2H_5)COOH$	111–113	8	1.4764	45	B	$C_5H_{10}O_2S$	23.89	24.25
$CH_3SCH_2CH_2CH_2COOH$	130	9	1.4823	65[a]	C	$C_5H_{10}O_2S$	23.89	23.44
$CH_3CH_2CH(SCH_3)COOH$	115–116	8	1.4788	71	A	$C_5H_{10}O_2S$	23.89	23.60
n-$C_3H_7SCH_2CH_2CH_2COOH$	168–170	23	1.4778	78[a]	C	$C_7H_{14}O_2S$	19.76	19.38
i-$C_3H_7OCH_2COOH$	96–98	9	1.4190	80	A	$C_5H_{10}O_3$	C, 50.83	50.99
							H, 8.53	8.60

[a] This yield is an over-all yield for condensation of a sodium mercaptide with a halogenated nitrile and hydrolysis of the resulting product.

TABLE II

ACID CHLORIDES

	B. p. °C.	Mm.	$n^{25}D$	Chlorination agent	Yield, %	Molecular formula	Analyses, % chlorine Calcd.	Found
CH_3SCH_2COCl	49–50	14	1.4967	E	45	C_3H_5ClOS	28.46	28.28
$C_2H_5SCH_2COCl$	61–64	14	1.4888	D	75	C_4H_7ClOS	25.58	25.57
n-$C_3H_7SCH_2COCl$	63–64	8	1.4846	D	92	C_5H_9ClOS	23.23	23.10
i-$C_3H_7SCH_2COCl$	57–58	8	1.4820	D	99	C_5H_9ClOS	23.23	23.55
n-$C_4H_9SCH_2COCl$	83–84	8	1.4828	D	90	$C_6H_{11}ClOS$	21.31	21.58
$C_6H_5SCH_2COCl$	117–119	6	1.5806	D	93	C_8H_7ClOS	18.99	18.80
$C_6H_5CH_2SCH_2COCl$	130	5.5	1.5682	D	67	C_9H_9ClOS	17.67	17.51
$CH_3SCH_2CH_2COCl$	96–97	45	1.4941	E	37	C_4H_7ClOS	25.58	25.60
$CH_3CH(SCH_3)COCl$	77–78	45	1.4873	E	52	C_4H_7ClOS	25.58	25.20
$CH_3CH(SC_2H_5)COCl$	56–57	8	1.4805	E	64	C_5H_9ClOS	23.23	23.35
$CH_3SCH_2CH_2CH_2COCl$	98–100	20	1.4898	E[a]	80	C_5H_9ClOS	23.23	22.98
$CH_3CH_2CH(SCH_3)COCl$	58–59	8	1.4835	E	83	C_5H_9ClOS	23.23	23.06
n-$C_3H_7SCH_2CH_2CH_2COCl$	106–108	9	1.4835	E	79	$C_7H_{13}ClOS$	19.62	19.45
i-$C_3H_7OCH_2COCl$	139–141	760	1.4188	E	92	$C_5H_9ClO_2$	26.00	25.70
$CH_3OCH_2CH_2COCl$	137–138	760	1.4260	E	70	$C_4H_7ClO_2$	28.93	29.40
$C_2H_5OCH_2CH_2COCl$	150–151	760	....	E	72	$C_5H_9ClO_2$	26.00	26.17
$CH_2CH_2CH_2CHCOCl$[b] (O)	80–81	30	1.4592	E	70	$C_5H_7ClO_2$	26.33	26.35
$C_2H_5COOCH_2COCl$	58	10	1.4265	..	..	$C_5H_7ClO_3$	22.64	22.54
$(CH_3SCH_2CO)_2O$	111–112	0.25	1.5162	..	62	$C_6H_{10}O_3S_2$	C, 37.09	37.12
							H, 5.18	5.32
							S, 28.77	28.98
$(C_2H_5SCH_2CO)_2O$	94	0.07	1.5030	..	60	$C_8H_{14}O_3S_2$	C, 43.36	43.52
							H, 6.33	6.61

[a] Using thionyl chloride, only tar results. [b] Decomposes violently on standing at room temperature for some time.

in 125 cc. of 35% sodium hydroxide solution and 125 g. of crushed ice. To this was added 25.8 g. (0.25 mole) of 4-chlorobutanenitrile in 100 cc. of 95% ethanol. The solution was refluxed for two and one-half hours. After diluting the reaction mixture with water, it was extracted with ether to remove unhydrolyzed nitrile. The alkaline solution was then acidified with hydrochloric acid and again extracted with ether. There resulted 18.6 g. of product, b. p. 129–130° at 9 mm.

***n*-Butylmercaptoacetyl Chloride (Method D).**—A mixture of 23.8 g. (0.16 mole) of *n*-butylmercaptoacetic acid and 29 cc. of thionyl chloride was heated gently on a steam-bath until evolution of hydrogen chloride ceased. The residue was distilled to give 24.2 g. of product, b. p., 83–84° at 8 mm.

2-Ethylmercaptopropanol Chloride (Method E).—A mixture of 21.3 g. (0.16 mole) of 2-ethylmercaptopropanoic acid and 8.8 g. (0.064 mole) of phosphorus trichloride was allowed to stand overnight and then heated on a steam-bath for one hour. The product was decanted from the sirupy phosphoric acids. Distillation gave 15.4 g. of product, b. p. 56–57°, at 8 mm.

Ethylmercaptoacetic Anhydride.—A solution of 370 g. (3.1 mole) of ethylmercaptoacetic acid in 1100 g. of acetic anhydride was refluxed for six hours and then fractionally distilled. The product was collected at 100–103° at 0.1 mm., yield 166 g.

Testosterone *n*-Butoxyacetate.—Six-tenths gram of testosterone was dissolved in 25 cc. of dry ether with 4 cc. of dry pyridine. To this was added 1 g. of *n*-butoxyacetyl chloride in 10 cc. of dry ether. A solid immediately precipitated. The suspension was refluxed for one-half hour and poured into water. The ether extract was washed with dilute sodium carbonate solution, dilute sulfuric acid and water. The ether was evaporated and the residue taken up in Skellysolve A containing about 20% of ether.

TABLE III

TESTOSTERONE ESTERS[d]

R	M. p., °C.	Activity[a]	Molar extinction coef. × 10^3	Position of max.[b] λ in mμ	$[\alpha]D^b$ at	X, °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Calcd.	Sulfur Found	Molecular formula
CH_3CH_2COO-	120–121	100	16.9	241	88.3	25	76.67	76.88	9.37	9.15			$C_{22}H_{32}O_3$
CH_3OCH_2COO-	110[c]	97	16.8	240–241	84.6	27	73.33	73.01	8.96	8.96			$C_{22}H_{32}O_4$
$C_2H_5OCH_2COO-$	122.5–124	121 × 7*	17.1	240–241	77.9	25	73.76	73.96	9.15	9.16			$C_{23}H_{34}O_4$
n-$C_3H_7OCH_2COO-$	88–89	103	17.0	240	75.9	29	74.20	74.33	9.35	9.23			$C_{24}H_{36}O_4$
i-$C_3H_7OCH_2COO-$	81–82	...	16.5	240–241	...	..	74.20	73.88	9.35	9.03			$C_{24}H_{36}O_4$
n-$C_4H_9OCH_2COO-$	61.5–63	111	15.6	240	63.0	29	74.58	74.66	9.51	9.43			$C_{25}H_{38}O_4$
$CH_3OCH_2CH_2COO-$	110–112	93 ± 6*	17.0	239–242	79.6	25	73.76	73.83	9.15	9.06			$C_{23}H_{34}O_4$
$C_2H_5OCH_2CH_2COO-$	53–55	102	16.6	240	74.7	29	74.20	74.40	9.35	9.12			$C_{24}H_{36}O_4$
i-$C_3H_7OCH_2CH_2COO-$	62–63.5	88	16.8	241	76.0	29	74.58	74.78	9.51	9.38			$C_{25}H_{38}O_4$
$CH_3OCH_2CH_2CH_2COO-$	55–57	123 ± 4*	17.1	240–241	88.4	26	74.20	74.03	9.35	9.19			$C_{24}H_{36}O_4$
$CH_2CH_2CHCOO-$ (ring)	149–151	<100	16.7	240–241	84.4	26	77.27	77.28	9.30	9.00			$C_{23}H_{32}O_3$
$CH_2CH_2CH_2CH—COO-$ (ring)	110–111	<100	16.5	240–241	80.7	24	77.79	77.83	9.25	9.11			$C_{24}H_{34}O_3$
$CH_2CH_2CH_2CHCOO-$ (ring, O)	116–117	<100	16.7	240–241	76.6	26	74.57	74.46	8.82	8.68			$C_{24}H_{34}O_4$
$CH=CH—CH=C—COO-$ (ring, O)	221[c]	<100	29.5	244–246	170.5	27	75.13	74.87	7.89	8.42			$C_{24}H_{30}O_4$
CH_3COOCH_2COO-	110–112[c]	*ca.* 100	16.5	240–241	65.3	27	73.76	73.83	9.15	9.06			$C_{23}H_{32}O_5$
$CH_3COOCH_2CH_2COO-$	112[c]	*ca.* 100	16.8	240–241	62.8	27	71.64	71.64	8.86	8.52			$C_{24}H_{34}O_5$
CH_3SCH_2COO-	100–101	133 ± 3*	17.3	239–240	82.5	26	70.17	70.19	8.57	8.59	8.52	8.77	$C_{22}H_{32}O_3S$
$C_2H_5SCH_2COO-$	99–100	123 ± 5*	17.1	240–241	84.4	25	70.73	70.68	8.77	8.64	8.21	8.18	$C_{23}H_{34}O_3S$
n-$C_3H_7SCH_2COO-$	69.5–70.5	121 ± 6*	17.4	240	85	26	71.24	71.10	8.97	8.98	7.91	8.02	$C_{24}H_{36}O_3S$
i-$C_3H_7SCH_2COO-$	75–76	111 ± 2*	17.2	240–242	87.5	29	71.24	71.30	8.97	8.87	7.91	7.84	$C_{24}H_{36}O_3S$
$C_6H_5SCH_2COO-$	120.5–122	99	22.7	240	76.1	29	73.93	73.29	7.81	7.54	7.31	7.56	$C_{27}H_{34}O_3S$
$C_6H_5CH_2SCH_2COO-$	80.5–82	46	18.2	239–241	76.4	26	74.29	74.37	8.03	8.01	7.09	7.20	$C_{28}H_{36}O_3S$
$CH_3SCH_2CH_2COO-$	85–86	<100	16.9	239–241	84.4	29	70.73	70.76	8.77	8.67			$C_{23}H_{34}O_3S$
$CH_3CH(SCH_3)COO-$	125–126	<100	17.7	240–241	76.7	24	70.73	70.70	8.77	8.81			$C_{23}H_{34}O_3S$
$CH_3CH(SC_2H_5)COO-$	84–86	81	17.3	240–242	87.1	29	71.24	71.18	8.97	8.86	7.91	7.77	$C_{24}H_{36}O_3S$
$CH_3SCH_2CH_2CH_2COO-$	64–66	75	16.8	240–241	86.0	27	71.24	70.97	8.97	8.92	7.91	7.90	$C_{24}H_{36}O_3S$
$CH_3CH_2CH(SCH_3)COO-$	118–119.5	27	17.9	241	72.8	29	71.24	71.14	8.97	9.02	7.91	7.63	$C_{24}H_{36}O_3S$

[a] Activity is measured by the effect on growth of seminal vesicles and prostate of castrated male rats. Daily subcutaneous injection for 3 days sacrificed 24 hours after last injection. Estimated activity based on testosterone propionate as 100%. All results based on 3 rats except starred results which indicate 10 rats were used. [b] All run in 1% w/v solution in U. S. P. grain alcohol except the rotation of the furoate ester which was run in the same concentration of C. P. chloroform. [c] Uncorrected m. p. [d] Yield varied from 30 to 90%.

The solution was passed through a column of activated alumina (Aluminum Ore Co., minus 80 mesh). The absorbed product was then washed off the alumina with 1:1 Skellysolve A–ether. This process of adsorption and elution was repeated several times giving 0.5 g. of a white crystalline mass. This was recrystallized from Skellysolve A to give one fraction, m. p. 61.5–63° (0.32 g.), a second fraction, m. p. 58–59° and a residual sirup. Analysis of the first fraction showed it to be pure ester.

Testosterone Ethylmercaptoacetate.—A mixture of 0.75 g. of testosterone in 1 cc. of ethylmercaptoacetic anhydride was heated for two hours on a steam-bath. The reaction mixture was poured into water and allowed to stand overnight. It was then extracted with ether and the extract washed with dilute sodium carbonate solution. The ether was diluted with three parts of Skellysolve A and the solution passed through a column of activated alumina. The adsorbed ester was eluted from the alumina with 1:1 ether–Skellysolve. This process was repeated three times. The solvent was evaporated, almost to dryness, diluted with a little Skellysolve A, and the product allowed to crystallize. These crystals were filtered off and recrystallized from Skellysolve B; yield 0.80 g., m. p. 99–100°.

Summary

A series of new alkoxy and alkylmercapto acids and their acid chlorides have been prepared. These have been used in the preparation of the corresponding testosterone esters.

RENSSELAER, N. Y. RECEIVED MARCH 16, 1949

[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE AND RENSSELAER POLYTECHNIC INSTITUTE]

The Preparation and Reactions of Some α-(4-Quinolyl)-phenylacetonitriles[1]

BY ROYAL A. CUTLER, ALEXANDER R. SURREY AND JOHN B. CLOKE

The object of the present investigation was the preparation of a variety of α-(4-quinolyl)-phenylacetonitriles and products derived therefrom to make them available for pharmacological testing.

The nitriles described in this paper were prepared by the condensation of phenylacetonitrile and α-substituted phenylacetonitriles with 4-chloro, 4,5-dichloro[2] and 4,7-dichloroquinolines.[2] Inasmuch as most of the preliminary experimental work was carried out with compounds derived from 4,7-dichloroquinoline, the following discussion will be confined mainly to this series.

The condensation of 4,7-dichloroquinoline (I) with phenylacetonitrile (II) to give α-(7-chloro-4-quinolyl)-phenylacetonitrile (III) was tried under a variety of conditions in order to obtain optimum yields. When the condensation of I and II with sodamide was carried out according to the procedure of Hancock and Cope[3] for the preparation of cyclohexylphenylacetonitrile, excessive decomposition occurred at the high temperatures employed; at temperatures below 35° no decomposition was apparent. However, only a 50% yield of the nitrile (III) was obtained and half of the 4,7-dichloroquinoline was recovered. It was observed that during the reaction a red precipitate formed which appeared to be the sodio derivative of III. The formation of such a derivative at the expense of the sodio salt of the less acidic phenylacetonitrile would explain the recovery of half of the dichloro compound. The explanation is apparently correct for, when I was allowed to react with two moles each of sodamide and phenylacetonitrile, practically quantitative yields of III resulted. This procedure was equally effective with other 4-chloroquinolines.

On standing in concentrated sulfuric acid at room temperature for fifteen hours, the nitrile (III) was converted quantitatively to α-(7-chloro-4-quinolyl)-phenylacetamide (IV). An attempted preparation of α-(7-chloro-4-quinolyl)-phenylacetic acid by hydrolysis of the nitrile (III) in refluxing aqueous potassium hydroxide yielded only amide[4] (IV). Complete hydrolysis of the nitrile (III) or the amide (IV) by refluxing for one hour with 60% sulfuric acid[5] resulted in the formation of 4-benzyl-7-chloroquinoline (V). The synthesis of 4-benzylquinoline by this method is simpler and gives superior yields to those described in the literature for its preparation.[6] The methiodides of the 4-benzylquinolines (VI) were prepared by the general method described by Alekseeva.[7] It is interesting to note that, whereas no difficulty was encountered in the preparation of the unsubstituted and 7-chloro-4-benzylquinoline methiodides, attempts to dry the 5-chloro compound overnight in a vacuum desiccator resulted in its decomposition. The presence of a strong odor of benzaldehyde indicated that oxidation had occurred at the methylene group.

The preparation of esters of α-(7-chloro-4-quinolyl)-phenylacetic acid by alcoholysis of the corresponding nitrile was unsuccessful when attempted by customary procedures. Thus, on refluxing the nitrile (III) with concentrated sulfuric acid and absolute ethanol for three hours, about 90% of the starting material was recovered unchanged. Extension of the refluxing time to twenty-two hours resulted in a practically quantitative yield of 7-chloro-4-benzylquinoline (V). Similarly, when dry hydrogen chloride was passed into a refluxing solution of the nitrile in absolute alcohol for four hours, a mixture consisting of some unchanged nitrile (III), amide (IV) and 4-benzyl-7-chloroquinoline (V) was obtained. After a period of eight hours, only the benzylquinoline (V) was recovered.

The passage of dry hydrogen chloride for six hours into a solution of the nitrile (III) in absolute methanol, initially at room temperature and without external cooling, gave a quantitative yield of the amide (IV). However, when the nitrile was added to a previously saturated solution of methanolic hydrogen chloride cooled to room temperature and the passage of hydrogen chloride continued for six hours, a 12% yield of the desired methyl ester (VII) was obtained, the remainder of the product consisting of amide (IV). By allowing the reaction mixture to stand for six days at room temperature, 23% of the theoretical amount of ester resulted.

It is well known that the hydrochloride of imido esters (see Chart II, C), intermediates in the alcoholysis of nitriles in the presence of hydrogen

(1) This paper is an abstract of a thesis submitted by Royal A. Cutler to the Faculty of Rensselaer Polytechnic Institute in partial fulfillment of the requirements for the degree, Doctor of Philosophy, June, 1947. The experimental work was carried out in the laboratories of Sterling-Winthrop Research Institute. The paper was presented before the Organic Division at the Washington, D. C., meeting of the American Chemical Society on August 30, 1948.

(2) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(3) Hancock and Cope, *Org. Syntheses*, **25**, 25 (1945).

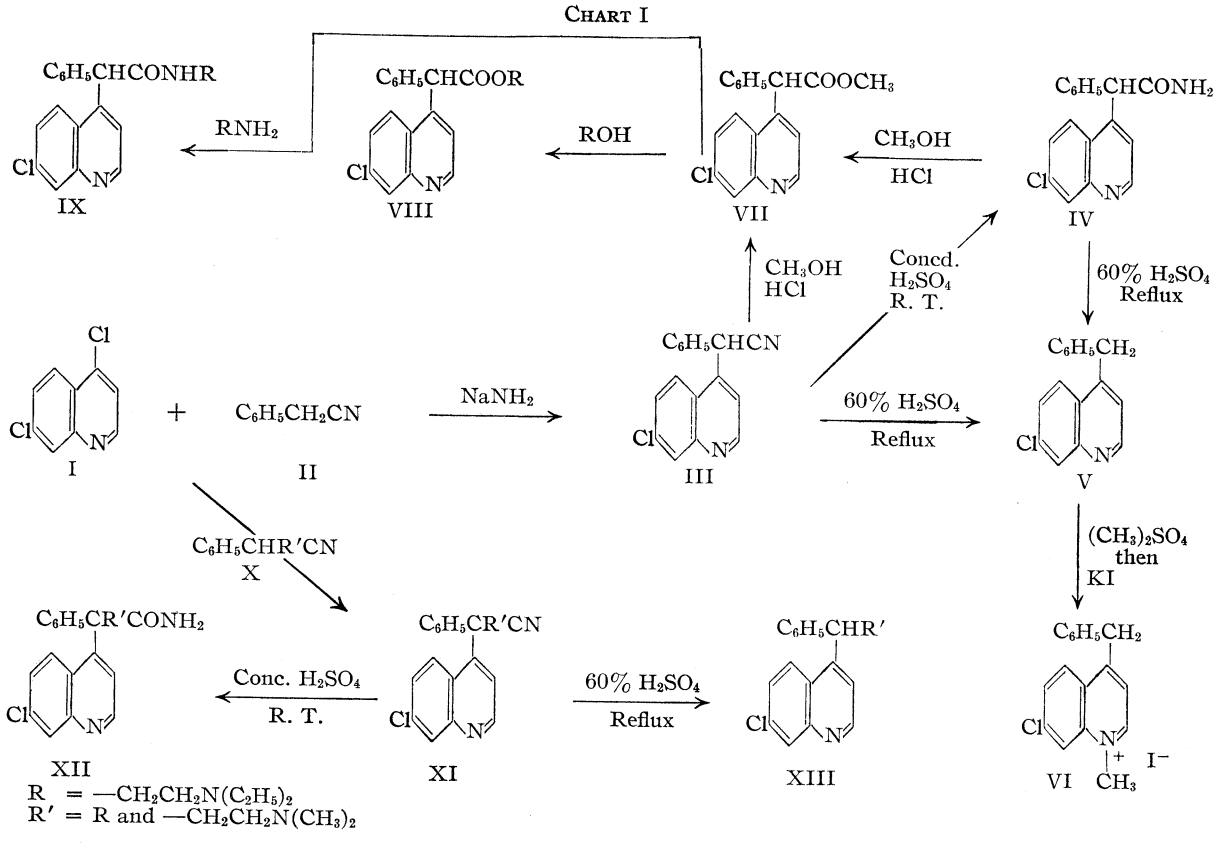
(4) It is interesting to note that when the nitrile (III) was hydrolyzed by means of sodium hydroxide and 75% ethanol, the sodium salt of IV separated from the reaction mixture in the form of pale pink needles. Treatment of this product with dilute hydrochloric acid gave the free amide (IV).

(5) When 80% sulfuric acid was used, a 40% yield of a monosulfonated 4-benzyl-7-chloroquinoline was obtained in addition to the expected product. The position of the sulfonic acid group was not determined.

(6) (a) Rabe and Pasternack, *Ber.*, **46**, 1026 (1913); (b) Bergmann and Rosenthal, *J. prakt. Chem.*, **135**, 267 (1932); (c) Dirstine and Bergstrom, *J. Org. Chem.*, **11**, 55 (1946).

(7) Alekseeva, *J. Gen. Chem. (U. S. S. R.)*, **10**, 263 (1940); *C. A.*, **34**, 7291[5] (1940).

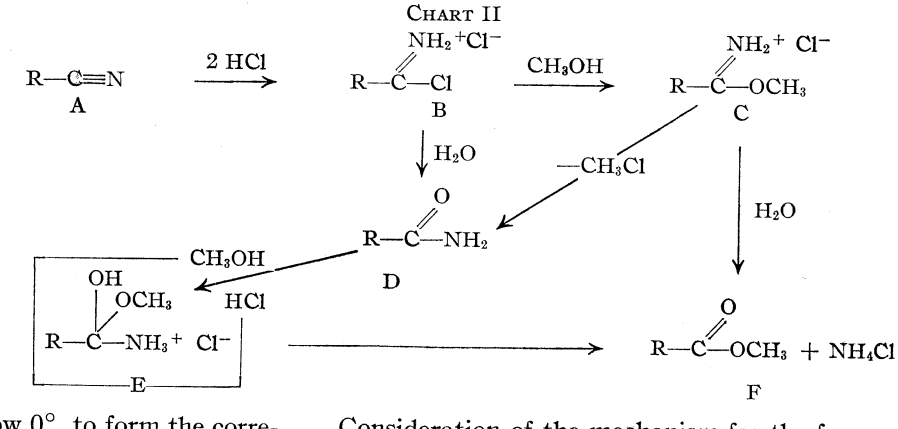
CHART I



chloride, lose the elements of alkyl halide upon heating to give amides (D).[8] The kinetics of this reaction for a number of imido ester hydrochlorides have been studied.[9] Furthermore, it has been demonstrated that the presence of highly negative groups in the position alpha to the nitrile group increases greatly the ease with which this type of reaction occurs. Thus trichloroacetonitrile,[10a] dichloroacetonitrile[10b] and nitroacetonitrile[10c] when treated with hydrogen chloride in methanol split out methyl chloride from the intermediate imido ester hydrochlorides, even at temperatures below 0°, to form the corresponding amides.

It was apparent, therefore, that in the alcoholysis of the nitrile (III) the negativity of the 4-quinolyl group combined with that of the phenyl group was sufficiently great to facilitate the split of methyl or ethyl chloride even at room temperature.[11] This accounts satisfactorily for the formation of large amounts of amide (IV) in the above-described experiments.

CHART II



Consideration of the mechanism for the formation of esters (F) from the intermediate imido ester hydrochloride (C) indicates that a molecule of water is necessary for the removal of the imido group by hydrolysis. In the usual alcoholysis of nitriles, this water is provided by pouring the

(8) (a) Pinner, *Ber.*, **16**, 352 (1883); (b) Pinner, "Die Imidoäther und ihre Derivate," R. Oppenheim, Berlin, 1892.

(9) Hartigan and Cloke, THIS JOURNAL, **67**, 709 (1945).

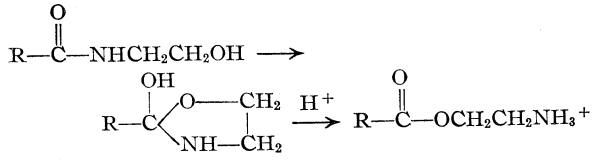
(10) (a) Steinkopf, *Ber.*, **40**, 1643 (1907); (b) Steinkopf and Malinowski, *ibid.*, **44**, 2898 (1911); (c) Steinkopf, *ibid.*, **42**, 617 (1909).

(11) The ease of formation of amide under non-hydrolytic conditions is shown by treating an ice-cooled solution of nitrile (III) in dry chloroform containing two equivalents of absolute ethanol with dry hydrogen chloride and allowing the solution to stand for three days at room temperature. The hydrochloride of the amide separated in quantitative yield.

reaction mixture into water after the imido ester hydrochloride has been formed. In the present series of nitriles (III), the intermediate imido methyl ester hydrochloride is too unstable to permit this type of treatment.[12] However, it was found that when water was incorporated into the reaction mixture, the rate of ester formation was materially increased. For example, when the nitrile (III) was added at room temperature to a solution of one part water and three parts of methanol, previously saturated with hydrogen chloride, and the passage of hydrogen chloride continued for six hours, a 32% yield of ester (VII) was obtained. On standing at room temperature for three days the yield was increased to 40% and after a period of three weeks to 70%.[13]

These results appear to indicate, according to the scheme outlined in Chart II, that the initial ester (F) formation results primarily from the hydrolysis of the imido ester hydrochloride (C). A considerable amount of amide (D) is formed concurrently due to the competing reactions; namely, the loss of methyl chloride from the imido ester hydrochloride (C) and probably also from the hydrolysis of some of the intermediate imido chloride hydrochloride (B). After the initial reaction, alcoholysis of the amide (D), to yield additional ester, proceeds at a slower rate. In order to test the latter hypothesis, the amide (IV) was subjected to the same conditions as described for the nitrile (III) to give an 18% yield of ester after six days and a 56% yield after three weeks. On employing anhydrous alcohols as the solvent a 7% yield of ester resulted from the amide after standing six days. The lower yield in the anhydrous media is probably due to the relative insolubility of the amide hydrochloride in this medium.

The alcoholysis of amides has been described previously. It is known that certain amides of β-aminoethanol rearrange in alcoholic solution under the influence of hydrogen chloride to give esters of β-aminoethanol. A possible mechanism for this type of reaction has been postulated by Phillips and Baltzly.[14] It was found that this reaction occurred rapidly even at room temperature. In one instance they reported an interconversion between the amide and ethanol, an example which still more closely resembles the present case. The authors found that, when the ethanolamide of phenylacetic acid was warmed with ethanolic hydrogen chloride, ethyl phenylacetate was obtained as one of the products.



Similar reasoning applied to the present problem would postulate that addition of methanol in the presence of excess hydrogen chloride would give the unstable addition compound, E (chart II). Loss of an ammonium ion would give the ester (F).

As an alternate method for the synthesis of ethyl α-(7-chloro-4-quinolyl)-phenylacetate, the condensation of ethyl phenylacetate with 4,7-dichloroquinoline was considered. The carbethoxylation of ethyl phenylacetate in 64% yield with ethyl carbonate or in 30% yield with ethyl chloroformate by means of sodamide in liquid ammonia has been reported.[15]

In the present work, 4,7-dichloroquinoline, ethyl phenylacetate and sodamide were stirred together at room temperature in dry benzene. After the temperature of the reaction mixture had risen to 50°, cooling was applied and the stirring continued overnight. From the reaction were isolated 20% of α-(7-chloro-4-quinolyl)-phenylacetamide (IV), about 1% of the desired ester (VII), a small amount of phenylacetamide and a 50% yield of ethyl α,γ-diphenylacetoacetate.[16] Apparently the ester is quite readily converted to the amide (IV) in the presence of sodamide. In order to avoid this latter action, sodium hydride was tried as the condensing agent. A mixture of sodium hydride, ethyl phenylacetate and 4,7-dichloroquinoline was refluxed for three hours in benzene to give a 75% yield of ethyl α,γ-diphenylacetoacetate and unchanged 4,7-dichloroquinoline. However, when a dilute benzene solution of ethyl phenylacetate was dropped very slowly into refluxing benzene containing 4,7-dichloroquinoline and an excess of sodium hydride, a 10% yield of ethyl α-(7-chloro-4-quinolyl)-phenylacetate was obtained. Inasmuch as suitable reaction conditions for the preparation of VII as well as for the corresponding ethyl ester by the alcoholysis of the nitrile (III) were finally worked out, as previously described, work on the above reaction was not pursued further.

Diethylaminoethyl α-(7-chloro-4-quinolyl)-phenylacetate (VIII) was prepared by the reaction of the corresponding methyl ester with diethylaminoethanol in refluxing Skellysolve E according to the procedure described by Surrey[17] for the *trans*-esterification of some methyl 4-quinolylmercaptoacetates. The presence of a trace of sodium decreased materially the reaction

(12) The imido ethyl ester hydrochloride is more stable. By passing hydrogen chloride into an absolute ethanol solution of the nitrile for six hours at 25° or into an aqueous-alcoholic solution cooled in an ice-salt-bath, the imido ester was obtained in good yield.

(13) The rate of alcoholysis of the nitriles in the three series studied showed a considerable variation. The rates in the order of decreasing velocity are as follows: unsubstituted > 7-chloro > 5-chloro. In the latter series only 56% of the ester was formed after five weeks whereas in the unsubstituted series a 90% yield of the ester was obtained after seventeen days.

(14) Phillips and Baltzly, THIS JOURNAL, **69**, 200 (1947).

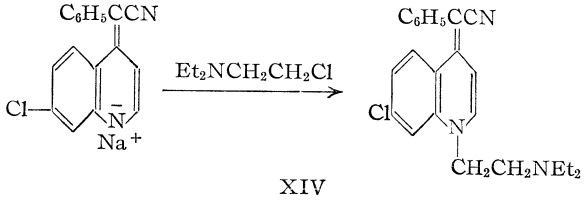
(15) Walker, Levine, Kibler and Hauser, *ibid.*, **68**, 672 (1946).

(16) A number of condensing agents have been used to prepare this compound. Its preparation in 82% yield by means of sodamide has recently been reported by Shivers, Dillon and Hauser, *ibid.*, **69**, 119 (1947).

(17) Surrey, *ibid.*, **70**, 2190 (1948).

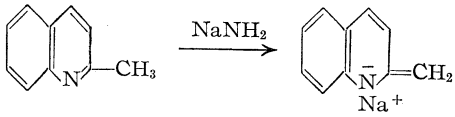
time and increased the yields. N-Diethylaminoethyl α-(7-chloro-4-quinolyl)-phenylacetamide (IX) was prepared similarly from the ester (VII) and N,N-diethylethylenediamine. The reaction was much slower than for the basic ester and was still slower in the presence of a trace of sodium. On the other hand, the presence of a little acid effectively catalyzed this reaction.

Attempts to prepare γ-diethylamino-α-(7-chloro-4-quinolyl)-phenylbutyronitrile (XI) by the condensation of the nitrile (III) with diethylaminoethyl chloride were unsuccessful. Instead, an isomeric compound was isolated in poor yield as its red-orange hydrochloride. The free base crystallized from Skellysolve B in two forms: namely, ruby-colored rectangular plates and long orange rods melting at 102–103° and 84–85°, respectively. These could be separated by mechanical means but on recrystallization either of the two forms again gave a mixture of the two crystalline modifications. The structure of the base is probably that of the N-alkylated compound (XIV) derived from the sodium salt whose structure is very likely that shown below.



XIV

Bergstrom[18] reported a similar type of salt formation in the case of 2-alkylquinolines. Treatment of the latter with alkali amides in liquid ammonia resulted only in salt formation with the enamic modification.



The preparation of γ-diethylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile (XI) was accomplished in excellent yields by the condensation of 4,7-dichloroquinoline with γ-diethylamino-α-phenylbutyronitrile (X)[19] in the presence of sodamide. In addition it was found that phenyllithium in ether or sodium hydride in refluxing benzene also brought about the condensation.

Treatment of the nitrile (XI) with concentrated sulfuric acid at room temperature for four to five weeks gave a 90% yield of the amide (XII). After standing for three days only a 15% yield of XII was obtained. XII also resulted in 15% yield from refluxing the nitrile (XI) with sodium hydroxide in 70% ethanol for twelve hours. When the nitrile (XI) was refluxed with 60% sulfuric acid for one hour a 15% yield of the amide (XII) was isolated; after refluxing for twelve hours, a practically quantitative yield of 7-chloro-4-(3-diethylamino-1-phenylpropyl)-quinoline (XIII) was obtained. As would be expected, the rates of hydrolysis of the nitrile (XI) were much slower than for III. In the preparation of 5-chloro-4-(3-diethylamino-1-phenylpropyl)-quinoline, some of the intermediate amide was still present after refluxing for forty-eight hours.

(18) Bergstrom, *ibid.*, **53**, 3027 (1931).

(19) Eisleb, *Ber.*, **74**, 1433 (1941).

Experimental[20]

α-(7-Chloro-4-quinolyl)-phenylacetonitrile (III).[21]—One hundred and ten grams (2.6 moles) of sodium amide[22] was added to a well-stirred, ice-cooled solution of 260 g. (2.2 moles) of phenylacetonitrile in one liter of dry benzene contained in a flask fitted with a soda-lime tube. The temperature rose gradually to 35° and the color of the solution changed from a pale yellow to a deep reddish black. After stirring for an hour, one mole (198 g.) of 4,7-dichloroquinoline was added portion-wise at a rate sufficient to maintain the temperature at 25–30° with strong external cooling. After the addition was complete, the ice-bath was removed and the reaction mixture stirred at room temperature for two hours. The bright red sodium salt of the product and excess sodium amide were decomposed by the cautious addition of water by means of a dropping funnel. The light reddish-orange benzene layer was washed once with water, followed by extraction with three 500-cc. portions of 9 *N* hydrochloric acid.[23] Ice was added to the acid extracts and the free base liberated by the addition of concentrated ammonium hydroxide. The red oil which formed was taken up in chloroform and dried over Drierite. Removal of the solvent gave a viscous oil which on treatment with ether and scratching yielded a pale yellow solid. In the case of IIIa[24] the oil was distilled at 0.1 micron, b. p. 140°, and the bright red distillate crystallized from a mixture of Skellysolve A and ether. Subsequent runs required no distillation.

The crude solids were obtained in practically quantitative yields and were used in subsequent reactions without further purification. Analytical samples were obtained by recrystallization from Skellysolve B or C.

α-(7-Chloro-4-quinolyl)-phenylacetamide (IV).—One part by weight of α-(7-chloro-4-quinolyl)-phenylacetonitrile was dissolved in four volumes of concentrated sulfuric acid and, after standing overnight at room temperature, the solution was poured into ice containing an excess of ammonium hydroxide. The solid amide was obtained in quantitative yield. Recrystallization from butanol gave a white crystalline solid. In the case of IVb,[24] ethanol was used as the recrystallization solvent.

7-Chloro-4-benzylquinoline (V).—Five parts by weight of the nitrile (III) and eight parts by volume each of concentrated sulfuric acid and water were refluxed vigorously for one hour. During the initial part of the reaction, carbon dioxide was evolved in copious amounts. At the end of the reaction, the yellow solution was poured onto ice

(20) All melting points are uncorrected. All analyses were performed by Mr. Auerbach and staff of these laboratories. Nitrogen, unless otherwise specified, was determined by means of a modified Kjeldahl procedure. Chlorine analyses, exceptions noted, were performed by means of the Parr-bomb method.

(21) The experimental procedures listed represent those for the compounds derived from 4,7-dichloroquinoline. The compounds in the unsubstituted and 5-chloro series were also prepared according to these methods with but few modifications which are noted.

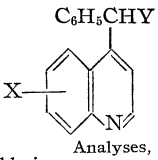
(22) The sodamide used was prepared in the factory of Winthrop-Stearns, Inc. The granular material was stored under toluene and ground under benzene or toluene before use. The resulting finely divided material was pressed out between filter papers and quickly weighed, an excess being used in each case to make allowance for any solvent present.

(23) 6 *N* Hydrochloric acid was used for IIIa (see Table I). In the case of IIIb the solid hydrochloride tends to form during the extraction and may cause difficulty during separation.

(24) See Table I.

TABLE I

α-(4-QUINOLYL)-PHENYLACETONITRILES AND RELATED COMPOUNDS



No.	X	Y	Yield,[a] %	M. p., °C.	Empirical formula	Analyses, % Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
IIIa	H	–CN	76[b]	86–86.5	$C_{17}H_{12}N_2$	...	...	11.47	11.38
IIIb	5-Cl	–CN	100	149.5–150.5	$C_{17}H_{11}ClN_2$	12.72	12.52	10.05	10.00
III	7-Cl	–CN	90[b]	117.5–118.5	$C_{17}H_{11}ClN_2$	12.72	12.46	10.05	9.97
IVa	H	$-CONH_2$	100	267–268	$C_{17}H_{14}N_2O$	...	...	10.68	10.49
IVb	5-Cl	$-CONH_2$	96	212–213	$C_{17}H_{13}ClN_2O$	11.95	12.09	9.44	9.42[c]
IV	7-Cl[d]	$-CONH_2$	100	283–284	$C_{17}H_{13}ClN_2O$	...	...	9.44	9.49
Va	H[e]	–H	95	52–52.5	$C_{16}H_{13}N$	[f]	...	6.39	6.23
Vb	5-Cl	–H	98	51–51.5	$C_{16}H_{12}ClN$	13.97	13.74	5.52	5.63
V	7-Cl	–H	98	93.5–94	$C_{16}H_{12}ClN$	13.97	13.91	5.52	5.31
VIIa	H	$-COOCH_3$	90	60.5–61.5	$C_{18}H_{15}NO_2$	[g]	...	5.05	5.04[h]
VIIb	5-Cl	$-COOCH_3$	56	114–114.5	$C_{18}H_{14}ClNO_2$	...	...	4.49	4.48[h]
VII	7-Cl	$-COOCH_3$	70	127–127.5	$C_{18}H_{14}ClNO_2$	11.37	11.49	4.49	4.49[h]
VIIIa	H	–COOR[i]	75	136–137[j]	$C_{23}H_{26}N_2O_2 \cdot HCl$	8.89	8.89[k]	[l]	
VIIIb	5-Cl	–COOR[i]	72	174–175[j]	$C_{23}H_{25}ClN_2O_2 \cdot HCl$	16.36	16.20	6.47	6.25
VIII	7-Cl	–COOR[i]	86	155.5–156.5[j]	$C_{23}H_{25}ClN_2O_2 \cdot HCl$	16.36	16.38	6.47	6.25
IXa	H[m]	$-CONHR^i$	6[n]	117.5–118	$C_{23}H_{27}N_3O$	...	...	11.63	11.50[c]
IX[b]	5-Cl[o]	$-CONHR^i$	22[p]	92–93	$C_{23}H_{26}ClN_3O$	...	...	7.08	7.03[h]
IX	7-Cl[q]	$-CONHR^i$	65[r]	132.5–133	$C_{23}H_{26}ClN_3O$	8.96	8.95	10.62	10.41

[a] Yields based on amount of crude product. Losses from purification amounted to from 5–15% in most instances. [b] Yield after crystallization of crude oil from ether. [c] Dumas nitrogen. [d] Hydrochloride, m. p. 267–268° dec.; *Anal.* Calcd. for $C_{17}H_{13}ClN_2O \cdot HCl$: Cl^-, 10.66; N, 8.40. Found: Cl^-, 10.92; N, 8.54. [e] Sulfate salt, m. p. 195–196°. *Anal.* Calcd. for $C_{16}H_{13}N \cdot H_2SO_4$: $SO_4^=$, 30.24. Found: $SO_4^=$, 30.67. [f] Calcd.: C, 87.64; H, 5.98. Found: C, 87.56; H, 5.71. [g] Calcd.: C, 77.96; H, 5.45. Found: C, 78.15; H, 5.72. [h] Titration of basic nitrogen by the method of Toennies and Callan, *J. Biol. Chem.*, **125**, 259 (1938). [i] R = $—CH_2CH_2N(C_2H_5)_2$. [j] Obtained as non-distillable oils. The melting points and analyses are those of the monohydrochlorides. [k] Ionic chlorine. [l] Calcd.: C, 69.25; H, 6.82. Found: C, 69.24; H, 6.86. [m] Monohydrochloride, m. p. 110–112°. *Anal.* Calcd. for $C_{23}H_{27}N_3O \cdot HCl$: Cl, 8.91. Found: Cl^-, 8.84. [n] Refluxed sixteen hours. Low yield due to addition of trace of sodium which inhibits this reaction. [o] Monohydrochloride, m. p. 99.5–101°. *Anal.* Calcd. for $C_{23}H_{26}ClN_3O \cdot HCl$: Cl, 16.40. Found: Cl, 16.15. [p] Refluxed twenty-six hours without catalyst. [q] Monohydrochloride, m. p. 156–157°. *Anal.* Calcd. for $C_{23}H_{26}ClN_3O \cdot HCl$: Cl, 16.40; N, 9.72. Found: Cl, 16.12; N, 9.55. [r] A trace of concentrated hydrochloric acid used as catalyst. Without catalyst the yield was 25%.

containing an excess of ammonium hydroxide. The product which separated was taken up in ether, dried over Drierite and the solvent evaporated to give a quantitative yield of a pale yellow oil which solidified on standing. Recrystallization from Skellysolve B gave long silky white needles.

In an initial experiment, 5 g. of the nitrile (III) was treated in a similar fashion using 12 cc. of concentrated sulfuric acid and 5 cc. of water. After extraction of the desired product (1.6 g.) with ether, acidification of the alkaline solution yielded 1.8 g. of a white solid which was purified by reprecipitation with acid from its sodium bicarbonate solution. Analysis indicated that it was a monosulfonated derivative of 7-chloro-4-benzylquinoline. The position of the sulfonic acid group was not determined.

Anal. Calcd. for $C_{16}H_{12}ClNO_3S$: Cl, 10.62; S, 9.60. Found: Cl, 10.51; S, 9.53.

7-Chloro-4-benzylquinoline Methiodide (VI).—The procedure was similar to the general method described by Alekseeva.[6] The product, obtained in quantitative yield, was recrystallized by stirring in 35 volumes of hot absolute alcohol followed by ice cooling, to give golden leaflets, m. p. 223–225° dec. Prolonged contact with hot alcohol results in considerable decomposition.

Anal. Calcd. for $C_{17}H_{15}ClIN$: I, 32.08; N, 3.54. Found: I, 31.60; N, 3.73.

4-Benzylquinoline methiodide obtained by the above procedure melted at 224–226° dec. (Rabe and Pasternack[6a] reported 226° dec.).

5-Chloro-4-benzylquinoline methiodide decomposed on drying in a vacuum desiccator overnight to give a dark brownish-red solid with a strong odor of benzaldehyde.

Methyl α-(7-Chloro-4-quinolyl)-phenylacetate (VII).—The following procedure gave the best yields of any method tried.

A solution of one part by volume of water in 3 parts by volume of methanol was saturated with gaseous hydrogen chloride with strong external cooling. The ice-bath was removed and one part by weight of the nitrile (III) added at 10–15°. The addition of hydrogen chloride was continued, the temperature rose to 35° and the solid soon dissolved completely to form a clear yellow solution. The white hydrochloride of the nitrile (III) soon separated and gradually redissolved over a period of two hours. (In the case of VIIa and VIIb[24] the hydrochloride of the corresponding nitrile did not separate.) The hydrogen chloride was bubbled slowly through the solution for a total of five or six hours. The resulting solution was stoppered and allowed to stand at room temperature for varying amounts of time. As ester formation occurred, ammonium chloride separated, the time required for the first appearance of this salt serving as a rough guide as to the rate of esterification. (The times required for the appearance of ammonium chloride for each of the compounds prepared were as follows: VIIa two to three hours; VII, ten to twelve hours; VIIb, about one week.) The reaction mixture was worked up by pouring into ice water and liberating the ester with aqueous sodium hydroxide in the presence of chloroform, care being taken to keep the solution cold by the addition of ice. Filtration at this point removed most of the amide present. The chloroform

layer upon separation, drying with Drierite, followed by evaporation, yielded the ester. The crude product was freed from small amounts of amide present[25] by dissolving in hot Skellysolve C (VIIb and VII) or a large volume of Skellysolve B (VIIa), filtering with charcoal, seeding and allowing to cool. The esters were recrystallized from the Skellysolves or methanol (VIIb) to give white crystalline solids. The crude yields of the three compounds prepared by this procedure are as follows: VIIa, 90% after standing seventeen days; VIIb, 56% after five weeks (yield after recrystallization from Skellysolve C); VII, 32% after six hours, 40% in three days, 70% after two weeks.

The methyl ester (VII) was also prepared from the amide (IV) by the same procedure. The yield of crude ester, after standing for six days, was 18% and 56% after three weeks.

Ethyl α-(7-Chloro-4-quinolyl)-phenylacetate.—This ester was prepared from the nitrile (III) according to the procedure outlined for the methyl ester. The yield after three days of standing was 54%, m. p., 125.5–126°, white thick needles.

Anal. Calcd. for $C_{19}H_{16}ClNO_2$: Cl, 10.88; N, 4.30. Found: Cl, 10.72; N, 4.24.

Ethyl α-(7-Chloro-4-quinolyl)-imidoacetate.—Twenty-eight grams (0.1 mole) of α-(7-chloro-4-quinolyl)-phenylacetonitrile (III) was added to 200 cc. of 95% ethanol, previously saturated with hydrogen chloride and thoroughly cooled in an ice–salt-bath. The passage of hydrogen chloride was continued with occasional shaking until solution was effected. After standing for three days in the ice-chest, the reaction mixture was diluted with two liters of ether, the resulting white crystalline precipitate collected on a filter and treated with dilute sodium bicarbonate solution. The mixture was shaken with chloroform and the insoluble amide (IV) collected on filter; yield, 5.5 g. The chloroform layer was separated from the filtrate, dried over anhydrous sodium sulfate, filtered with charcoal and the solvent removed by distillation to give 19.5 g. (0.06 mole) of almost white solid, m. p. 149–151°. Recrystallization from Skellysolve C, including treatment with charcoal, gave large white crystals, m. p. 155–157° (cor.).

Anal. Calcd. for $C_{19}H_{17}ClN_2O$: C, 70.25; H, 5.28; Cl, 10.92; N, 8.63. Found: C, 70.62; H, 5.13; Cl, 10.68; N (Dumas), 8.49.

The imido ester was also formed in good yield by adding the nitrile (III) to a saturated hydrogen chloride solution of absolute ethanol and passing in hydrogen chloride for six hours.

Diethylaminoethyl[c] α-(7-Chloro-4-quinolyl)-phenylacetate (VIII).—A mixture of 15 g. (0.048 mole) of methyl α-(7-chloro-4-quinolyl)-phenylacetate (VII), 30 cc. of diethylaminoethanol, 110 cc. of Skellysolve E and a small piece of freshly cut sodium[26] about the size of a grain of wheat was placed in a 500-cc. round-bottomed flask fitted with a water separator, reflux condenser, and a drying tube. The mixture was refluxed (sixteen to twenty-four hours) at a rate just sufficient to allow the methanol formed in the reaction to distil over into the water separator. The cooled reaction mixture was diluted with an equal volume of ether and extracted with 0.5 *N* hydrochloric acid. The combined extracts were made just alkaline to litmus with 10% sodium hydroxide and extracted with ether to remove any unchanged ester together with small amounts of the 7-chloro-4-benzylquinoline formed due to the action of the sodium alkoxide present. The aqueous layer was then made alkaline to phenolphthalein with caustic, extracted with ether, the ether extracts dried with Drierite, and the solvent removed by distillation; yield, 16.35 g. (86%). In the case of VIIIa[24] and VIIIb the yields were 75 and 72%, respectively.

(25) In the preparation of VIIb, about one-quarter of the product at this point was amide because of the greater solubility of this compound in chloroform.

(26) A run made under similar conditions, but without sodium, gave only a 39% yield.

The free basic esters (VIIIa, VIIIb, and VIII) were all light orange-yellow oils. An attempted distillation of VIIIa was interrupted because of excessive decomposition. The mono-hydrochlorides of these compounds were readily obtained by dissolving the base in three volumes of acetone or isopropyl alcohol, adding slightly less than the calculated amount of alcoholic hydrogen chloride, diluting with ether just to turbidity and scratching or seeding to start crystal formation. Where necessary, the hydrochlorides were recrystallized from isopropyl alcohol or acetone. The hydrochlorides are stable, white crystalline substances easily soluble in water.

N-Diethylaminoethyl α-(7-Chloro-4-quinolyl)-phenylacetamide (IX).—The basic amide was prepared by the same procedure described above for the basic ester using N,N-diethylethylenediamine. In the presence of a trace of sodium the yield was 6%. Without the catalyst, the yields ranged from 20–25% and were increased to 65% when an acid catalyst (a trace of concentrated hydrochloric acid) was used. The product was recrystallized from Skellysolve B or C to give a white crystalline solid.

The monohydrochlorides of the bases (IXa,[24] IXb and IX) were prepared by the addition of slightly less than the equivalent amount of alcoholic hydrogen chloride to an isopropanol or acetone solution of the base.

Alkylation of α-(7-Chloro-4-quinolyl)-phenylacetonitrile. Preparation of XIV.—Sodamide (7 g.) was added to a stirred mixture of 40 g. of the nitrile (III) and 43 g. of diethylaminoethyl chloride in dry benzene at room temperature. The solution turned a ruby-red color as the red sodium salt of III separated. After stirring for thirty hours, the mixture was still a bright red; but, on standing for sixty hours more, it became black. After the cautious addition of water, the benzene layer was extracted with 1 *N* hydrochloric acid until the washings were but slightly colored. Evaporation of the benzene solution gave 17 g. of the starting material (III). The acid extracts were made just alkaline to congo red with sodium hydroxide, the black gum which separated was discarded and the solution filtered with charcoal to give a deep ruby-red filtrate. The latter was made alkaline to phenolphthalein, extracted with chloroform, the chloroform extracts dried over Drierite, filtered with charcoal and evaporated to give 30 g. of a black oil. This was taken up in ether, filtered from the solid which separated, and evaporated to give 20 g. of black oil which was in turn taken up in 60 cc. of isopropyl alcohol and 20 cc. of 3.6 *N* alcoholic hydrogen chloride added. On standing in the ice-chest, 2.6 g. of red needles separated. These were recrystallized from 200 cc. of isopropyl alcohol to yield 1.8 g. of fine red-orange needles, m. p. 215–216° dec. A mixed melting point with an authentic sample of γ-diethylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile hydrochloride (m. p. 211–212°) melted at 175–190°. The analysis, however, indicated an isomeric compound.

Anal. Calcd. for $C_{23}H_{24}ClN_3 \cdot HCl$: Cl, 66.50; H, 6.07; Cl, 17.11. Found: C, 66.41; H, 5.97; Cl, 16.98.

Conversion of a sample of the above hydrochloride to the free base yielded a dark ruby viscous oil which was crystallized from Skellysolve B to give a mixture of dark ruby-red rectangular plates and orange rods. The two were separated by hand picking, the former melting at 102–103° and the latter at 84–85°. A mixed melting point appeared slightly moist at 82° but melted at 84–87°. Recrystallization of either solid from Skellysolve B resulted in the formation of a mixture of the two modifications. The ruby-red plates analyzed as follows:

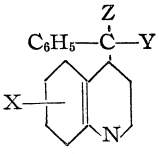
Anal. Calcd. for $C_{23}H_{24}ClN_3$: C, 73.10; H, 6.40; N, 11.12. Found: C, 73.31; H, 6.18; N, 11.11.

γ-Dialkylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile (XI).[27]—To a dry benzene solution (750 cc.)

(27) The γ-diethylamino and γ-dimethylamino compounds in this series (see Table II) were prepared in the same fashion and so will be treated under the general heading, γ-dialkylamino, exceptions being noted. The general procedure used in the preparation of these nitriles is similar to that described by Cloke, *et al.*, THIS JOURNAL, **53**, 2791 (1931), and Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

TABLE II

γ-DIALKYLAMINO-α-PHENYL-α-(4-QUINOLYL)-BUTYRONITRILES AND RELATED COMPOUNDS



No.	X	Y	Z	Yield,[a] %	M. p., °C.	Bases: Empirical formula	Bases: Chlorine Calcd.	Bases: Chlorine Found	Bases: Nitrogen Calcd.	Bases: Nitrogen Found	Monohydrochlorides: M. p., °C.	Monohydrochlorides: Chlorine Calcd.	Monohydrochlorides: Chlorine Found	Monohydrochlorides: Nitrogen Calcd.	Monohydrochlorides: Nitrogen Found
XIa	H	-CN	[b]	88	69.5–70.5	$C_{21}H_{21}N_3$	...	...	8.88	8.84[c]	224–226	[d]	...	11.94	11.69
XIb	5-Cl	-CN	[b]	86	115.5–116	$C_{21}H_{20}ClN_3$	10.13	10.12	12.01	11.87[e]	274–275	18.36	18.08	10.88	10.60
XI	7-Cl	-CN	[b]	95	104.5–105.5	$C_{21}H_{20}ClN_3$	10.13	10.12	12.01	11.82[e]	260–262	18.36	18.08	10.88	10.65
XIIa	H	$-CONH_2$	[b]	64[f]	170.5–171.5	$C_{21}H_{23}N_3O$	...	...	8.41	8.34[c]	254–255	9.59	9.48[g]	11.36	11.59[e]
XIIb	5-Cl	$-CONH_2$	[b]	91	203–204 d.	$C_{21}H_{22}ClN_3O$	9.64	9.36	11.43	11.19	221–222	8.71	8.71[g]	10.40	10.22
XII	7-Cl	$-CONH_2$	[b]	97	187–188	$C_{21}H_{22}ClN_3O$	...	...	7.61	7.58[c]	248–249	17.54	17.00	10.40	10.22
XIIIa	H	-H	[b]	97	89–89.5	$C_{20}H_{22}N_2$	...	...	9.65	9.65[c]	155.5–156.5	10.85	10.96[g]	8.57	8.25
XIIIb	5-Cl	-H	[b]	76	[h]	$C_{20}H_{21}ClN_2$	...	...	8.63	8.50[c]	195–196	9.81	9.92[g]	7.74	7.44
XIII	7-Cl	-H	[b]	97	77–78[i]	$C_{20}H_{21}ClN_2$	10.92	10.97	8.63	8.61	[j]	...	...	...	...
XIa	H	-CN	[k]	97	72.5–73[l]	$C_{23}H_{25}N_3$	...	...	12.24	12.08	211.5–212.5	9.33	9.20[g]	[m]	...
XIb	5-Cl	-CN	[k]	98	120.5–121	$C_{23}H_{24}ClN_3$	9.38	9.50	11.12	10.80	237–239	8.55	8.40[g]	10.14	9.92
XI	7-Cl	-CN	[k]	91	91–92	$C_{23}H_{24}ClN_3$	9.38	9.31	11.12	10.92	211–212	17.11	17.10	10.14	9.97
XIIa	H	$-CONH_2$	[k]	85	135–136[n]	$C_{23}H_{27}N_3O$	...	...	7.75	7.74[c]	247–248	8.91	8.70[e]	[o]	...
XIIb	5-Cl	$-CONH_2$	[k]	81	174–175	$C_{23}H_{26}ClN_3O$	8.96	9.01	10.62	10.89[e]	225–226	8.20	8.29[g]	[p]	...
XII	7-Cl	$-CONH_2$	[k]	76[f]	147.5–148.5	$C_{23}H_{26}ClN_3O$	8.96	9.03	10.62	10.48	236 d.	8.20	8.10[g]	9.72	9.57
XIIIa	H	-H	[k]	88	[q]	$C_{22}H_{26}N_2$	...	...	8.80	8.66[c]	173–174 d.	9.99	10.00[g]	7.90	7.61
XIIIb	5-Cl	-H	[k]	80	[r]	$C_{22}H_{25}ClN_2$	...	...	7.94	7.88[c]	178.5–179.5	9.11	9.12[g]	7.20	7.11
XIII	7-Cl	-H	[k]	94	[s]	$C_{22}H_{25}ClN_2$	10.05	10.00	7.94	7.70	196.6–197.5[t]	18.21	18.06	7.20	7.06

[a] Yields represent the crude products. Losses from purification amounted to from 5–15% in most cases. [b] Z = $-CH_2CH_2N(CH_3)_2$. [c] Titration of basic nitrogen. [d] Calcd.: C, 71.68; H, 6.30. Found: C, 71.66; H, 6.04. [e] Dumas nitrogen. [f] Lower yield due to accidental loss of product. [g] Ionic chlorine. [h] Yellow oil distilled at 150° at 0.1 micron; $n^{25}D$ 1.6200. [i] First obtained as a pale yellow tinted oil by distillation at 154° at 0.1 micron; $n^{25}D$ 1.6124. [j] No solid hydrochloride was obtained. [k] Z = $-CH_2CH_2N(C_2H_5)_2$. [l] Appears to exist in two crystalline modifications. When first isolated it melted at 96–104°. [m] Calcd.: C, 72.71; H, 6.90. Found: C, 72.58; H, 7.01. [n] Exists in a lower melting solvated form, m. p. 90–92°, when recrystallized from benzene. Analytical sample dried *in vacuo* for one hour at 100°. [o] Calcd.: C, 69.42; H, 7.49. Found: C, 69.47; H, 6.97. [p] Calcd.: C, 63.89; H, 6.29. Found: C, 64.39; H, 6.36. [q] Pale yellow oil; b. p. 190° at 0.5 mm.; $n^{25}D$ 1.5942. [r] Yellow oil; b. p. 209° at 0.8 mm.; $n^{25}D$ 1.6052. [s] Pale yellow oil distilled at 155–156° at 0.1 micron; $n^{25}D$ 1.5986. [t] Corrected melting point; sample immersed at 140° and bath raised 3° per minute. When the melting point is taken rapidly it melts at 158–160° (uncor.).

of the 4,7-dichloroquinoline (0.5 mole) and one-half mole of γ-dialkylamino-α-phenylbutyronitrile[28] in a two-liter, three-necked flask fitted with a stirrer, thermometer, and drying tube was added 28 g. of fresh,[29] powdered sodamide. External cooling was applied when necessary to keep the temperature of the reaction mixture below 45°. At the end of two to three hours, the temperature had dropped to room temperature and stirring was continued for an additional four to five hours. Water was added cautiously and the dark colored solution changed to a light orange color. The benzene layer was washed twice with water and dried over Drierite. It was filtered with charcoal and evaporated to give a practically quantitative yield of the base. When the base was obtained as a viscous oil, it was stirred with a little ether to induce crystallization. Recrystallization from Skellysolve B or C yielded a pure sample of white crystalline solid.

The monohydrochlorides of the basic nitriles (see Table II) were prepared by dissolving the base in three to four volumes of warm isopropyl alcohol and adding slightly less than the calculated amount of alcoholic hydrogen chloride. In some instances ether was added to turbidity and the solution scratched to induce crystallization. The hydrochlorides were dried at 120° *in vacuo*.

γ-Dialkylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyramide (XII).—A solution of one part by weight of the nitrile (XI) in four volumes of concentrated sulfuric acid was allowed to stand at room temperature for four to five weeks. The yellow solution was poured onto ice, treated with an excess of sodium hydroxide solution and extracted with chloroform. The combined extracts were dried over Drierite, filtered with charcoal and the chloroform distilled to give 80% yields or better of the amides. The crude products were crystallized from benzene or toluene to give white crystalline solids.

When the nitrile (III) was allowed to stand for three days in concentrated sulfuric acid, only a 15% yield of the amide was obtained. Refluxing the nitrile with an equal weight of sodium hydroxide in eight volumes of 70% ethanol for twelve hours or by heating 5 g. of the nitrile, 8 cc. of water and 8 cc. of concentrated sulfuric acid at reflux for one hour gave approximately 15% yields of the amide.

The monohydrochlorides were prepared by a procedure similar to that used in the preparation of the corresponding salts of the basic nitriles (XI). Larger volumes (5–20) of isopropyl alcohol were required to dissolve the amides. The salts were recrystallized from ethanol and dried *in vacuo* at 140°.

7-Chloro-4-(3-dialkylamino-1-phenylpropyl)-quinoline (XIII).—A solution of 30 g. of γ-dialkylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile (XI) in 50 cc. of water and 50 cc. of concentrated sulfuric acid was refluxed for twelve to forty-eight hours. In some cases, the completeness of the reaction was determined by passing nitrogen over the surface of the reaction mixture and bubbling the escaping gases through barium hydroxide solution. When no cloudiness resulted after a minute or so, the reaction was regarded as complete. The reaction mixture was poured into ice containing an excess of sodium hydroxide solution, extracted with ether, the ether dried, filtered with charcoal and evaporated to give a pale yellow oil. In the case of XIIIb, some intermediate amide was isolated even after refluxing for forty-eight hours. This

(28) γ-Diethylamino-α-phenylbutyronitrile[19] and γ-dimethylamino-α-phenylbutyronitrile (Kwartler and Lucas, THIS JOURNAL, **68**, 2395 (1946)) were prepared in about 80–90% yields by the condensation of phenylacetonitrile with diethylaminoethyl chloride and dimethylaminoethyl chloride, respectively, under conditions similar to those described for the preparation of III.

(29) The use of sodamide which had been stored under toluene for long periods of time (four to six months) gave yields as low as 20%.

was removed by dissolving the oil in Skellysolve B, seeding with amide and allowing to stand twenty-four hours. Evaporation of the filtered solution gave the desired base. These bases could be converted to the monohydrochlorides without further purification or distilled under vacuum to give pale yellow tinted oils. The latter are all quite stable to heat but on standing for several days at room temperature, where dialkyl is diethyl, the bases develop a beautiful lavender or purple color. In two instances (see Table II) the bases solidified and were recrystallized from Skellysolve B.

The monohydrochlorides were prepared by dissolving the free base in three volumes of isopropyl alcohol and adding slightly less than the equivalent amount of alcoholic hydrogen chloride. In order to induce crystallization, ether was added to turbidity, the inside of the flask scratched and the solution allowed to stand. The analytical samples were dried *in vacuo* at about 120°.

The monohydrochloride of 7-chloro-4-(3-dimethylamino-1-phenylpropyl)-quinoline could not be induced to crystallize. A dihydrochloride, m. p. 215–217°, was prepared but gave an unsatisfactory analysis.

Summary

The condensation of phenylacetonitrile with 4-chloro-, 4,5-dichloro- and 4,7-dichloroquinoline has been investigated under a variety of conditions. The resulting α-(4-quinolyl)-phenylacetonitriles were converted to the corresponding α-(4-quinolyl)-phenylacetamides and 4-benzylquinolines.

The preparation of the methyl α-(4-quinolyl)-phenylacetates from the corresponding nitriles and some basic esters and basic amides is reported.

The reaction of γ-dialkylamino-α-phenylbutyronitrile with 4-chloroquinolines is also described. The nitriles so formed were converted to the corresponding amides and 4-(3-dialkylamino-1-phenylpropyl)-quinolines.

RENSSELAER, NEW YORK RECEIVED APRIL 15, 1949

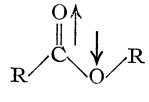
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA AND THE RESEARCH DIVISION OF CUTTER LABORATORIES]

The Dipole Moment of Methyl Benzylpenicillinate

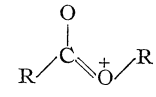
BY W. D. KUMLER, I. F. HALVERSTADT AND EDWARD L. ALPEN

Methyl benzylpenicillinate has been reported to have a dipole moment of approximately 8 from measurements in chloroform and anhydrous ethanol solutions.[1] It seems improbable that the molecule would have such a large moment if the commonly accepted structure of penicillin is correct. The large moment would mean that the individual moments were lined up in nearly the same direction, which is rather unlikely.

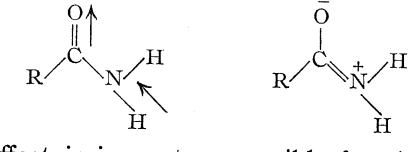
The group moments contributing to the over-all resultant moment are those of the ester (1.8), sulfide (1.6), amide (3.8)[2] and lactam (3.8 estimated). The moment of the lactam might be increased somewhat over an ordinary amide as a result of the ring formation, just as a lactone has a higher moment (4.1)[3] compared with an ester (1.8) but this increase in case of the lactam amide would be considerably less than in the case of the lactone. The ester is almost entirely in a form in which the ether dipole almost directly opposes the carbonyl dipole.



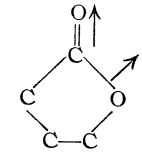
The molecule is held in this configuration by the contribution from the resonating form



which gives some double bond character to the carbonyl carbon–ether oxygen bond. The amides likewise are probably held in a similar configuration by resonance but here the moment of the amine portion (0.6–1.2) is not only smaller than that of the ether (1.3), but its resultant is not opposed to that of the carbonyl moment.



This effect is in part responsible for the dipole moment of amides being greater than that of a ketone (2.8), while that of an ester is considerably less. When an ester is bent around to form a lactone the moments are no longer directly opposed



but augment one another to some extent. However, when an amide is closed into a lactam there will not be nearly as much enhancement because there was originally not as much opposition to the

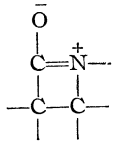
(1) O. S. R. D. Report Sh 4, 34 (1944) Shell Development Co. also the "Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, p. 407. This value was offered as an approximate value only. Although some workers interpreted this value as evidence for a zwitterion structure for penicillin, the Shell workers pointed out that although the value of 8 was intermediate between the moment of molecules without a separation of charge and the moment of zwitterion molecules, the fact that the molecule did not show a positive dielectric increment was evidence against its being a zwitterion.

(2) Kumler and Porter, THIS JOURNAL, **56**, 2549 (1934).

(3) Marsden and Sutton, *J. Chem. Soc.*, 1383 (1936).

carbonyl moment and the ring closure still leaves one of the N–H or N–C moments opposed to the carbonyl moment.

The lactam moment would also be reduced as a result of a decrease in the contribution of the resonating form



due to the additional strain in the four-membered ring caused by the double bond between carbon and nitrogen. There is evidence for this effect from the X-ray crystallographic studies. The carbonyl carbon–nitrogen distance in the lactam ring is given as 1.38 Å. and the carbonyl carbon–nitrogen distance in the amide as 1.33 Å.[4] The accuracy of the measurements is not sufficiently great to be certain of this difference but the reported distances are in the direction expected for less resonance in the lactam as compared with the amide. Not knowing the exact magnitude of either of these two effects we have assumed that the two cancel and the lactam has the same moment as the amide.

Taking the distances and angles given by the X-ray evidence for the solid, plus the above moments for the polar groups, we calculate the moment of methyl benzylpenicillin to be 5.2. The amide side-chain undoubtedly is not held in the same position in solution as it is in the solid. It would be expected to have some freedom of rotation, if not complete freedom of rotation, in solution. Assuming freedom of rotation for the amide side-chain the moment of the molecule is calculated to be 4.4. The expected moment of the compound is then somewhere between the two values.

The dipole moment of methyl benzylpenicillinate has been measured in dioxane solution at 25°. The method used in calculating the moment was that of Halverstadt and Kumler.[5] The ϵ_{12} values

$$p_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{2_0} = p_{2_0} M_2$$

$$\mu = 0.01281 \sqrt{(P_{2_0} - P_{E_{2_0}})T}$$

were linear with respect to ω_2. The v_{12} values departed somewhat from linearity on the first series of measurements. Four additional solutions were then measured and the v_{12} values of these were linear with respect to ω_2. The values of ϵ_1 and v_1 were obtained by extrapolating the ϵ_{12} and v_{12} values to $\omega_2 = 0$. $P_{E_{2_0}}$ values were obtained from the refractive index of the more concentrated solutions.

(4) Chain (from work of Crowfoot, Bunn, Rogers-Low and Turner-Jones), *Endeavour*, **7**, 152 (1948).

(5) Halverstadt and Kumler, THIS JOURNAL, **64**, 2988 (1942).

MEASUREMENTS IN DIOXANE AT 25°, METHYL BENZYLPENICILLINATE

ω_2	ϵ_{12}	v_{12}
0.001951	2.2311	0.97353
.004392	2.2505	.97315
.006669	2.2690	.97277
.007647	2.2787	.97268
.008992	2.2892	.97259
.001262		.97291
.001875		.97382
.003981		.97333
.007306		.97268

ϵ_1 extrap.	v_1 extrap.	α	β	P_{2_0}	$P_{E_{2_0}}$	μ
2.2147	0.97418	8.28	−0.209	550.8	93.0	4.73

The observed dipole moment of methyl benzylpenicillinate is 4.73 with an estimated accuracy of ±0.02. The value is within the range of the moment calculated using the accepted structure of benzylpenicillin. This value of the dipole moment is further confirmatory evidence for the correctness of the generally accepted structure of penicillin and removes any support which the higher reported dipole moment value of 8 gave to the previously proposed zwitterion-incipient azlactone structure for penicillin.[6]

Materials

Dioxane.—Dioxane was purified as before.[7]

Methyl Benzylpenicillinate.—Fifteen grams of potassium benzylpenicillin assaying 1577 units per mg. was treated by a modification of the procedure given in the Merck O.S.R.D. Report M-15b p. 1, and also in the "Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, p. 93. The ether solution of the free acid was dried by freezing out the ice at −70° and filtering. The solution was treated with a slight excess of diazomethane. Esterification was complete in fifteen minutes. The solution was concentrated *in vacuo* to an oily residue weighing 30 g. which was diluted with 70 g. of carbon tetrachloride and seeded with crystals by courtesy of D. S. Melstrom of Shell Development Co. After standing overnight the crystals were filtered off and dried; yield 10 g. Additional material was recovered to make a total of 11.26 g. This material was crystallized once from ether and once from carbon tetrachloride to yield 9.55 g. which softened at 94–95° and melted at 96–97° at 3° per min.

Summary

The dipole moment of methyl benzylpenicillinate was measured in dioxane and found to have a value of 4.73. This observed value is consistent with the calculated value using the usual group moments and the accepted structure of penicillin. Any support which the previously reported moment of 8 gave to the once proposed zwitterion-incipient azlactone structure for penicillin is thus removed.

SAN FRANCISCO, CALIFORNIA
BERKELEY, CALIFORNIA

RECEIVED APRIL 30, 1949

(6) Committee on Medical Research O. S. R. D., Washington, and Medical Research Council, London, *Science*, **102**, 627 (1945).

(7) Kumler and Halverstadt, THIS JOURNAL, **64**, 1941 (1942).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Rotatory Dispersions of Some *p*-Phenylazophenyl β-D-Glycosides[1]

BY WILLIAM A. BONNER

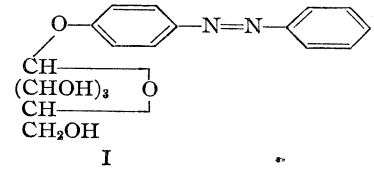
Measurements of rotatory dispersion shown by simple sugars and their derivatives have indicated that specific rotation varies with wave length in the visible spectrum according either to a simple Drude equation of the type

$$[\alpha]\lambda = k/(\lambda^2 - \lambda_0^2) \qquad (1)$$

where k is the "rotation constant" and λ_0^2 the "dispersion constant," or to a more complex equation involving several terms similar to that in equation (1). In common with other optically active compounds, however, the simple or complex rotatory dispersions characteristic of measurements on sugars with visible light may become anomalous[2] in the ultraviolet regions as the wave length of the light approaches that corresponding to a specific absorption band in the molecule. It is known that the light absorbing group must be located in the close vicinity of the asymmetric center, and it is believed[2] that the asymmetric center imparts an induced dissymmetry to the chromophoric group which in turn contributes to the optical activity of the molecule, giving rise to anomalous dispersion when disturbed by light of the proper frequency. Thus the dispersion constant, λ_0^2, in equation (1) frequently corresponds to the wave length characteristic of an absorbing group near the asymmetric center.

There have been reported no experiments designed to test the possibility that absorbing groups further situated from an asymmetric center might also give rise to dispersion anomalies when coupled with the asymmetric center by appropriate conjugation. Experiments designed to test this possibility are reported in the present paper.

The absorption spectra of *p*-phenylazophenyl β-D-glycosides such as I have recently been meas-



I

ured.[3] Such spectra for a number of glycosides related to I have been found almost identical and, as was expected, quite similar to the spectra of the phenolic aglycone. Two distinct absorption bands were observed between 240 and 800 mμ: a relatively low intensity "R-band"[4] with a maximum around 436 mμ and a high intensity "K-band" with a maximum around 338 mμ. A third and more intense band below 240 mμ was also evident. It has been suggested[4] that the R-band in compounds such as I is due to the isolated azo linkage, and the K-band to the conjugated *p*-phenylazophenyl chromophore as a whole.

To the extent that this interpretation of the spectra of azo compounds is valid, one would expect the optical activity of compounds such as I to be affected by the *p*-phenylazophenyl chromophore causing the K-band, since this chromophore had its origin close to the first center of optical activity. We have attempted to determine if the azo chromophore causing the R-band might also affect the optical activity. At long wave lengths where solutions of I are transparent such an effect might not be expected, but it seemed reasonable to look for anomalous dispersion when wave lengths in the vicinity of the R-band were employed. Electronic disturbances of the azo chromophore by light of the R-band wave lengths might interact through the conjugation of the benzene ring with the first asymmetric center in I thus causing anomalous effects.

A serious experimental difficulty has prevented us from observing the optical effects we desired to study. The molar extinction coefficients of compounds such as I were in the neighborhood of 24000 for the high intensity K-band and 890 for the low intensity R-band.[3] These extinctions were so high that, even at high dilution, it was impossible to make polarimetric readings with light even in the longer wave length regions of the R-band. As soon as the initial R-band wave lengths were approached (*i. e.*, in the vicinity of 540 mμ) the optical densities of our solutions became so great that accurate polarimetric measurements were impossible. Thus with compounds such as I we have been unable to test the effect of distant chromophores which are conjugated with centers of optical activity on the rotations caused by these optically active centers. This problem is being studied at the present time with compounds whose absorption bands are characterized by lower extinction coefficients.

We have, however, been able to study the rotatory dispersion of compounds such as I for wave lengths above their R-band region. Since difficulties due to strong light absorption were anticipated, *p*-phenylazophenyl β-D-glucoside and *p*-phenylazophenyl β-D-galactoside were employed in these studies because of their relatively high specific rotations.[5] The dispersions of these compounds were measured in dioxane in the region from 667 to 524 mμ. The observed dispersions and their close similarities are illustrated graphically

(1) Presented before the Division of Sugar Chemistry, Portland, Oregon, September, 1948.

(2) Harris, Hirst, *et al.*, *J. Chem. Soc.*, 1403 (1935), 1658 (1936); Lowry, Wolfrom, *et al.*, *ibid.*, 696 (1933); 1179 (1935); Dimler and Link, THIS JOURNAL, **62**, 1216 (1940).

(3) Zelinski and Bonner, *ibid.*, **71**, 1791 (1949).

(4) Burawoy, *J. Chem. Soc.*, 1865 (1937).

(5) Hurd and Zelinski, THIS JOURNAL, **69**, 243 (1947).

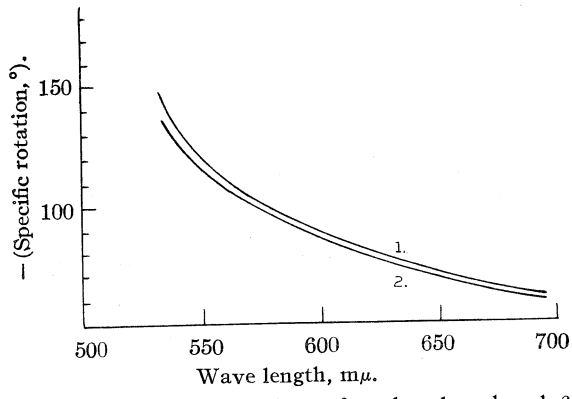


Fig. 1.—Rotatory dispersions of *p*-phenylazophenyl β-D-glucoside and β-D-galactoside, Ar = *p*-$C_6H_4N{=}NC_6H_4$–: 1, Ar β-D-glucoside; 2, Ar β-D-galactoside.

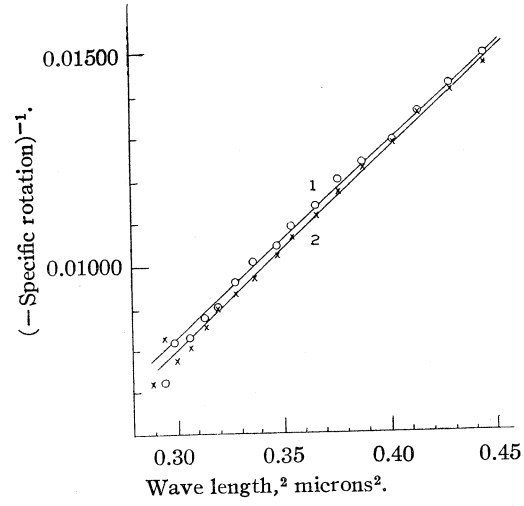


Fig. 2.—$1/[\alpha]$ *vs.* λ^2 for *p*-phenylazophenyl β-D-glucoside and β-D-galactoside: 1, Ar = *p*-$C_6H_4N{=}NC_6H_4$–: 1, Ar β-D-glucoside, O; 2, Ar β-D-galactoside, ×.

in Fig. 1. The curves in Fig. 1 can be expressed mathematically with fair accuracy by means of the simple Drude formula of equation (1). On plotting the reciprocal of the observed specific rotation against the square of the wave length (Fig. 2) the linear relation characteristic of simple dispersion was found very nearly to hold. The slopes of the lines in Fig. 2 give rotation constants of −21.90 and −21.05, respectively, for *p*-phenylazophenyl β-D-glucoside and β-D-galactoside. Now knowing k of equation (1) for each compound it is possible, by substituting a measured specific rotation and wave length into the equation, to evaluate λ_0^2 and thus λ_0. This dispersion constant was determined to be 339 mμ for the glucoside and 342 mμ for the galactoside. These values are in striking agreement with the 338 mμ measured spectrophotometrically[3] for the position of maxima of the high intensity K-bands in compounds of type I. It is thus quite apparent that the conjugated *p*-phenylazophenyl chromophore is the one which affects the optical activity of type I compounds in the transparent regions of their spectrum. This observation, incidentally, is in accord with Burawoy's assignment[4] of the two absorption bands to their respective chromophores in the molecule.

As a further test of the simple dispersion observed in the transparent spectral regions we have used our values of k and λ_0 to calculate the specific rotation at each of our measured wave lengths. The calculated specific rotations, the observed specific rotations, and the average deviations from the means of the latter are recorded in Table I. With respect to the glucoside it is seen that the observed rotations agree with the calculated quite within the experimental error for longer wave lengths. From about 572 mμ downward, however, there seems to be a divergence in calculated and observed rotations which is beyond experimental error. This occurs in those very regions of the spectrum where the R-band absorption is just becoming evident and suggests that there is some interaction due to conjugation between the distant azo chromophore and the C-1 center of asymmetry as the electronic system of the azo chromophore becomes disturbed. It is most unfortunate that the high extinction coefficients characteristic of the absorption bands in our compounds prevented further polarimetric observation at the very point that this interesting divergence began to appear.

The agreement betwen observed and calculated specific rotations for the galactoside is not as satisfactory as in the case of the glucoside, due apparently to the fact that the dispersion of the galacto-

TABLE I

ROTARY DISPERSIONS OF SEVERAL *p*-PHENYLAZOPHENYL β-D-GLYCOSIDES

Wave length, mμ	Specific rotation, ° Glucoside Calcd.	Glucoside Observed	Galactoside Calcd.	Galactoside Observed	Acetylated galactoside Calcd.	Acetylated galactoside Observed
693			−58.0	−58.9[a]	+16.4	+13.2[b]
679			61.5	62.5	17.3	14.8[g]
667	−66.4	−66.6[a]	64.3	65.3	18.1	16.3[b]
655	69.9	70.0	67.5	68.1	19.0	18.2[g]
643	73.3	73.4	70.9	70.9	20.0	20.0
633	76.6	77.3	74.2	74.4	20.9	20.4
622	80.5	80.6	78.0	78.0	22.0	22.0
613	84.0	83.4	81.4	82.0	22.9	22.3
604	87.8	87.8[b]	84.9	85.4	23.9	25.0
595	91.7	91.7	88.9	89.4	25.0	25.8
589	94.5	95.5	91.6	93.4	25.8	25.0[b]
580	99.2	99.5	96.1	97.8	27.1	27.2[e]
572	103.2	104.4	100.1	101.6	28.2	31.8
565	107.2	110.6	104.1	105.5	29.3	33.3
559	110.6	113.9	107.2	110.5[e]	30.2	32.6
553	114.6	120.0[c]	111.2	116.0	31.4	36.4[h]
547	119.0	122.2	115.6	120.0[f]		
542[1]	122.2	138.1[d]	118.9	113.5		

Average deviation from mean value[2]: [a] 0.5 to 0.6; [b] 1.0 to 1.2; [c] 2.2; [d] 6.4; [e] 1.5 to 1.8; [f] 3.3; [g] 0.7 to 0.8; [h] 4.5.

[1] Measurements below 542 mμ were subject to such large experimental errors due to the high optical density of the solutions that the data are of doubtful significance and, therefore, not included.

[2] The deviation for an unlettered figure is that of the first lettered figure appearing above it.

side is not strictly simple. This trend away from simple dispersion is even more evident in *p*-phenylazophenyl tetraacetyl-β-D-galactoside, where the discrepancies in rotation between those observed and those calculated by equation (1) are even greater. It is interesting to note in Table I that the negative rotation of the unacylated glycosides become more negative with decreasing wave length, whereas the positive rotation of the acetylated galactoside becomes more positive. No attempts were made to extend dispersion measurements to other *p*-phenylazophenyl β-D-glycosides because of the comparatively low specific rotations of the known members of this class[5] and the high extinction coefficients of their absorption bands.[3]

Experimental Part

Dispersion measurements were made with a Lippich–Landolt precision polarimeter no. 80 and spectroscope monochromator no. 85[6] manufactured and calibrated by O. C. Rudolph and Sons. Solutions of the *p*-phenylazophenyl β-D-glycoside (10^{-1} molar for the glucoside and galactoside and 5×10^{-2} molar for the acetylated galactoside) were made in commercial dioxane and placed in a 10-ml. 1-dcm. polarimeter tube. Measurements were made at room temperature (*ca.* 23°) with no thermostating. Readings were taken at wave lengths indicated in Table I. The half-shade angle of the polarimeter was kept at 5 on its scale during all readings, and the slit widths on the monochromator were varied between 0.3 and 0.6 mm. depending upon the amount of light which would traverse the solution. Measurements were made at the concentrations indicated until increasing optical densities with decreasing wave length made matching of the polarimeter field impossible. At this point the solutions were diluted to 50% of their initial concentration with dioxane. Readings were continued until dilution was again necessary. One or two dilutions were usually sufficient to obtain data as in Table I. The dilution technique could not be employed to permit lower wave length readings as the observed rotation rapidly decreased with each dilution until the experimental errors of measurement made the results meaningless for comparative purposes.

(6) Purchased with a grant kindly furnished by The Research Corporation, New York.

Summary

Rotatory dispersion measurements on *p*-phenylazophenyl β-D-glucoside, β-D-galactoside, and tetraacetyl-β-D-galactoside have been conducted in order to see if the isolated azo chromophore of the aglycone might cause anomalous dispersion by interacting with the asymmetric centers through the conjugation of the benzene ring. The high extinction coefficients characteristic of the absorption bands in the aglycone, however, prevented dispersion measurements as the wave length of the first absorption band was approached.

In the transparent regions of the spectrum the dispersion of the unacylated glycosides was very nearly simple. Divergencies from simple behavior of possible significance were observed as the first absorption band of the aglycone was approached.

The wave length of the active absorption band calculated from a simple Drude equation agreed very well with the wave length of the ultraviolet absorption band as measured spectrophotometrically, indicating that the isolated azo chromophore in the aglycone had no effect on the rotation in the visible regions of the spectrum.

STANFORD, CALIFORNIA RECEIVED APRIL 18, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Thermal Data on Organic Compounds. XXV. Some Heat Capacity, Entropy and Free Energy Data for Nine Hydrocarbons of High Molecular Weight

BY GEORGE S. PARKS, GEORGE E. MOORE, MELVIN L. RENQUIST, BENJAMIN F. NAYLOR, LESLIE A. MCCLAINE, PAUL S. FUJII AND JOHN A. HATTON

In a series of investigations carried out at Stanford University between 1937 and 1944 heat capacity measurements were made upon twelve hydrocarbons of high molecular weight. From the data thus obtained the corresponding molal entropies were derived and in most instances the free energies of formation were also computed with the aid of available heats of combustion. Results for three of these hydrocarbons (11-*n*-decylheneicosane,[1] and *cis*- and *trans*-decahydronaphthalene[2]) have already been published in other connections. In the present paper we shall present similar results for the remaining nine compounds: *n*-hexadecane, *n*-octadecane, *n*-tetracosane, *n*-dotriacontane, ethylcyclohexane, *n*-heptylcyclohexane, *n*-dodecylcyclohexane, 11-cyclohexylheneicosane and 11-phenylheneicosane.

Materials

The hydrocarbon samples were the best obtainable at the time of these measurements, although more recently *n*-hexadecane and ethylcyclohexane have become available in much purer form. Most of the materials were also used in This Laboratory in determinations of the heats of combustion, in which work non-hydrocarbon impurities are especially serious. Accordingly, appropriate tests were run for ash content, the presence of halogens and in

(1) F. B. Fischl, B. F. Naylor, C. W. Ziemer, G. S. Parks and J. G. Aston, THIS JOURNAL, **67**, 2075 (1945).

(2) G. S. Parks and J. A. Hatton, *ibid.*, **71**, 2773 (1949).

some cases the carbon–hydrogen ratio. The results of such tests were entirely satisfactory for the materials used in this study. The observed melting points and the mole % purity, as estimated in the course of fusion determinations, are given in Table I. In all cases the impurities in the samples must have been primarily isomers or neighboring members of a homologous series, and these should not produce appreciable errors in the measured heat capacities except in the temperature region approaching the melting point.

TABLE I

MELTING POINTS AND ESTIMATED PURITY

Hydrocarbon	Formula	M. p., °K.	Purity, mole %
n-Hexadecane	$C_{16}H_{34}$	290.2	95.
n-Octadecane	$C_{18}H_{38}$	300.8	96.0
n-Tetracosane	$C_{24}H_{50}$	323.0	..
n-Dotriacontane	$C_{32}H_{66}$	342.7	..
Ethylcyclohexane	C_8H_{16}	161.2	99.1
n-Heptylcyclohexane	$C_{13}H_{26}$	232.0	97.1
n-Dodecylcyclohexane	$C_{18}H_{36}$	285.6	98.8
11-Cyclohexylheneicosane	$C_{27}H_{54}$	266.5	96.7
11-Phenylheneicosane	$C_{27}H_{48}$	294.0	97.7

The sources of our samples of *n*-hexadecane and *n*-octadecane were Eastman Kodak Co. materials, which were further purified in the procedures described, respectively, by Richardson and Parks[3] and by Parks[4] and coworkers. On the other hand, the Eastman *n*-tetracosane and *n*-dotriacontane were used without any additional purification. The ethylcyclohexane was part of a preparation from the laboratory of Professor C. E. Boord of Ohio State University. The samples of *n*-heptylcyclohexane and *n*-dodecylcyclohexane were prepared at Stanford University under the direction of Professor C. R. Noller, and their properties have been described in detail by Moore, Renquist and Parks.[5] The 11-cyclohexylheneicosane and 11-phenylheneicosane were compounds prepared in the work of American Petroleum Institute Research Project 42 at the Pennsylvania State College.[6]

Experimental Results

In principle, the method of Nernst was employed with an aneroid calorimeter in determining the "true" specific heats and the fusion data. The apparatus and details of experimental procedure have been fully described in other places.[7] In view of the accuracy of the various measurements involved, the absolute error in the experimental values thereby obtained is ordinarily less than 0.7%, except insofar as impurities in a sample may cause premelting at the upper temperatures of the crystals. The fortuitous errors are usually under 0.25%; and this latter figure may also be considered our probable *relative* error in making comparisons among these hydrocarbons.

Generally more than forty specific heat determinations in the temperature interval between 78 and 300°K. were made on each hydrocarbon. The results were then plotted on a large scale, a smooth curve through the experimental data was drawn, and specific heat values were read off from this curve for various even temperatures. For the sake of spatial economy and ease of comparison these derived values, rather than the more numerous experimental ones, are recorded in Table II. They and also the fusion data of Table III are expressed in terms of the *defined* conventional calorie[8] and with all weights reduced to a vacuum basis.

Three of these hydrocarbons exhibited small but distinct "humps" in the specific heat curves for the crystals. In the case of *n*-octadecane this hump came within the interval 228–240°K. and yielded a locally maximum C_p value of 0.365 cal. per gram at 237°. For *n*-tetradecane the hump range was 250–265° with a maximum of 0.420 cal. per gram for C_p at 262°, and for *n*-dodecylcyclohexane the range was 229–249° with a maximum of about 0.380 at 245°K.

Several of these liquid hydrocarbons could be supercooled to some extent, and in particular the ethylcyclohexane was first obtained as a typical glassy material at the temperature of liquid air. In this state it showed C_p values per gram of 0.175, 0.330 and 0.328 at 97, 100 and 110°K., respectively.

Apparently the recent investigation of the heat capacities of ethylcyclohexane by Huffman, Todd and Oliver[9] provides us with the only comparable data now available for any of these compounds. These investigators worked with a purer material than ours, and obtained specific heats which, outside of our premelting range, average 0.35% lower than our curve and a heat of fusion which is 0.68% above our mean value.

Entropy Data

Using the heat capacity data contained in the preceding section in conjunction with the third law of thermodynamics, we have calculated the entropies at 298.16°K. for these nine hydrocarbons. The detailed data are given in Table IV. In these calculations we have employed the extrapolation method of Kelley, Parks and Huffmann[10] for estimating the entropy increases of the crystals from 0 to 80°K. The various increments from 80 to 298.16°K., which appear in the next three columns, were obtained by the usual methods directly from the experimental data. The results for the total entropy are then given in the second column from the right under the designation "S^0_{298}"; they are probably reliable to within 1% in an absolute sense and to about half this figure for comparative purposes. In this connection it should be noted that the later and more ac-

(3) J. W. Richardson and G. S. Parks, THIS JOURNAL, **61**, 3543 (1939).

(4) G. S. Parks, T. J. West, B. F. Naylor, P. S. Fujii and L. A. McClaine, *ibid.*, **68**, 2524 (1946).

(5) G. E. Moore, M. L. Renquist and G. S. Parks, *ibid.*, **62**, 1505 (1940).

(6) F. C. Whitmore, J. N. Cosby, W. S. Sloatman and D. G. Clarke, *ibid.*, **64**, 1801 (1942).

(7) G. S. Parks, *ibid.*, **47**, 338 (1925); also G. S. Parks and K. K. Kelley, *J. Phys. Chem.*, **30**, 47 (1926).

(8) The factor 1/4.1833 has been used in converting the international joule to the defined calorie.

(9) H. M. Huffman, S. S. Todd and G. D. Oliver, THIS JOURNAL, **71**, 584 (1949).

(10) K. K. Kelley, G. A. Parks and H. M. Huffman, *J. Phys. Chem.*, **33**, 1802 (1929). In the case of compounds like 11-cyclohexylheneicosane, a weighted mean of the entropy extrapolations as calculated with the aliphatic and cyclic constants has been used.

TABLE II

SPECIFIC HEATS (C_p) IN CALORIES PER GRAM OF SUBSTANCE

s = crystalline; l = liquid

T, °K.	$C_{16}H_{34}$	$C_{18}H_{38}$	$C_{24}H_{50}$	$C_{32}H_{66}$	C_8H_{16}	$C_{13}H_{26}$	$C_{18}H_{36}$	$C_{27}H_{54}$	$C_{27}H_{48}$
80	0.1591 *s*	0.1552 *s*	0.1498 *s*	0.1477 *s*	0.1407 *s*	0.1432 *s*	0.1388 *s*	0.1411 *s*	0.1375 *s*
90	.1745	.1707	.1653	.1613	.1531	.1557	.1513	.1560	.1493
100	.1885	.1842	.1800	.1745	.1654	.1680	.1630	.1681	.1610
110	.2013	.1967	.1935	.1875	.1775	.1801	.1742	.1788	.1725
120	.2134	.2082	.2057	.2004	.1896	.1922	.1855	.1902	.1840
130	.2251	.2200	.2165	.2126	.2019	.2047	.1968	.2015	.1945
140	.2360	.2318	.2262	.2228	.216	.2180	.2072	.2125	.2040
150	.2464	.2426	.2359	.2320	.252 *s*	.2314	.2173	.2234	.2128
160	.2565	.2535	.2465	.2417	.3410 *l*	.2410	.2275	.2345	.2224
170	.2675	.2648	.2582	.2524	.3475	.2500	.2378	.2436	.2318
180	.2784	.2762	.2705	.2639	.3540	.2628	.2485	.2538	.2413
190	.2895	.2881	.2825	.2757	.3605	.279	.2598	.2657	.2510
200	.3010	.3011	.2947	.2885	.3676	.302 *s*	.2719	.2778	.2620
210	.3135	.3153	.3074	.3030	.3750	.....	.2838	.2899	.2737
220	.3265	.3285	.3230	.3176	.3823	.....	.2955	.3019	.2850
230	.341	.349	.3396	.3333	.3895	.....	.3110	.3164	.2968
240	.359	.355	.358	.349	.3967	.4269 *l*	.338	.3340	.3090
250	.380	.365	.382	.367	.4050	.4344	.338	.358 *s*	.3210
260	.405	.381	.413	.386	.4150	.4421	.359	.....	.334
270	.445 *s*	.404	.410	.405	.4250	.4505	.416 *s*	.471 *l*	.352
280	.....	.456 *s*	.432	.426	.436	.460	.....	.482	.388 *s*
290	.528 *l*	.....	.474	.447	.447	.469	.488 *l*	.491	.....
300	.533 *l*	.530 *l*	.526 *s*	.469 *s*	.458 *l*	.478 *l*	.496 *l*	.498 *l*	.491 *l*

TABLE III

FUSION DATA[a]

Hydrocarbon	M. p., °K.	Heat of fusion (cal. per g.) I	II	Mean
n-Hexadecane	291.1	54.40	...	54.40
n-Octadecane	301.3	56.68	56.93	56.80
Ethylcyclohexane	161.4	17.64	17.61	17.63
n-Heptylcyclohexane	232.8	28.97	29.29	29.13
n-Dodecylcyclohexane	285.8	43.42	43.36	43.39
11-Cyclohexylheneicosane	266.9	30.82	30.63	30.73
11-Phenylheneicosane	294.3	41.56	41.52	41.54

[a] In the calculation of these fusion values, the somewhat more rapid rise in the specific heat of the crystals as the melting point is approached was attributed to premelting; and the heat absorbed in this region in excess of that obtained by extrapolation of the specific heat data at lower temperatures was added to the heat absorbed at the melting point.

curate entropy result of Huffman[9] and co-workers for ethylcyclohexane is only about 0.23% less than our value tabulated here.

For the cases of *n*-octadecane and *n*-dotriacontane, which are crystalline substances at 298.16° K., we have also computed the entropy changes in the hypothetical fusion process at this temperature so as to be able to compare these compounds with others in the liquid state. In these computations we have used for the octadecane our own fusion data in Table III and for dotriacontane the estimate made by Parks and Rowe[11] for the heat of fusion.

The values of the entropies of formation (ΔS_f^0) given in the extreme right-hand column of Table IV represent simply the differences between the S_{298}^0 for each hydrocarbon and the corresponding values for the entropies contained therein. For this purpose we have used 31.211 e. u. for the entropy of hydrogen and 1.361 e. u. for C (β-graphite).[12]

While it is the intention of the senior author to present elsewhere in the near future a review of entropy regularities among both hydrocarbons and representative organic compounds containing oxygen, a few significant features relating to these tabulated S_{298}^0 values may be briefly noted here. Thus there is a fairly constant effect per CH_2 increment. Starting with the value of 70.76 e. u. as obtained by Douslin and Huffman[13] for liquid *n*-hexane, we find an average increase of 7.90 per CH_2 in going up the liquid paraffin series to *n*-hexadecane, 7.98 to *n*-octadecane and 8.05 e. u. to the hypothetical liquid *n*-dotriacontane. Likewise, there is an average increase of 7.98 e. u. per CH_2 increment in the liquid cyclohexane series from the ethyl to the dodecyl compound. By similar reasoning, the value of 51.3 e. u. may be assigned as the entropy contribution of the cyclohexyl group in a normal cyclohexane series involving liquids. On the other hand, the introduction of the cyclohexyl and phenyl groups in the middle of the heneicosane chain apparently produces entropy decreases, due to branching, of 7.6 and 5.4 e. u., respectively.

Free Energy Data

We have also calculated the free energies of formation of these hydrocarbons (except *n*-tetra-

(11) G. S. Parks and R. D. Rowe, *J. Chem. Phys.*, **14**, 507 (1946).

(12) D. D. Wagman, J. E. Kirkpatrick, W. J. Taylor, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Standards*, **34**, 143 (1945).

(13) D. R. Douslin and H. M. Huffman, THIS JOURNAL, **68**, 1704 (1946).

TABLE IV

ENTROPIES OF THE HYDROCARBONS IN CALORIES PER DEGREE PER MOLE

s = crystalline; l = liquid

Substance	Molecular weight	Crystals 0–80°K.	Crystals Above 80°K.	Fusion	Liquid	S^0_{298}	$-\Delta S^0_f$ at 298.16°K.
n-Hexadecane (*l*)	226.432	27.88	76.82	42.31	2.83	149.8	402.56
n-Octadecane (*s*)	254.484	30.52	88.21			118.7	498.81
n-Octadecane (*l*)				47.77		166.5	451.01
n-Tetracosane (*s*)	338.640	38.36	117.23			155.6	657.34
n-Dotriacontane (*s*)	450.848	51.33	152.21			203.5	870.01
n-Dotriacontane (*l*)				76.5		280.0	793.51
Ethylcyclohexane (*l*)	112.208	13.80	14.55	12.25	26.66	67.3	193.28
n-Heptylcyclohexane (*l*)	182.338	21.52	42.28	22.82	20.17	106.8	316.63
n-Dodecylcyclohexane (*l*)	252.468	28.51	75.02	38.33	5.22	147.1	439.19
11-Cyclohexylheneicosane (*l*)	378.702	41.80	105.60	43.59	20.28	211.3	668.14
11-Phenylheneicosane (*l*)	372.654	41.12	111.36	52.60	2.37	207.4	578.41

cosane) by means of the fundamental thermodynamic equation, $\Delta F = \Delta H - T\Delta S$. The results as well as the contributing enthalpy data are recorded in Table V, where for comparative purposes we have included a result for 11-*n*-decylheneicosane, based on the entropy value of Naylor and Parks.[1]

TABLE V

ENTHALPIES AND FREE ENERGIES AT 298.16°K.

In kcal. per mole

Substance	ΔH^0_f	ΔF^0_f
n-Hexadecane (*l*)	−108.72	11.30
n-Octadecane (*s*)	−135.92	12.80
n-Octadecane (*l*)	−121.54	12.94
n-Dotriacontane (*s*)	−231.82	27.58
n-Dotriacontane (*l*)	−205.36	31.23
Ethylcyclohexane (*l*)	−50.72	6.91
n-Heptylcyclohexane (*l*)	− 84.51	9.90
n-Dodecylcyclohexane (*l*)	−112.01	18.94
11-*n*-Decylheneicosane (*l*)	−201.72	30.38
11-Cyclohexylheneicosane (*l*)	−165.07	34.14
11-Phenylheneicosane (*l*)	−120.83	51.63

The tabulated value for the enthalpy of formation (ΔH^0_f) of ethylcyclohexane has been taken from the work of Prosen, Johnson and Rossini.[14] That for *n*-hexadecane has been computed from a molal heat of combustion of 2557.50 kcal., which value represents a weighted (6 to 1) mean of the combustion determinations of Prosen and Rossini[15] and of Richardson and Parks.[3] The ΔH^0_f values for the remaining hydrocarbons have been taken from the combustion studies of Parks and co-workers,[3,4,5] with appropriate revisions, where necessary, to the present-day standards.[16]

In general, the free energies as derived from these ΔH^0_f quantities and the ΔS^0_f values in Table IV are probably reliable to within 0.05 or 0.06 kcal. per carbon atom, although in one or two instances, including that of *n*-heptylcyclohexane, the error may be appreciably greater than these figures. In this connection it should be noted that such calculations of free energy put a much heavier requirement for accuracy upon the measurement of the heat of combustion than upon the evaluation of the entropy. For example, in the case of 11-*n*-decylheneicosane an error of 1% in the molal entropy amounts to 2.62 e. u. and corresponds to 0.78 kcal. in free energy, while a mere 0.03% error in the heat of combustion corresponds to 1.47 kcal.

On the basis of these tabulated free energies we have deduced 1.21 kcal. for the average change in molal free energy per CH_2 increment in the series of liquid normal paraffins and normal alkylcyclohexanes. Likewise, through these and other data we have arrived at 12.8 kcal. as the approximate contribution of the cyclohexyl group in a series of liquid straight-chain compounds.

Summary

1. The specific heats of nine hydrocarbons of high molecular weight have been measured between 78 and 300° K. The corresponding heats of fusion have also been determined in seven cases.

2. The entropies of these hydrocarbons in the liquid or crystalline states at 298.16° K. have been calculated from the foregoing heat capacity data, and certain structural contributions have been noted.

3. The corresponding molal free energies have also been calculated. From these and other data values of 1.21 kcal. and 12.8 kcal. have been deduced for the respective contributions of a CH_2 increment and a cyclohexyl group in liquid straight-chain compounds.

STANFORD, CALIFORNIA RECEIVED MAY 18, 1949

(14) E. J. Prosen, W. H. Johnson and F. D. Rossini, *J. Research Natl. Bur. Standards*, **37**, 51 (1946).

(15) E. J. Prosen and F. D. Rossini, *ibid.*, **33**, 255 (1944).

(16) R. S. Jessup, *ibid.*, **29**, 247 (1942).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Photochemical Studies. XLI. The Photochemistry of Dimethyl Mercury[1]

BY ROBERT GOMER[2] AND W. ALBERT NOYES, JR.

It was found during an investigation to be reported later that methyl radicals are almost certainly intermediates in the direct photochemical decomposition of ethylene oxide. The study of the reactions of CH_3 radicals with that molecule was, therefore, advisable and for this purpose the photochemical decomposition of $Hg(CH_3)_2$ was found to be convenient. Certain aspects of the decomposition of the latter molecule need further clarification.[3]

Experimental

Dimethyl mercury was prepared by the method of Gilman and Brown.[4] It was purified by fractional distillation in a column and then by bulb to bulb distillation at low temperatures. Vapor pressures agreed with the values of Linnett and Thompson.[5] The compound was degassed repeatedly after condensation by dry ice.

Two quartz reaction vessels were used: (a) 20 cm. length, 2.4 cm. inside diameter; (b) 3.5 cm. length, 2.0 cm. inside diameter. They were attached by quartz to Pyrex graded seals through mercury cut-offs to a line without stopcocks. The dead space during illumination was about 3 cc. In the case of the short cell it was necessary to replenish the $Hg(CH_3)_2$ periodically to prevent more than 10% decomposition.

The cells were placed in a brass cylinder about 10 cm. in diameter which could be heated electrically. Temperatures were read on thermometers placed in holes in the brass cylinder and by a thermocouple placed in a well in the vessel near the rear window. Extreme variations did not exceed three degrees.

Two different light sources were used: (a) a Hanovia medium pressure arc, S353; (b) a General Electric Company AH-6 high pressure arc. Filters were not used and radiation passing through a hole in a diaphragm next to the arc was made approximately parallel by a quartz lens, so that the cells were filled as completely and as uniformly as possible with radiation.

The absorption spectum of $Hg(CH_3)_2$ has been investigated by several authors, particularly Thompson and Linnett[6] and Terenin and Prileshayewa.[7] These authors agree that the spectrum is continuous in the neighborhood of 2500 Å., but long wave limits are placed at 2550 and 2800 Å., respectively.

The products uncondensed by liquid nitrogen (CH_4 with some C_2H_6) were separated from the $Hg(CH_3)_2$ by Toepler pumps. The remaining C_2H_6 and C_2H_4 (if any) were separated from $Hg(CH_3)_2$ by use of a modified Ward apparatus.[8] Combustions with oxygen over a heated platinum wire were usually used, but unsaturates were determined by fuming sulfuric acid, using a Blacet–Leighton apparatus.[9]

Light intensities with a given arc were varied by neutral density filters. These consisted of quartz plates, 1 mm.

TABLE I

RATES OF FORMATION OF METHANE AND OF ETHANE DURING PHOTOCHEMICAL DECOMPOSITION OF $Hg(HC_3)_2$

V = 590 cc. (for measurement of gas pressures of products); cell, 20 cm. long, 2.4 cm. diameter (V = 90.4 cc.); pressure of $Hg(CH_3)_2$ = 5 mm. (at 300°K.); rates in microns/hr. (at 300°K.).

Run	Temp., °C.	R_{CH_4}	$R_{C_2H_6}$	$R_{C_2H_6}/R_{CH_4}$
DM-8	175	20.1	1298	64.6
E-5		13.8	631	45.7
DM-9		11.0	422	38.4
E-1		3.22	55.7	17.3
2		1.77	22.5	12.7
3		0.742	4.84	6.52
8		.794	5.50	6.93
4		.544	2.16	3.97
Blank		.04	.....	...
DM-11	220	41.0	836	20.4
10		29.1	450	15.5
12		9.46	67.2	7.10
13		9.04	60.3	6.67
15		5.49	23.7	4.32
14		2.37	3.78	1.59
Blank		0.658	2.84	...

TABLE II

RATES OF FORMATION OF METHANE AND OF ETHANE DURING PHOTOCHEMICAL DECOMPOSITION OF $Hg(CH_3)_2$

V = 590 cc. (for measurement of gas pressures of products); cell, 3.5 cm. long, 2.0 cm. diameter (V = 11.0 cc.); rates in microns/hr. (at 300°K.); T = 175°C.

Run	R_{CH_4}	$R_{C_2H_6}$	$Hg(CH_3)_2$ Pressure, mm.	$R_{C_2H_6}/R_{CH_4}$
F-11	12.4	508.5	20 (at 175°)	41.0
9	10.2	395.6		38.8
1	10.0	355.9		35.6
6	7.21	233.8		32.4
2	5.84	130.1		22.3
5	5.13	118.9		23.1
14	3.42	50.6		14.8
3	2.55	29.1		11.4
4	1.98	20.3		10.3
12	20.1	700.5	30 (at 175°)	34.9
16	11.7	287.8		24.6
7	10.5	223.6		21.3
10	9.78	224.3		22.9
8	6.03	107.4		17.8
13	4.98	55.2		11.1
15	3.21	24.3		7.58

(1) This work was supported in part by Contract N6onr-241, Task I, with the Office of Naval Research, United States Navy.

(2) E. I. du Pont de Nemours and Company Fellow during 1948–1949.

(3) See W. A. Noyes, Jr., and P. A. Leighton, "The Photochemistry of Gases," The Reinhold Publishing Corporation, New York, N. Y., 1941, for a review of work through 1939. Later references will be given in the present article.

(4) H. Gilman and R. E. Brown, THIS JOURNAL, **52**, 3314 (1930).

(5) J. W. Linnett and H. W. Thompson, *Trans. Faraday Soc.*, **32**, 681 (1936).

(6) H. W. Thompson and J. W. Linnett, *Proc. Roy. Soc.* (*London*), **A156**, 108 (1936).

(7) A. Terenin and N. Prileshayewa, *Acta Physicochimica, U. S. S. R.*, **1**, 759 (1935).

(8) E. C. Ward, *Ind. Eng. Chem., Anal. Ed.*, **10**, 169 (1938); see W. Davis, Jr., and W. A. Noyes, Jr., THIS JOURNAL, **69**, 2155 (1947).

(9) F. E. Blacet and P. A. Leighton, *Ind. Eng. Chem., Anal. Ed.*, **3**, 266 (1931); for list of references see R. N. Smith and P. A. Leighton, *ibid.*, **14**, 758 (1942).

in thickness, coated with a Cr–Al alloy by evaporation.[10] These filters were placed in such a way as to minimize local variations in density, although their uniformity was such as to render this precaution probably unnecessary.

Results

Table I shows data on rates of formation of CH_4 and of C_2H_6 in the large cell at 175° and at 220°. Table II shows similar data at 175° obtained in the small cell. Since the rate of C_2H_6 production is roughly proportional to the intensity, it can be seen that the intensity has been varied about 600-fold.

Table III shows data obtained in the large cell and over a range of temperature from 25 to 250° at approximately constant intensity.

TABLE III

RATES OF FORMATION OF METHANE AND OF ETHANE DURING PHOTOCHEMICAL DECOMPOSITION OF $Hg(CH_3)_2$

V = 590 cc. (for measurement of gas pressures of products); cell, 20 cm. long, 2.4 cm. diameter (V = 90.4 cc.); intensity constant; pressure of $Hg(CH_3)_2$ = 20.0 mm. (at 300°K.); arc – S 353; rates in microns/hr. (at 300°K.).

Run	Temp., °C.	R_{CH_4}	$R_{C_2H_6}$	$R_{C_2H_6}/R_{CH_4}$
DM-0	25	0	56.1	....
1	100	1.28	81.7	63.8
2	125	2.62	83.2	31.8
3	150	5.15	88.6	17.2
4	175	9.81	89.9	9.2
B-1	175	9.95	97.4	9.8
5	175	10.4	95.4	9.2
DM-5	200	19.4	97.9	5.04
B-4	200	19.5	100.8	5.17
3	220	33.9	102.4	3.02
7	220	35.4	104.0	2.94
8	218	30.3	94.1	3.10
DM-6	225	47.5	113.4	2.39
7	250	75.2	116.5[a]	(1.55)
B-2	248	72.0	129.3[a]	(1.79)
6	250	71.0	121.6[b]	1.71

[a] Total C_2 hydrocarbons, C_2H_4 not determined. [b] 1.8×10^{-2} mm. C_2H_4 formed in addition.

Discussion

The data in Table III show that at constant intensity the rate of C_2H_6 formation increases markedly between 25 and 100° but that the change is very gradual as the temperature is increased further. This is in general agreement with the quantum yields determined by Linnett and Thompson[11] and the results of Cunningham and Taylor.[12] These facts may be connected with a decrease in stability of the $HgCH_3$ radical with increasing temperature. Thus if the primary process were $Hg(CH_3)_2 + h\nu = CH_3 + HgCH_3$ followed by a thermal decomposition of $HgCH_3$, $HgCH_3 = Hg + CH_3$, a recombination reaction could acccount for a low quantum yield of $Hg(CH_3)_2$ disappearance at low temperatures. The solid compound mercury methyl is, however, known not to be very stable even at room temperature.[13] The situation may resemble in important respects that found in acetone.[14] There is, however, evidence pointing to a reaction between CH_3 radicals and $Hg(CH_3)_2$ to give C_2H_6[15,19] and this may account for the gradual increase in $R_{C_2H_6}$ at higher temperatures.

The chief conclusions to be drawn in this paper are independent of the nature of the primary process provided, of course, CH_3 radicals are produced.[6,12]

For the sake of clarity of presentation it may be best to list at once the various steps in the mechanism and to follow them with evidence in favor. It will be assumed in agreement with all other authors who have studied this molecule that CH_3 radicals are formed.[12]

$$CH_3 + CH_3 = C_2H_6;\ R_{C_2H_6}(1) = k_1(CH_3)^2 \quad (1)$$

$$CH_3 + Hg(CH_3)_2 = A;\ R_A = k_2(CH_3)(D) \quad (2)$$

$$A = CH_3 + Hg(CH_3)_2;\ -R'_A = k_3(A) \quad (3)$$

$$CH_3 + A = C_2H_6 + Hg + 2CH_3 \text{ (or } CH_3 + HgCH_3 \text{ or } Hg(CH_3)_2);\ -R''_A = k_4(CH_3)(A) \quad (4)$$

$$CH_3 + Hg(CH_3)_2 = CH_4 + H_2CHgCH_3;\ R_{CH_4} = k_5(CH_3)(D) \quad (5)$$

$$CH_3 + H_2CHgCH_3 = C_2H_5HgCH_3;\ R(6) = k_6(CH_3)(H_2CHgCH_3) \quad (6)$$

(D) = concentration of $Hg(CH_3)_2$.

The rate of CH_4 formation will be the rate of (5) and the rate of C_2H_6 formation will be the rate of (1) plus the rate of (4). If $R_{C_2H_6}(T)$ is the total rate of C_2H_6 formation, the following equation can be derived by assumption of the steady state for the intermediate A

$$\frac{R_{C_2H_6}(T)}{R_{CH_4}} = \frac{k_1 R_{CH_4}}{k_5^2(D)^2} + \frac{k_2 R_{CH_4}}{k_5} \frac{1}{(k_3 k_5(D)/k_4 + R_{CH_4}} \quad (7)$$

Equation (7) should be valid regardless of the units chosen for the various rates, but if comparison between constants for $Hg(CH_3)_2$ and for other molecules is desired, the rates should be expressed in standard units. For this purpose the rates have been converted to molecules cc.$^{-3}$ sec.$^{-1}$ with the assumption that CH_4 and C_2H_6 are produced uniformly throughout the reaction vessel. The validity of this assumption will be examined in a later paragraph.

It can be seen from the data in Tables I and II (Figs. 1 and 2) that a plot of $R_{C_2H_6}(T)/R_{CH_4}$ *vs.* R_{CH_4} gives a straight line except for low values of R_{CH_4} and that this straight line does not pass through the origin. The data for the short cell (Fig. 2) show more scatter than those for the long cell. This is due, undoubtedly, to the necessity for replenishing $Hg(CH_3)_2$ to prevent excessive decomposition during a run.

(10) The authors wish to express their appreciation to Dr. Harry Polster, Department of Optics, University of Rochester, for preparing these filters.

(11) J. W. Linnett and H. W. Thompson, *Trans. Faraday Soc.*, **33**, 501, 874 (1937).

(12) J. P. Cunningham and H. S. Taylor, *J. Chem. Phys.*, **6**, 359 (1938).

(13) F. O. Rice and B. L. Evering, THIS JOURNAL, **56**, 2405 (1934)

(14) See W. A. Noyes, Jr., and L. M. Dorfman, *J. Chem. Phys.*, **16** 788 (1948).

(15) See K. W. Saunders and H. A. Taylor, *ibid.*, **9**, 616 (1941).

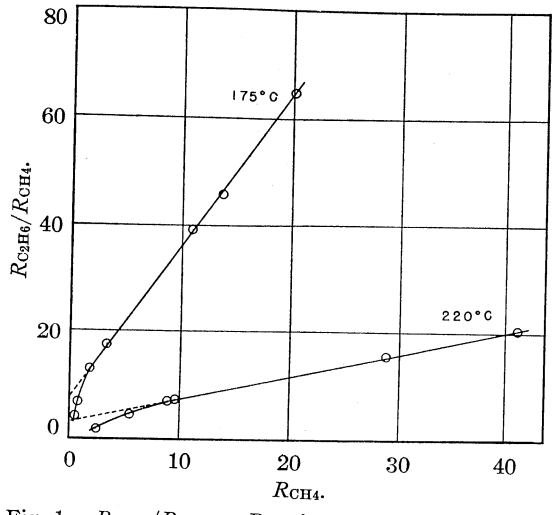


Fig. 1.—$R_{C_2H_6}/R_{CH_4}$ *vs.* R_{CH_4} in quartz cell 20.0 cm. long and 2.4 cm. internal diameter at 175° and at 220°C. The pressure of $Hg(CH_3)_2$ is 5.0 mm. (measured at 300°K.). Rates are in microns/hr. measured in a volume of 590 cc. at 300°K. Rates should be multiplied by 5.83×10^{10} to convert them to molecules/cc./sec. in the reaction vessel.

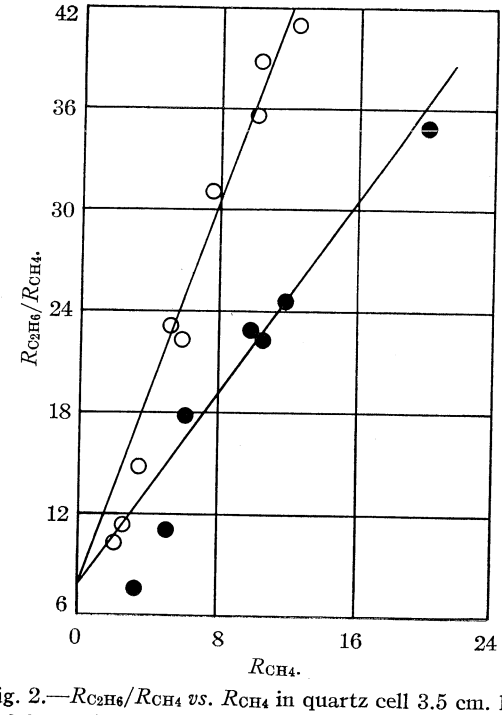


Fig. 2.—$R_{C_2H_6}/R_{CH_4}$ *vs.* R_{CH_4} in quartz cell 3.5 cm. long and 2.0 cm. internal diameter. Pressures of $Hg(CH_3)_2$ are 13.4 mm. (empty circles) and 20.1 mm. (solid circles) both measured at 300°K., $T = 175°$. The points are experimental and the lines are calculated from rate constants determined in the long cell at 175°C. (Fig. 1.). Rates are in micron/hr. and should be multiplied by 4.79×10^{11} to convert them to molecules/cc./sec.

A linear plot with positive intercept is obtained from equation (7) when $R_{CH_4} \gg k_3k_5(D)/k_4$. This situation would be obtained when the CH_3 concentration is sufficiently high to make (4) rapid compared to (3). The rate of formation of C_2H_6 by action of CH_3 on $Hg(CH_3)_2$ would be controlled by the rate of (2). The intercept would be k_2/k_5 and should be independent of (D) at constant temperature. This is seen to be true within experimental error (Fig. 2).

The slope of the linear plot would be $k_1/k_5^2(D)^2$ and hence should vary with $1/(D)$.[2] This is also found to be true within experimental error for the data in Tables I and II at 175°.

For this linear portion of the plot equations (2), (3) and (4) could be replaced simply by $CH_3 + Hg(CH_3)_2 = C_2H_6 + Hg + CH_3$, but the data necessitate a variable slope for low values of R_{CH_4} and the curve apparently tends toward the origin. This is satisfactorily accounted for by the complete mechanism embodied in equations (1) to (6) inclusive. While the authors have been unable to suggest any other mechanism which accounts for all of the facts, it should be emphasized that this does not constitute a proof that the proposed mechanism is a unique solution of the problem.

Equation (7) is, therefore, of the right form to fit the data in Tables I and II (Figs. 1 and 2). The smooth curves in Fig. 2 are calculated with the aid of rate constants obtained from the data in Table I and the fit to the experimental points adds strong support to the belief that the data are self-consistent.

It is not desired at the present time to enter into any detailed discussion of the theory of reaction rates, but a standard form of equation must be used for intercomparisons of various types of data. Hence the various rate constants are expressed in the form $aT^{1/2}e^{-E/RT}$ where $a = 2\sigma^2(\pi k/m)^{1/2}$ when the two colliding particles are identical (equation (1)) and $a = 2\sigma^2(2\pi k(m_1 + m_2)/m_1m_2))^{1/2}$ when the two colliding particles are different (equations (2), (4), (5), and (6)). k is the Boltzmann constant and σ^2 may be referred to as the "effective cross section" for the reaction.

If k_1 and k_5 are written in the above form it is seen that

$$\ln (k_1/k_5^2) = \ln (a_1/a_5^2) - {}^1/_2 \ln T - (E_1 - 2E_5)/RT \quad (8)$$

and $E_1 - 2E_5$ can be obtained from the slopes in Fig. 1 at two different temperatures. In this way it is found that $E_5 = 9000 + {}^1/_2 E_1$. This may be contrasted with approximately $5700 + {}^1/_2 E_1$ for the corresponding reaction of CH_4 formation in acetone.[16] The value of E_1 is not known precisely but is undoubtedly low.[17]

It is next possible to calculate a_1/a_5^2 and hence a relationship between the cross sections for C_2H_6 formation from radicals and for methane forma-

(16) L. M. Dorfman and W. A. Noyes, Jr., *J. Chem. Phys.*, **16**, 557 (1948).

(17) See ref. 12 and also S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Company, Inc., New York, N. Y., 1941, p. 260.

tion. The results are: $a_5 = a_1^{1/2} \times 4.6 \times 10^{-9}$ (molecules^{-1} sec.$^{-1}$ cc.)$^{1/2}$; $\sigma_5^2 = 3.5 \times 10^{-11}\ \sigma_1$. In other words if $CH_3 + CH_3$ is a very fast reaction with a "normal" collision diameter of about 5 $\times 10^{-8}$ cm., the "effective cross section" for CH_4 formation is very low, roughly 10^{-3} times that which would be expected on a simple collision picture with 100% efficiency for each collision providing enough energy. It is interesting to note that the cross section obtained in this way is almost exactly the same as for the similar reaction in acetone[14,16] after suitable correction for the volume of the vessel.

The intercept of the straight line portion of the curves in Figs. 1 and 2 gives directly the ratio of $R_{C_2H_6}$ (4)/R_{CH_4}, *i. e.*, the ratio of the rate of C_2H_6 formation to that of CH_4 formation when CH_3 radicals react with $Hg(CH_3)_2$. By use of the intercepts at two different temperatures one finds $E_5 - E_2$ to be approximately 9000 calories, *i. e.*, the energies of activation for C_2H_6 formation by the two different processes are about the same.

This result is somewhat surprising because reactions (2), (3) and (4) together could give rise to a chain reaction. Reaction (4) could be sufficiently exothermic to produce two CH_3 radicals.[18] The answer must be found in the very low a term for reaction (2), *i. e.*, it is found that $a_2 = 3.5 \times 10^{-4}\ a_5$. Since the same particles are involved the "cross section" for ethane formation from $CH_3 + Hg(CH_3)_2$ is also 3.5×10^{-4} times that for CH_4 formation. Thus in spite of a low activation energy the chain propagating step would be so slow as to be unimportant under most conditions.

Reference may now be made to the data in Table III to obtain a rough check on the energy of activation of the step leading to CH_4 formation. The CH_3 steady state concentration as obtained from the complete mechanism is

$$(CH_3) = -(k_5/2k_1)(D)(1 - (1 + 4I_a\, k_1/(k_5^2(D)^2)^{1/2}) \quad (9)$$

where I_a = number of quanta absorbed per cm.^{3} per second and two CH_3 radicals are assumed to be formed per quantum absorbed. From the rate of C_2H_6 formation a rough estimate can be made of I_a and this combined with the value determined above for k_1/k_5^2 indicates that $4I_ak_1/k_5^2(D) \gg 1$. Even the square root of this quantity is probably 10 to 100. Since $R_{CH_4} = k_5(CH_3)(D)$, one may write to a first approximation

$$R_{CH_4} = k_5 I_a^{1/2}(D)/k_1^{1/2} \quad (10)$$

At constant intensity and constant (D) a plot of ln R_{CH_4} *vs.* $1/T$ should give a straight line with slope $-(E_5 - {}^1/_2\, E_1)/R$. The assumptions made are probably least valid at high temperatures, but $E_5 - {}^1/_2\, E_1$ is found from the data in Table III to be approximately 10,000 cal., about as good a check as could be expected with the 9000 calories previously calculated from the data in Table I.

The mechanism postulated fits all of the data described in this article and as far as can be ascertained agrees well with data in the literature. A reaction between CH_3 radicals and $Hg(CH_3)_2$ to give C_2H_6 has been postulated frequently but the work of Harris and Steacie[19] affords the best proof for its occurrence. These authors studied the reaction of H atoms with $Hg(CH_3)_2$ and found that the ratio CH_4/C_2H_6 in the products was even less than unity under some conditions. If C_2H_6 were produced solely by combination of CH_3 radicals this ratio would have a minimum value of 2. It is necessary, therefore, to postulate a second method of formation of C_2H_6. Since the work just described seems to necessitate reactions (2), (3) and (4) for this method, it may or may not correspond to a simple inversion. Little more can be said about this matter at the present time.

The calculations which have been made are based on a uniform distribution of CH_3 radicals throughout the vessel, although they would be approximately valid (with minor changes in numerical values) if the distributions were similar from one run to another. Dr. T. L. Hill[20] has made approximate calculations of CH_3 distribution in a cell in the case of acetone where a situation similar to that in $Hg(CH_3)_2$ is encountered. The character of the distribution is very markedly dependent on the fate of radicals when they reach the walls, *i. e.*, under the conditions used in most of these experiments gas phase reactions will not be fast enough to prevent diffusion of many radicals to the walls. If the radicals are totally reflected a reasonably uniform distribution in a given cross section of the vessel is to be expected, although there will be a progressive decrease in concentration as the distance from the window through which the radiation is incident on the vessel increases.

Very little quantitative information is available on the fate of CH_3 radicals when they encounter walls under conditions obtaining in experiments of the type herein described. It appears probable, although the data are not exact enough to warrant a definite conclusion, that a very large fraction of encounters between CH_3 radicals and walls must lead to reflection. Otherwise the data would not be as consistent as they seem to be. More positive information on this point would certainly be of great value. The self-consistency of data in two different cells and the further fact that the addition of several hundred millimeters of carbon dioxide in one experiment did not affect the results, offer evidence that the methods of calculation used are justified.

In conclusion it should be reëmphasized that the pre-exponential factors in the rate constants for reactions (5) and (2) are very low. For many bimolecular reactions $aT^{1/2}$ is of the order of magnitude of 10^{13} to 10^{14} if concentrations are expressed in moles/cc. For reaction (5) (CH_4 forma-

(18) See N. V. Sidgwick and H. D. Springall, *Nature*, **156**, 599 (1945), and H. S. Gutowsky, *J. Chem. Phys.*, **17**, 128 (1949).

(19) G. M. Harris and E. W. R. Steacie, *J. Chem. Phys.*, **13**, 559 (1945).

(20) Private communication.

tion) $aT^{1/2}$ is about 2×10^{11} in these units and low values of this magnitude are found for other similar reactions if the assumption is made that the association reaction for CH_3 radicals is "normal." If the latter is low the constant for CH_4 formation will be reduced even further. For reaction (2) (the rate determining step for C_2H_6 formation from CH_3 and $Hg(CH_3)_2$), $aT^{1/2}$ is about 7×10^6, a very low value compared to most other bimolecular reactions.

Summary

1. The rates of formation of C_2H_6 and of CH_4 during irradiation of $Hg(CH_3)_2$ have been studied as functions of intensity, pressure, and temperature.

2. At temperatures below 250° CH_4 seems to be formed solely by the reaction $CH_3 + Hg(CH_3)_2 = CH_4 + CH_2HgCH_3$.

3. Ethane must be formed by at least two processes, one of which is the combination of CH_3 radicals and the other of which is a reaction of CH_3 radicals with $Hg(CH_3)_2$ which apparently proceeds through an unstable intermediate addition complex.

4. The pre-exponential factor in the rate constant for CH_4 formation is very much smaller than for ethane formation by radical combination.

5. The activation energy for reaction of CH_3 radicals with $Hg(CH_3)_2$ to form C_2H_6 is very low, about the same as for C_2H_6 formation by radical combination, but the pre-exponential factor is so low that the rate is small and a chain reaction is of relatively minor importance.

6. A mechanism consistent with the facts has been proposed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BOSTON UNIVERSITY]

The Heats of Reaction of Lithium, Sodium, Potassium and Cesium with Ammonium Ion in Liquid Ammonia at −33°

BY LOWELL V. COULTER AND ROBERT H. MAYBURY

The thermochemistry of oxidation–reduction reactions involving the alkali metals in liquid ammonia is of twofold interest. From a long range view the heats of reaction of the metals with ammonium ion in liquid ammonia, for example

$$M + NH_4^+ = M^+ + NH_3 + {}^1/_2H_2 \qquad (1)$$

may provide basic thermal values which when combined with corresponding free energy changes permit evaluation of relative partial molal ionic entropies in this solvent. In addition to the use of ionic entropies in the calculation of oxidation–reduction potentials not measurable directly, these ionic properties also permit evaluation of relative entropies of solvation of ions in liquid ammonia in a manner developed by Latimer[1] for water solutions. The existing scarcity of accurate free energy data for reactions occurring in liquid ammonia imposes temporary restrictions on the development of a set of reliable ionic entropies for this medium. However, the presumably simpler nature of liquid ammonia as compared with water arising from weaker hydrogen bonding would appear to simplify somewhat the theoretical treatment of the solvation process in this medium and therefore justify the exploration of this solvent.

Of immediate interest is the utilization of thermal data for the above reaction for the comparison of the nature of liquid ammonia solutions of the ammonia soluble metals. Prevailing concepts of these systems, while differing with regard to the equilibria involved in the more concentrated solutions and though incomplete as to the exact nature of the ammoniated electron, agree that the dilute solutions consist of solvated metal ions and single electrons resulting from essentially complete ionization in the dilute range of concentration. An exact similarity for these solutions has been observed by Gibson and Argo,[2] who have reported identical absorption spectra for dilute solutions of lithium, sodium, potassium and cesium. It is to be expected that these systems would likewise possess identical thermochemical properties for reactions involving the solvated electron of these solutions with a common oxidizing agent, as for example

$$e^-_{(am)} + NH_4^+{}_{(am)} = {}^1/_2H_{2(g)} + NH_{3(l)}$$

Direct measurement of the thermal effect associated with this reaction has not seemed experimentally feasible. It may be obtained indirectly, however, as the difference between the heat of solution of the metal in pure liquid ammonia and the heat of reaction of the metal with ammonium ion in liquid ammonia. The latter heat of reaction for solid lithium, sodium, potassium and cesium determined in this research combined with the literature values for the heats of solution of the metals has made possible the evaluation of the heat of this reaction. For dilute solutions of each of these metals we have obtained heats of reaction ranging from 39.7 kcal. for potassium to 41.6 kcal. for cesium with a mean of 40.4 kcal. This we regard as indicative of a common reaction for these solutions involving the solvated electron which energetically appears identical within experimental error in all cases.

(1) Latimer, *Chem. Rev.*, **18**, 349 (1936).

(2) Gibson and Argo, THIS JOURNAL, **40**, 1327 (1918).

Experimental

The calorimeter employed was essentially of the type used by Kraus and Schmidt[3] but differed in size and method of collecting the gaseous products of the reaction, hydrogen and vaporized ammonia. The calorimeter I of Fig. 1 consisted of a Pyrex vacuum-jacketed test-tube capped with a removable top G by means of a ground glass joint. The top was connected through F to a manifold and served as a point of suspension for the thermocouple well E, sample crushing rod K and the reciprocating stirrer B-J suspended by the spring A. Intermittent energizing of the solenoid C provided a stirring rate of 60 strokes per minute.

Sample bulbs of the metals were held near the bottom of the calorimeter in a platinum stirrup L located directly below the sample crushing rod K to which the holder was loosely attached. The crushing rod extended beyond the calorimeter top through a gas tight seal at D. A fine mesh platinum gauze enclosed the sample bulbs and served as a bubble trap whereby continuous contact of metal and solution was prevented and a controlled reaction rate obtained. The calorimeter was thermostated by boiling liquid ammonia contained in the closed Dewar vessel M of Fig. 1.

The gas collecting system consisted of a six-liter flask P thermostated at 25.0 ± 0.1°, and a manometer Q which were connected to the manifold through a small metal needle valve O. Withdrawal of gas from the calorimeter into the evacuated collecting system was made by manual adjustment of the valve during the reaction period. The entire gas collecting system had a total volume of 6715 ml. The connecting lines which were not thermostated amounted to about 1% of the total volume.

For each thermochemical measurement a weighed amount of ammonia, usually between 110 and 120 g., was introduced at N and condensed in the calorimeter to a liquid depth of about 14 cm. as indicated by the dotted line in Fig. 1. Temperature measurements were made with a copper–constantan thermocouple, calibrated at the sublimation point of carbon dioxide and the freezing point of mercury. Potentials were measured with a Type K-2 Leeds and Northrup potentiometer with a matched galvanometer having a sensitivity of 20 mm. per microvolt for a scale at a distance of 15 ft. from the galvanometer.

Commercial anhydrous liquid ammonia of 99.2% purity, according to the supplier, was used for the thermostating liquid. Stock ammonia for the calorimeter reaction medium was prepared by distillation of the ammonia from the large commercial cylinders into a small cylinder containing sodium metal as a drying agent.

The metals employed in the research were of the following grades as indicated by the supplier and were used without further purification except for cesium which underwent a distillation in the process of sample preparation: lithium, Lithaloy, low sodium quality (typical analysis as furnished by the supplier, N, 0.15; Si, 0.05; Fe, 0.02; Al, 0.01; Ca, 0.10; Na, 0.15; K, 0.05%); sodium, Baker, Analytical Reagent; potassium, Baker, C. P.; cesium, Fairmount Chemical Co.; C. P. Baker Analytical Reagent ammonium chloride and bromide dried at 100° were the oxidizing agents in the reactions. Samples of oxide-free sodium and potassium for the reaction were prepared in small thin-walled glass bulbs in the manner described by Kraus.[4] The cesium samples were prepared by a high vacuum distillation of the metal from the shipping ampoules into the weighed sample bulbs. Lithium samples with clean surfaces were prepared by cutting cylinders of the metal from the ingots under oil followed by removal of the oil with dried benzene rinses.

Procedure.—The net measured heat effect associated with reaction (1) was a composite of heat absorbed by the vaporization of ammonia during the reaction and the thermal change resulting from the temperature change of the calorimeter and contents. The experimental determination of the first of these quantities involved the withdrawal

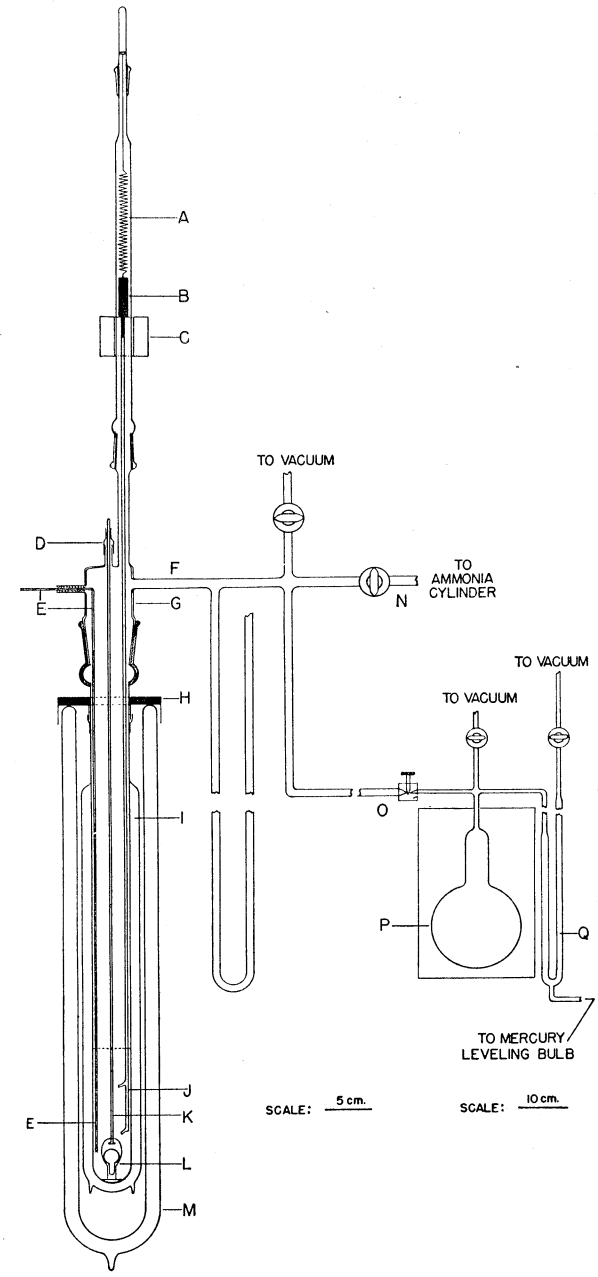


Fig. 1.

of gas during the reaction period from the calorimeter manifold into the calibrated gas collecting system through the manually controlled needle valve at such a rate as to maintain a constant pressure in the calorimeter. The second of these quantities was obtained from the measured temperature change of the calorimeter, as determined by the thermocouple measurements, and the total heat capacity of the calorimeter and contents.

Following the assembly of the calorimeter containing the reactants and liquid ammonia the temperature of the calorimeter was allowed to approach a steady state value.

When a constant temperature or temperature drift was attained, usually less than a thousandth of a degree per minute the sample bulb was fractured by a downward thrust of the crushing rod which initiated the reaction. During the reaction period withdrawal of vaporized ammonia and product hydrogen from the manifold into the

(3) Kraus and Schmidt, THIS JOURNAL, **56**, 2297 (1934).

(4) Kraus, *ibid.*, **30**, 1197 (1908).

TABLE I

SUMMARY OF HEAT EFFECTS

Expt.	G. atoms of metal or moles of salt	Moles of NH_4 salt in soln.	$-\Delta T$, cor.	C, (total ht. cap.)	$q_1 = C \times \Delta T$	G. of NH_3 vaporized	q_2 = Sp. ht. vap. × G. vap.	Net heat $q_1 + q_2$	Reacn. time, min.	$-\Delta H$ kcal. per g. atom
	Li and NH_4Br									
F	0.00240	0.00257	0.561	140.1	− 78.6	0.6070	199	120	5	50.3
E	.00248	.00248	.361	140.0	− 50.5	0.5406	177	126	2	51.1
G	.00463	.00528	.995	139.7	−139	1.133	371	232	5	50.3
C	.00615	.00640	1.01	136.8	−138	1.381	452	314	1.5	51.2
15	.01326	.0227	1.083	131.8	−142.7	2.450	799.3	656.6	8	49.7
16	.01447	.0227	1.123	140.5	−157.8	2.695	882.7	724.9	7	50.3
	Na and NH_4Cl									
3	.004961	.0283	0.525	149.6	− 78.5	0.8238	269.2	190.7	1.5	38.4
4	.00958	.0115	1.316	148.6	−195.6	1.748	572.4	376.8	24	39.3
5	.01050	.0115	1.418	143.7	−203.8	1.865	612.3	408.5	19	38.8
2	.01317	.0283	1.433	150.3	−215.4	2.227	728.1	512.7	30	38.9
6	.02220	.0254	1.474	142.9	−210.6	3.242	1061.8	851.2	13	38.3
	Na and NH_4Br									
9	.01718	.0227	1.450	145.2	−210.5	2.665	871.8	661.3	10	38.5
8	.02072	.0227	1.391	146.4	−203.6	3.059	1001.7	798.1	6.5	38.5
	K and NH_4Br									
10	.01053	.0227	1.218	146.6	−178.6	1.829	598.6	420.0	9	39.9
11	.01209	.0227	1.278	146.6	−187.4	2.038	666.9	477.7	8.5	39.6
12	.01542	.0227	1.331	146.4	−194.9	2.461	805.4	610.5	9.5	39.6
	Cs and NH_4Br									
H	.005843	.00641	1.13	137.6	−156	1.221	400	244	18	41.8
I	.008911	.00986	1.17	139.3	−163	1.626	531	368	28	41.3
	Li									
J	.0718	.0000	−0.089	138.8	12.4	2.064	673.7	686.1	6	9.55
	NH_4Br									
K	.04380	.0000	−0.25	137.0	34.0	1.172	382	416	10	9.50

gas collecting system was accompanied by approximate temperature readings of the calorimeter in order to establish the temperature–time pattern from which the graphically determined mean temperature was calculated. During the post reaction period regular temperature measurements were again recorded for a period of fifteen to thirty minutes during which time a steady temperature drift was apparent. The corrected temperature change taking into account radiation heat gain was calculated from the temperature patterns so obtained in the usual manner for this type of calorimeter.[5] Although the reactions studied were exothermic, a temperature lowering of the calorimeter always occurred because of the release of gaseous hydrogen within the liquid. The mean calorimeter temperature was approximately −33°.

From the known volume, temperature and pressure of the gas collected in the gas collecting system the weight of ammonia vaporized was calculated by means of Berthelot's equation of state and the critical constants for ammonia.[6] The vaporization heat effect was determined from the net amount of ammonia vaporized and the specific heat of vaporization of ammonia[7] at the mean calorimeter temperature. Pressures were determined by a mercury manometer read by a cathetometer to 0.05 mm. Correction was made for the hydrogen gas liberated by the reaction and collected along with the ammonia in the manifold or gas collecting system on the assumption that the hydrogen gas behaved ideally. A correction was also applied to the weight of ammonia vaporized in those experiments having a net pressure change in the calorimeter system.

The heat capacity of the calorimeter was determined in a fashion similar to a heat measurement except that an electric heater was substituted for a sample of metal. To reproduce the temperature pattern as nearly as possible, hydrogen gas was measured into I through a side arm not shown in Fig. 1 and allowed to bubble through the solvent ammonia in the calorimeter simultaneously with the introduction of measured quantities of electrical energy. The dependence of the calorimeter heat capacity on depth was determined electrically at 25° with water in the calorimeter. For a depth of 15 cm. the heat capacity of the calorimeter was 21 cal. per degree at −33°.

Specific heats for liquid ammonia and the alkali metals were taken from the work of Overstreet and Giauque[8] and the compilation by Kelley.[9] A specific heat of 0.2 cal./g. was assumed for Pyrex glass in evaluating the small contributions of sample containers and glass rod to the total heat capacity of the calorimeter.

The heat effect associated with the crushing of an evacuated sample bulb containing no sample was determined in a manner identical with the reaction heat measurements. No pressure or temperature change (±0.01°) was found associated with the process.

Discussion

The observed heat effects for each of the thermochemical measurements are summarized in Table I. The total heat capacity and corresponding corrected temperature change of the calorime-

(5) W. P. White, "The Modern Calorimeter," Chemical Catalog Co. (Reinhold Publishing Corp.), New York, N. Y., 1929, pp. 40–42.

(6) "International Critical Tables," McGraw–Hill Book Co., Inc., New York, N. Y., Vol. III, 1928, p. 234.

(7) Osborne and Van Dusen, *Bur. of Standards, Bull.* **14**, 439 (1917).

(8) Overstreet and Giauque, THIS JOURNAL, **59**, 254 (1937).

(9) Kelley, *Bur. of Mines, Bull.*, 434 (1940).

ter resulting from the reaction are tabulated in columns 4 and 5. The thermal effect, q_1, associated with the temperature change follows in column 6. The vaporization effect, q_2, listed in column 8 has been calculated from the grams of ammonia vaporized, tabulated in column 7 and the specific heat of vaporization of ammonia at the mean reaction temperature. The total net heat effect per sample and the change in heat content per gram atom for eq. (1) appear in columns 9 and 11, respectively. The values for the latter have been corrected only in the case of lithium for an effective 0.5% impurity.

Comparison of the heats of reaction fail to reveal any significant dependence of the reaction heat on concentration in the range investigated. In the case of lithium the mean of the values for experiments F and E is almost identical with the mean of G and C in which the concentrations were more than doubled. A further increase in concentration does appear, however, to give a slightly decreased reaction heat as evidenced by the mean of experiments 15 and 16 which is about 1.5% less. An analogous trend is to be observed for sodium. Experiment 6, for example, has a heat of reaction about 2% smaller than experiments 4 and 5 in which the dilution was greater. However, in view of an experimental error of at least 1% which must be assigned these values, we are inclined at the present to regard the dilution heat effects to be within the final experimental error to be assigned these measurements. By analogy with similar aqueous systems it is to be noted that dilution heat effects arising from differences in relative heat contents at these concentrations, approximately 400 moles of solvent per mole of solute, are considerably less than 1% of the heats of reaction measured in this research. We shall, consequently, employ these values at this time as the heats of reaction for infinite dilution. On this assumption the heats of reaction for each metal have been averaged and summarized in column 2 of Table II.

TABLE II

Reactants	ΔH_1, kcal. per g. atom	ΔH_2, kcal. per g. atom	ΔH_3, kcal. per equiv.
Li and NH_4Br-1	−50.5	(−8.0)[a]	(−42.5)
Li and NH_4Br-2	−50.5	−9.6[b]	−40.9
Na and NH_4Br	−38.5	+1.40[a]	−39.9
Na and NH_4Cl	−38.8	+1.40[a]	−40.2
K and NH_4Br	−39.7	0[c]	−39.7
Cs and NH_4Br	−41.6	0[c]	−41.6

[a] Kraus and Schmidt, THIS JOURNAL, 56, 2298 (1934). [b] This research. [c] Schmidt, Studer and Sottysiak, *ibid.*, 60, 2780 (1938).

The heats of solution of the alkali metals in pure liquid ammonia at low concentrations have been determined by Kraus and Schmidt,[10] and Schmidt, Studer and Sottysiak[11] at −33° and are tabulated for convenience in column 3 of Table II as ΔH_2 values. Subtraction of the solution reaction

$$M_{(s)} = M^+_{(am)} + e^-_{(am)} \qquad (2)$$

and the associated heat of solution, ΔH_2, from our measured heats of reaction, ΔH_1, has given for each metal solution the molar heat effect, ΔH_3, for the common reaction

$$e^-_{(am)} + NH_4^+{}_{(am)} = NH_{3(l)} + {}^1/_2H_{2(g)} \qquad (3)$$

These values are tabulated in the last column of Table II.

It has been assumed in writing the foregoing equations that essentially complete dissociation of the metals and electrolytes involved occurs in liquid ammonia. That such may not be the case with electrolytes is indicated by their conductance in liquid ammonia. Gur'yanova and Pleskov[12] have found the Debye–Onsager theory inadequate for these systems and have accounted for conductance properties with some success on the basis of ion pairs. However, as is to be seen from a comparison of the reaction heats of sodium with the two ammono acids, ammonium chloride and ammonium bromide, appreciable differences in ionic association leading to energy effects are not revealed in the concentration range investigated. This is also evident from the apparent independence of the heats of reaction on concentration in general.

Calculation of ΔH_3 for the lithium solution based on the heat of solution reported by Kraus and Schmidt,[10] and Schmidt and co-workers,[11] led to the value −42.5 kcal. designated as lithium–ammonium bromide-1 in Table II, differing by about 6% from the mean obtained for sodium and potassium. Since this appeared to exceed a reasonable experimental error of 1 to 2% on the basis of a similarity for all alkali metal solutions we redetermined the heat of solution of lithium in pure liquid ammonia and obtained a heat of solution of 9.55 kcal. (see expt. J of Table I) which when combined with ΔH_2 gave for ΔH_3 −40.9 kcal. in better agreement with the values for sodium and potassium solutions. Further measurements in connection with other work now in progress substantiate this observation. We have not been able to account for this discrepancy in the heat of solution of lithium in a satisfactory manner.

The possibility that a heat of amide formation was contributing to our heat of solution does not appear likely in view of the observed stability of the solution. The nature of the temperature–time pattern for the heat of solution of the metal in comparison with other reactions likewise gave no indication of a significant side reaction.

Since our disagreement with previous workers on the heat of solution of lithium could be accounted for on the basis of instrumental and procedural differences, we remeasured the heat of solution of ammonium bromide which has also

(10) Kraus and Schmidt, THIS JOURNAL, **56**, 2298 (1934).
(11) Schmidt, Studer and Sottysiak, *ibid.*, **60**, 2780 (1938).
(12) Gur'yanova and Pleskov, *J. Phys. Chem.* (*U. S. S. R.*), **8**, 345 (1936).

been studied by Schmidt and co-workers[13] in the same calorimeter employed for the lithium measurements. We have obtained 9.50 kcal. for the exothermic heat of solution of ammonium bromide at a concentration of 147 moles of ammonia per mole of ammonium bromide. This value is 2.5% lower than the interpolated value of 9.76 obtained from a large scale plot of values obtained by Schmidt. Since these two values are essentially in agreement on the basis of a 1% error for each value, it does not appear that the difference for lithium amounting to about 20% can be ascribed to instrumental differences. It is our intention, however, to redetermine the heat of solution of this metal along with others in a larger calorimeter now under construction which will afford an opportunity to examine these heat effects at much lower concentrations and at the same time eliminate any radiation effect on the solution reaction which might conceivable be involved with the partially jacketed calorimeters employed so far in liquid ammonia studies.

The slightly higher values obtained for ΔH_3 of the cesium solution, -41.5 kcal., which exceeds the mean for lithium, sodium and potassium, -40.2 kcal., by 3% may be indicative of some difference between this solution and the other alkali metals. However, in view of the fact that a few tenths of a per cent. impurity of one of the lighter alkali metals or calcium can account for this observed deviation, it does not appear appropriate to assign any uniqueness to the dilute ammonia solutions to cesium at this time.

In general, then, it appears that all of the dilute alkali metal solutions investigated in this research are energetically identical within about 1 kcal. Weighting all values equally we obtain for the reaction represented by eq. (3) at $-33°$: $\Delta H = -40.4 \pm 1$ kcal.

This heat of reaction will now furnish a basis for the investigation of the nature of solutions of the alkaline earth metals, calcium in particular. On the basis of the absorption spectra[2] and the magnetic susceptibility[14] of dilute calcium ammonia solutions, a difference appears to exist between calcium and the alkali metals in the first instance and between calcium and barium in the second. Measurements are now in progress to determine whether or not the heat of reaction of the calcium solution with ammonium ion indicates normal ionization of calcium or the formation of Ca_2^{++} and one electron ionization per gram atom of calcium as proposed by Yost and Russell.[15]

The relative partial molal ionic entropies of the alkali metal ions in liquid ammonia may now be calculated from the measured heats of reaction for eq. 1 and the corresponding free energy changes derived from cell measurements by Pleskov and Monoszon.[16] These values appear in column 3 of Table III along with our measured heats of reaction from which the partial molal ionic entropies relative to $\bar{S}^0_{NH_4^+} = 0$ at $-33°$ have been calculated in the usual manner.[1] It does not appear that the free energy changes employed in the calculation are above criticism because of the presence of liquid junction potentials in the cells employed by Pleskov and Monoszon and in view of the approximation of activity coefficients made for the solutes in the cell solutions in obtaining the standard electrode potentials.

TABLE III

IONIC AND SOLVATION ENTROPIES IN LIQUID AMMONIA AT $-33°$

Ion	ΔH^0 kcal.		ΔF^0 kcal.	$\bar{S}^0_{240}$°K. cal./deg.	ΔS of solvation cal./deg.
Li^+	$(-66.380)^a$	-50.6	-51.4	-26.8	-52
Na^+	$(-57.520)^a$	-38.7	-42.4	-9.5	-38
K^+	$(-60.340)^a$	-39.7	-45.6	$+2.6$	-27
Rb^+	$(-61.210)^a$	-40.0^b	-44.4	-2.4	-34
Cs^+	$(-62.040)^a$	-41.6	-44.9	-3.0	-42

[a] Corresponding values for the reaction $M + H_3O^+_{(aq)} = M^+_{(aq)} + {}^1/_2H_2 + H_2O$ at 25° [Latimer, *Chem. Rev.*, 18, 349 (1936)]. [b] Estimated from value for potassium.

Comparison of the ionic entropies obtained for the metal ions indicates a departure of $\bar{S}^0_{Rb^+}$ and $\bar{S}^0_{Cs^+}$ from the consistent and expected trend for lithium, sodium and potassium. This is emphasized in a consideration of the relative solvation entropies of each of the ions in the last column of Table III, where ΔS of solvation $= \bar{S}_{M^+} - S_{(\text{gas ion})}$. Although smaller negative values for the solvation entropy of Rb^+ and Cs^+ are expected in comparison with K^+ because of the larger ionic radius and consequently less ordering effect on the solvent, the reverse occurs. The admitted uncertainties in the standard potentials undoubtedly will account for these inconsistencies. It is of interest that solvation entropies of the lithium, sodium and potassium ions appear to be linearly dependent on the reciprocal of the ionic radius as already observed for aqueous ions by Latimer[1] and Buffington[17] and that the slope of the curve is approximately the same as obtained for these ions in water solution.[1]

For comparison purposes we have included in Table III the reaction heats of the alkali metals with hydronium ion in water solution. These values appear in parentheses with the corresponding values in column 2 obtained in this research for the reaction represented by eq. (1). It is to be noted that in both systems a minimum value is obtained for $-\Delta H$ for the sodium reaction. Although the difference between the reaction heats in the two systems is about constant at 20 to 21 kcal. for potassium, rubidium and cesium, the dif-

(13) Schmidt, Sottysiak and Kluge, THIS JOURNAL, **58**, 2509 (1936).

(14) Freed and Sugarman, *J. Chem. Phys.*, **11**, 354 (1943).

(15) Yost and Russell, "Systematic Inorganic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1944, p. 148.

(16) Pleskov and Monoszon, *J. Phys. Chem.* (*U. S. S. R.*), **4**, 696 (1933); *Acta Physicochim.* (*U. R. S. S.*), **2**, 615 (1935).

(17) Latimer and Buffington, THIS JOURNAL, **48**, 2297 (1926).

ference in the case of lithium amounts to only 16 kcal., thereby indicating a relatively greater interaction energy of the lithium ion with ammonia than with water.

Acknowledgment.—We wish to express our appreciation to the Research Corporation for a Frederick Cottrell grant in aid of research which made this investigation possible. We are also indebted to the Sigma Xi for an earlier grant supporting exploratory work. We acknowledge the assistance of Mr. Sumner P. Wolsky who performed some of the calibration experiments.

Summary

The heats of reaction of lithium, sodium, potassium and cesium metals with dilute solutions of ammonium bromide and ammonium chloride have been determined in a liquid ammonia calorimeter at −33°. Combination of these heats of reaction with the known heats of solution of the metals in pure liquid ammonia has given the heat of reaction of each dilute metal solution with ammonium ion. Exothermic heats of reaction varying from 39.7 to 41.6 kcal. (mean 40.4 ± 1 kcal.) indicate within experimental error an identical reaction in each case and, therefore, a close similarity in the nature of the dilute solutions of the alkali metals in liquid ammonia. A redetermination of the heat of solution of lithium in liquid ammonia gave −9.6 kcal. for ΔH instead of the reported value −8.0 kcal. From the measured heats of reaction and corresponding free energy changes relative partial molal ionic entropies and entropies of solvation of the alkali metal ions in liquid ammonia have been calculated.

BOSTON, MASS. RECEIVED JANUARY 5, 1949

[CONTRIBUTION FROM THE LABORATORY FOR THE STUDY OF HEREDITARY AND METABOLIC DISORDERS AND THE DEPARTMENTS OF BIOLOGICAL CHEMISTRY AND MEDICINE, UNIVERSITY OF UTAH COLLEGE OF MEDICINE]

The Relationship between Homoserine and its Lactone[1]

BY MARVIN D. ARMSTRONG

The preparation of the optical isomers of homoserine (α-amino-γ-hydroxybutyric acid) was described in a previous publication[2] and a brief review was made of its earlier literature. Since the first synthesis of homoserine by Fischer and Blumenthal in 1907[3] little appeared to have been added to our knowledge of the physical and chemical properties of the compound and its derivatives. The purpose of the present investigation was to examine some of these properties, particularly the relationship of homoserine to its γ-lactone and its diketopiperazine.

The early studies of homoserine by Fischer and Blumenthal indicated that in acid solutions it possibly existed only in the lactone form; the conversion to a lactone is in analogy with the behavior of homocysteine which forms the corresponding thiolactone.[4] Fischer and Blumenthal also prepared free α-aminobutyrolactone from its hydrochloride and found that it reacts with itself to form a diketopiperazine. The formation of a diketopiperazine is likewise similar to the reaction of homocysteine thiolactone which reacts with itself in neutral solution to form homocysteine diketopiperazine.[5] It thus was of interest to find whether homoserine could exist in the open form in acid solutions and whether the lactone of homoserine reacted in aqueous solution to form the corresponding diketopiperazine as well as opening to form homoserine.

The nitrous acid amino nitrogen determination showed both homoserine and its lactone to contain the calculated amount of amino nitrogen; homoserine diketopiperazine showed no amino nitrogen under the conditions of the determination. Solutions, ranging from 1 N in sodium hydroxide to 6 N in hydrochloric acid, of the free acid after standing for several days suffered no loss in their content of amino nitrogen; this indicated that no measurable amount of diketopiperazine was formed from homoserine itself. Solutions of the lactone behaved somewhat differently; in the presence of even a slight amount of base the lactone ring opened to form homoserine, and its solutions showed no loss of amino nitrogen. Dilute (1%) neutral or slightly acidic (less than 1 mole of acid/mole of lactone) solutions of the lactone did not show the formation of any significant amount of diketopiperazine; more concentrated neutral or slightly acidic solutions of the lactone, however, showed the formation of a mixture of homoserine and its diketopiperazine. The formation of homocysteine diketopiperazine in good yield from homocysteine thiolactone may be understood to occur as a result of the much greater insolubility of this diketopiperazine in water; this would speed the formation of diketopiperazine at the expense of the reaction forming homocysteine.

The availability of optically active homoserine and its lactone hydrobromide made it appear likely that the relationship of the free amino acid to its lactone could be studied polarimetrically,

(1) This research was supported by a grant from the United States Public Health Service. Presented in part before the Division of Biological Chemistry at the 112th meeting of the American Chemical Society, New York, September 16, 1947.

(2) M. D. Armstrong, THIS JOURNAL, **70**, 1756 (1948).

(3) E. Fischer and H. Blumenthal, *Ber.*, **40**, 106 (1907).

(4) B. Riegel and V. du Vigneaud, *J. Biol. Chem.*, **112**, 149 (1935–1936).

(5) V. du Vigneaud, W. I. Patterson and M. Hunt, *J. Biol. Chem.*, **126**, 217 (1938).

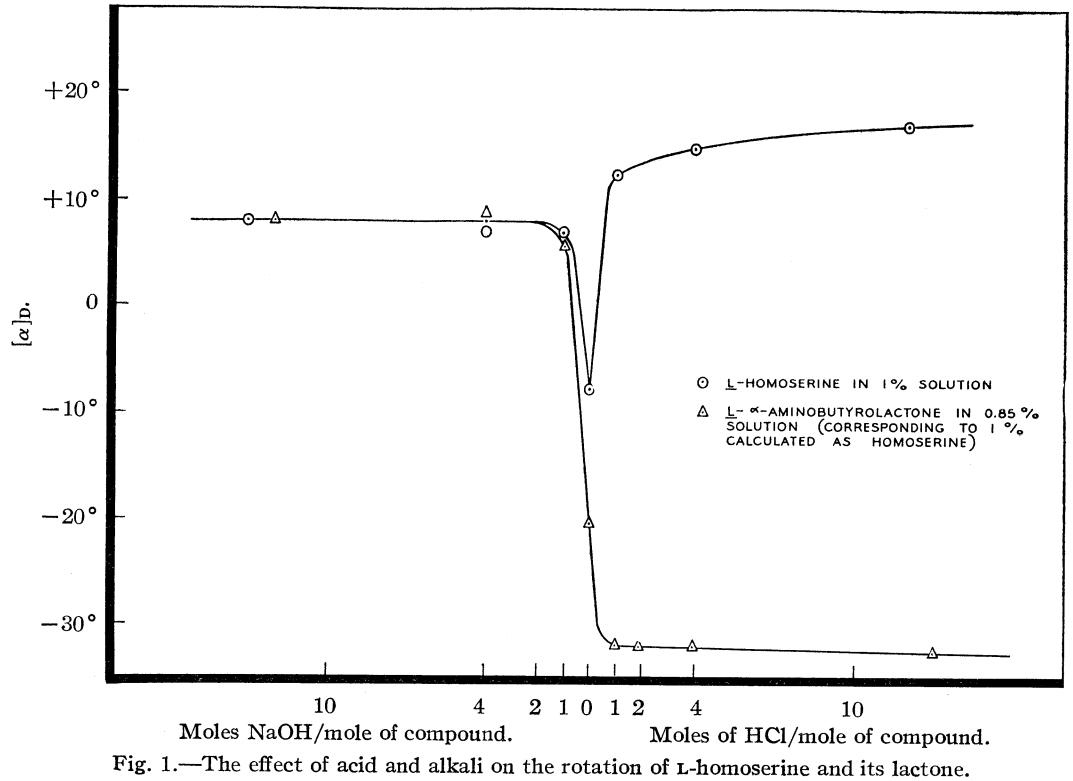
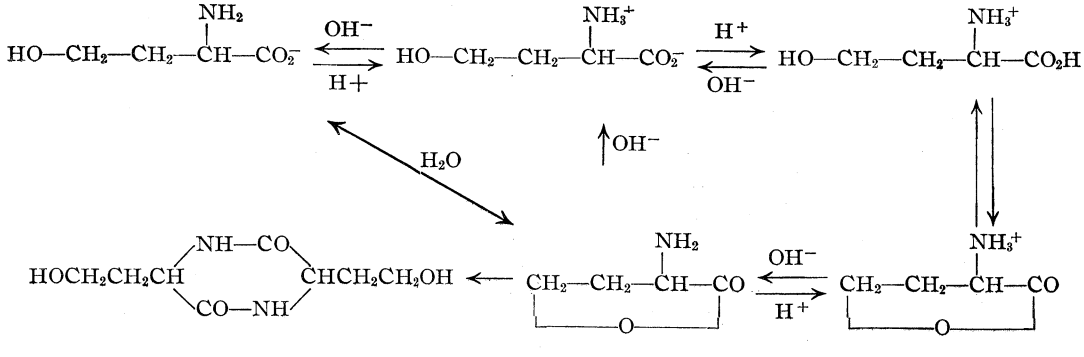


Fig. 1.—The effect of acid and alkali on the rotation of L-homoserine and its lactone.

provided the initial rotations of homoserine and its lactone were widely enough separated. Accordingly, measurements were made of the rotations of L-homoserine and of L-α-aminobutyrolactone in solutions containing varying amounts of acid and alkali. For convenience a concentration of the lactone hydrobromide equivalent in molarity to a 1% solution of homoserine was used and the specific rotations are reported on this basis. The results (Fig. 1) show that the specific rotation of L-homoserine is affected by acid and alkali in the same manner as that of the other natural amino acids. L-α-Aminobutyrolactone, on the other hand, shows a quite different behavior. In the presence of 1 mole of base the lactone ring is immediately opened to yield a salt of homoserine; 1 mole of acid causes it to exhibit a negative maximum of rotation which is not increased significantly at higher acid concentrations.

Mutarotation was found to occur in acidic solutions of the amino acid or its lactone. The change in rotation with respect to time is shown in Fig. 2 for three concentrations of acid; the speed with which equilibrium was reached varied with the strength of acid. With the use of the observed initial rotations of homoserine and of its lactone (extrapolated to zero time) it became possible to calculate the percentage of each present in an equilibrium mixture. In Fig. 3 is shown the effect of acid concentration on the percentage of homoserine present in such a solution.

The above data indicate that in solutions of homoserine the following changes may occur.



Experimental

L- and DL-homoserine, L- and DL-α-aminobutyrolactone hydrobromide, and inactive homoserine diketopiperazine were prepared in the manner previously described.[1]

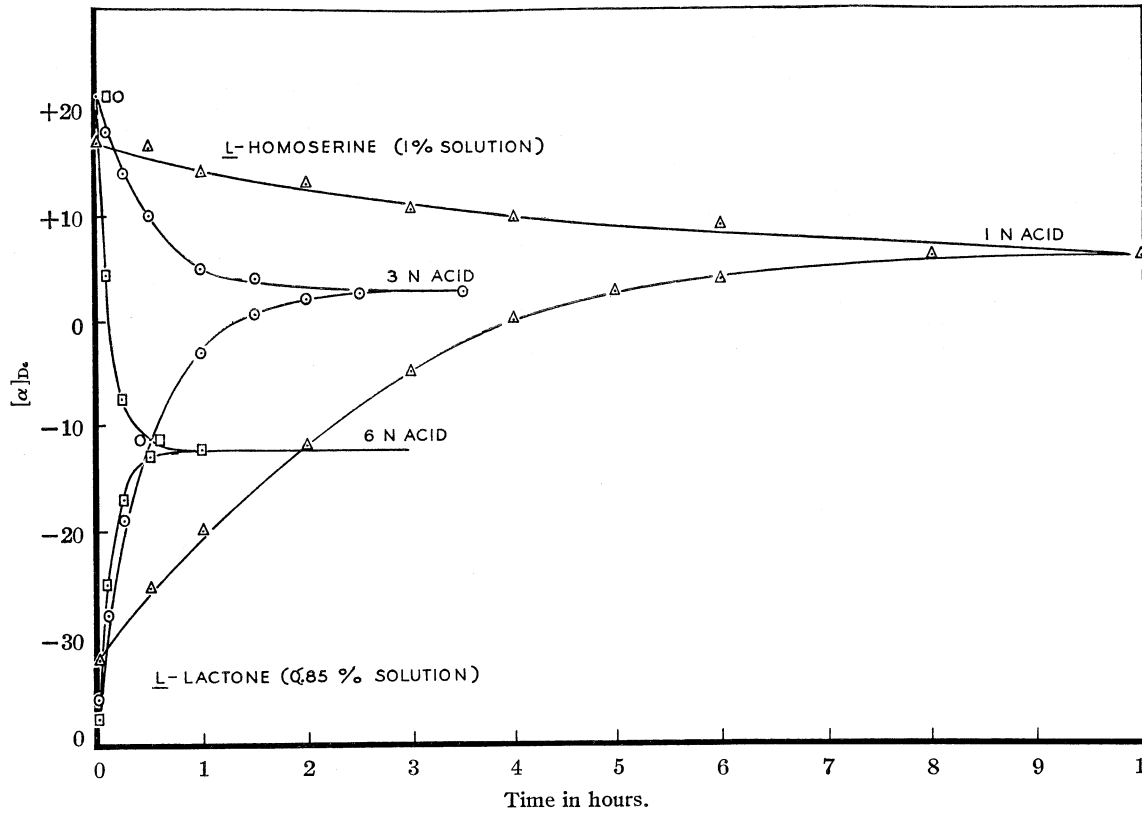


Fig. 2.—The effect of acid concentration on the equilibration of homoserine and its lactone.

The Solubility of L- and DL-Homoserine.—Because of the high solubility of these compounds in water and the unavailability of a considerable amount of the optically active compound for experimentation, a roughly quantitative estimate of their solubility was made as follows: 500.0 mg. of the compound was placed in a tared flask and distilled water was added dropwise to the flask until most of the compound had dissolved. The flask was shaken for a period of two hours between the addition of each drop of water. The amount of water necessary just to dissolve the compound was determined by reweighing the flask. DL-Homoserine: temperature, 30°; 504.4 mg. required 400 mg. of water; solubility, 125 g. of DL-homoserine in 100 g. of water. L-Homoserine: temperature, 30°; 404.4 mg. required 367 mg. of water for complete solution; solubility, 110 g. of L-homoserine in 100 g. of water. It will be noted that this approximation gives a minimum value for the solubility of the compounds.

Test for Diketopiperazine Formation from Homoserine and α-Aminobutyrolactone.—Analytical data were determined for homoserine and its derivatives:

TABLE I

	N Calcd., %	N Found, % Kjeldahl	Amino	Ninhydrin
Homoserine	11.76	11.93	11.77	11.78
α-Aminobutyrolactone hydrobromide	7.69	7.75	8.15[6]	0
Homoserine diketopiperazine	13.86	13.81	0	0

One per cent. solutions of homoserine and of α-aminobutyrolactone[7] were allowed to stand for several days with varying amounts of acid or alkali; at the end of this time the solutions showed no change in amino nitrogen content.

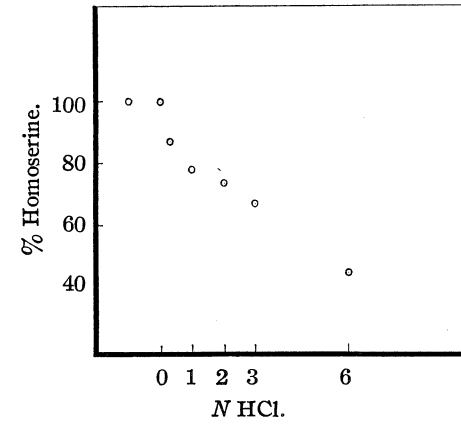


Fig. 3.—The effect of acid concentration on the composition of an equilibrium mixture of homoserine and its lactone. One per cent. solutions were used.

Opening of the Lactone Ring of α-Aminobutyrolactone in Aqueous Solution.—An attempt was made to follow the experimental conditions which gave a 95.5% yield of homocysteine diketopiperazine from homocysteine thiolactone hydrochloride.[5] To a solution of 10.0 g. of DL-α-

(6) After standing under conditions which open the lactone ring, a value of 7.72% amino N is found.

(7) Solutions of α-aminobutyrolactone were obtained by adding the calculated amounts of standard acid or alkali to a solution of its hydrobromide.

aminobutyrolactone hydrobromide in 100 ml. of water was added 4.62 g. of sodium bicarbonate. The resulting solution was allowed to stand overnight at room temperature. No precipitate had formed at this time so the solution was evaporated on a steam-bath to yield a thick semi-crystalline sirup. This sirup was dissolved in 18 ml. of water and the resulting solution was diluted with 100 ml. of absolute ethanol and let stand overnight in a refrigerator. The crystalline product was collected on a filter, washed with absolute alcohol, and was air dried; yield, 5.0 g.; m. p., 160–163° dec. An additional 0.6 g. of product having the same melting point was obtained by reworking the mother liquors.

The combined fractions were recrystallized by dissolving them in 20 ml. of hot water, adding 40 ml. of absolute ethanol, and allowing the solution to stand for several days in a refrigerator; 0.7 g. of flat parallelograms, m. p. 197–200°, was obtained. This compound gave a negative ninhydrin test and a mixed melting point with *meso*-homoserine diketopiperazine (m. p. 200–202°) showed no depression.

Anal. Calcd. for $C_8H_{14}O_4N_2$: N, 13.86. Found: N, 13.61.

The filtrate from this compound was diluted with 20 ml. of absolute ethanol and was allowed to stand in a refrigerator several more days: 1.4 g. of well formed flat needles was obtained, m. p. 183–185° dec. This compound gave a strongly positive ninhydrin test and a mixed melting point with DL-homoserine (m. p. 186–187°) showed no depression.

Anal. Calcd. for $C_4H_9O_3N$: N, 11.76. Found: N, 11.75.

A solution of homoserine in water was evaporated to dryness on a steam-bath in the same manner as in the above experiment. After it was redissolved in water an amino nitrogen determination showed that no loss in amino nitrogen had occurred, hence no diketopiperazine had formed under the conditions used.

The Optical Rotation of L-Homoserine and L-α-Aminobutyrolactone.—Rotation was measured using a 2-dm. tube and monochromatic light from a sodium vapor lamp. A 1% solution of homoserine was used in aqueous solutions containing varying amounts of acid and alkali; a 1.53% solution of α-aminobutyrolactone hydrobromide (equimolar with the 1% solution of homoserine) was used in a corresponding manner. The proper ratios of acid and alkali to the compounds were obtained by previously preparing standardized solutions containing the correct amounts of acid or alkali. The finely powdered compounds were dissolved in the solvent, placed in a polarimeter tube and the rotations of the solutions were measured as quickly as possible and thereafter at intervals. In cases where rapid mutarotation occurred the rotations at zero time were estimated by extrapolation. All rotations were measured at 25 ± 3°; there is no measurable error over this amount of variation in temperature due to a temperature coefficient for these compounds.

The results of the experiments are shown graphically in Figs. 1, 2 and 3.

Summary

The relationships between homoserine, its lactone and its diketopiperazine have been studied.

In basic and in neutral aqueous solution homoserine itself is stable and does not transform into either its lactone or diketopiperazine. In acidic solution homoserine is in equilibrium with its lactone; increasing amounts of the lactone are present in more strongly acid solutions.

In basic solution the lactone ring of α-aminobutyrolactone is opened to form homoserine; in solutions containing 1 mole or more of acid per mole of lactone the lactone is in equilibrium with homoserine. In dilute neutral solution the lactone ring opens to form homoserine and in dilute solutions containing less than 1 mole of acid per mole of lactone the lactone is in equilibrium with homoserine; in more concentrated neutral and slightly acidic solutions a mixture of homoserine and its diketopiperazine is formed.

SALT LAKE CITY, UTAH RECEIVED APRIL 18, 1949

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

The Synthesis of Pseudoconhydrine[1]

BY LÉO MARION AND WILLIAM F. COCKBURN

Pseudoconhydrine, one of the Hemlock group of alkaloids, occurs in the common hemlock, *Conium maculatum* L., along with coniine, N-methylconiine, γ-coniceine and conhydrine. It was discovered in the residues from the isolation of coniine and found to be an isomer of conhydrine, with the empirical formula $C_8H_{17}ON$.[2] Further investigation showed the base, like conhydrine itself, to be an hydroxyconiine,[3] while a study of the exhaustive methylation demonstrated that the hydroxyl group occupies position 5 of the piperidine nucleus.[4] Pseudoconhydrine is thus 5 - hydroxy - 2 - *n* - propylpiperidine[4] (VI), a structure now confirmed by the total synthesis of the alkaloid, the resolution of the synthetic base into its optical isomers and the preparation of derivatives.

Attempts to sulfonate conyrine (2-propylpyridine) in the 5-position with oleum and a mercury catalyst were largely unsuccessful, apparently owing to oxidation of the propyl side-chain, with the formation of tarry by-products. A small amount of impure material was isolated, but the method was not considered sufficiently profitable and was abandoned. The following scheme, however, proved successful.

2-Methylpyridine-5-sulfonic acid (I) was obtained by sulfonation of α-picoline[5] and converted to 5-hydroxy-2-methylpyridine (II) by potash fusion.[6] Addition of ethereal diazomethane to an aqueous–methanolic solution of II yielded the

(1) Published as National Research Council Bull. No. 2002.

(2) A. Ladenburg and G. Adam, *Ber.*, **24**, 1671 (1891).

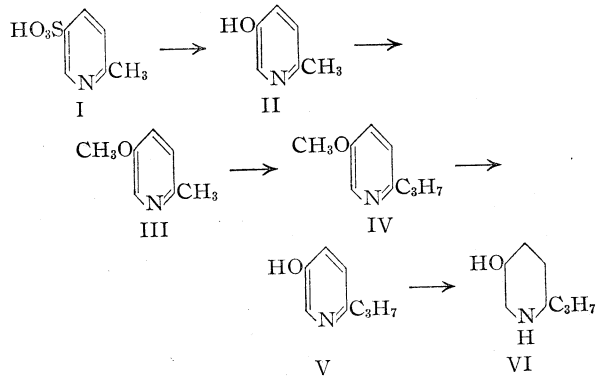
(3) K. Löffler, *ibid.*, **42**, 116, 960 (1909).

(4) E. Späth, F. Kuffner and L. Ensfellner, *ibid.*, **66**, 591 (1933).

(5) S. M. McElvain and M. A. Goese, THIS JOURNAL, **65**, 2233 (1943).

(6) O. Wulff, U. S. Patent 1,880,645; *C. A.*, **27**, 513 (1933).

methyl ether (III) which was condensed with ethyl chloride in the presence of freshly prepared



potassamide to give 5-methoxy-2-propylpyridine (IV). Although the yield for this last reaction was only 22% for a single run, most of the unchanged α-picoline derivative could be recovered in a pure state and recycled, raising the "conversion" to 66%. A similar experiment employing phenyllithium as condensing agent gave only a 5% yield of the desired compound contaminated with other material, while sodium triphenylmethide failed to effect any conversion at all. Demethylation of IV was brought about by refluxing with 48% hydrobromic acid in glacial acetic acid, and the resulting phenolic compound (V) hydrogenated at 50 lb. pressure in presence of Adams catalyst. The hydrogenation product (VI) was obtained as a yellowish semi-crystalline mixture, fairly readily separable by vacuum distillation into approximately equal amounts of a white crystalline solid and a colorless oil. These are presumably the two racemic diastereomers to be expected on the basis of the two asymmetric carbon atoms in the molecule of pseudoconhydrine. The solid isomer, like the natural alkaloid, appears to hydrate very readily, and was dried by vacuum-sublimation at 70° (0.05 mm.) being then pure, m. p. 91.5–92°. Since the natural alkaloid melts at 105–106°, it seemed probable that this isomer was racemic pseudoconhydrine.

This compound, like synthetic conhydrine,[7] failed to form a crystalline salt with *d*-tartaric acid, and was therefore resolved with the optically active 6,6′-dinitro-2,2′-diphenic acids[8–10] into *l*- and *d*-pseudoconhydrine. Measurement of the optical activity gave $[\alpha]^{26}D$ − 10.75° and $[\alpha]^{23}D$ + 11.09° for the *l*- and *d*- isomers, respectively, the latter value being in excellent agreement with the values of +10.98 and +11.06° recorded for the natural alkaloid.[2] The melting points of the free base, 105–106°, the hydrochloride, 214–215°, and the N-benzoyl derivative, 131–132°, also correspond to those obtained by Löffler[3] and Späth[4] for the natural product and the corresponding derivatives, and identity is assumed.

Acknowledgment.—The authors wish to acknowledge with thanks their indebtedness to the Goldsmiths' Company of London, England, for the award of a Travelling Fellowship to one of them (W. F. C.).

Experimental

2-Methylpyridine-5-sulfonic Acid (I).—α-Picoline was sulfonated with oleum in presence of a mercury catalyst as described by McElvain and Goese.[5] The free sulfonic acid was obtained as a tan-colored crystalline solid, m. p. 334–338° (uncor.).[11] McElvain reports this as 338–341° (cor.); yield 54%.

5-Hydroxy-2-methylpyridine (II).—The free sulfonic acid (I) was fused with excess potassium hydroxide in a nickel crucible, with some iron filings as catalyst.[6] After cooling, the melt was dissolved in water and partly neutralized with hydrochloric acid, neutralization being completed with carbon dioxide. The precipitated phenolic compound was filtered off, dried in a desiccator, and extracted with ether in a Soxhlet. The aqueous mother liquors were also extracted overnight in a liquid–liquid extractor, and the two extracts combined and concentrated. The crude 5-hydroxy-2-methylpyridine which crystallized was purified by sublimation in a large Pyrex tube at 130° (0.1 mm.) being obtained as an almost white crystalline solid m. p. 167–169°. This is reported as 164–166°.[6] It gave a red color with aqueous ferric chloride.

Anal. Calcd. for C_6H_7ON: C, 66.06; H, 6.46. Found: C, 66.22, 66.34; H, 6.40, 6.30.

5-Methoxy-2-methylpyridine (III).—Ten grams (0.10 mole) of 5-hydroxy-2-methylpyridine was dissolved in 150 ml. of methanol containing 10% of water, and the solution chilled in an ice–salt-bath. A solution of 11.0 g. (0.26 mole) of diazomethane in 300 ml. of ether was added slowly with swirling from a dropping funnel, the stem of which projected below the surface of the liquid. A brisk effervescence accompanied the addition, which was interrupted several times in order to boil off the accumulated ether. If the latter procedure, which serves to keep the polarity of the solution at a maximum, was omitted, or more nearly equivalent quantities of phenol and methylating agent employed, the yield of methyl ether was much lower, although a greater recovery of unchanged phenol was possible. After being allowed to stand in the ice-box overnight, the methanol solution was acidified with hydrochloric acid, and most of the ether and methanol removed by concentration on the steam-bath. The resulting sirup was diluted with water and the solution exhausted with ether. It was then alkalized with sodium hydroxide pellets, and again extracted with ether. This second extract was dried over potassium hydroxide pellets, the ether removed by distillation, and the residual oil vacuum distilled. The product was a colorless oil, b. p. 43–45° (1 mm.) or 188–189° (760 mm.), $n^{25}D$ 1.5088.

Anal. Calcd. for C_7H_9ON: C, 68.28; H, 7.36. Found: C, 68.30, 68.37; H, 7.17, 7.35.

The maximum yield obtained was 40%, but some of the phenol was recoverable, the amount depending on the exact procedure followed.

5-Methoxy-2-propylpyridine (IV).—Potassium (5 g., 0.128 atom) was converted to potassamide in liquid ammonia (80 ml.) with ferric nitrate (0.2 g.) as catalyst. The reaction was carried out in a 100-ml. three-necked, ground-glass flask equipped with a stirrer and a cold-finger Dry Ice condenser with nitrogen inlet, while the third neck was closed with a stopper and used for the addition of reagents. When all the metal had been converted to amide, the ammonia was allowed to evaporate past the

(7) C. Engler and F. W. Bauer, *Ber.*, **27**, 1775 (1894).
(8) E. Späth and F. Kesztler, *ibid.*, **69**, 2725 (1936); **70**, 70 (1937).
(9) F. Galinovsky and H. Mulley, *Monatsh.*, **79**, 427 (1948).
(10) A. W. Ingersoll and J. R. Little, THIS JOURNAL, **56**, 2123 (1934).
(11) All melting points are corrected, unless otherwise stated.

loose stopper, the last traces being driven off by warming under nitrogen in a water-bath. The solid cake of potassamide was carefully broken up with a spatula in a strong stream of nitrogen, and the cold-finger filled with Dry Ice. Ten grams (0.081 mole) of 5-methoxy-2-methylpyridine was added, and allowed to stir for fifteen minutes, during which time the solution developed a deep purplish-red color. To the mixture was added 9.5 ml. (0.135 mole) of ethyl chloride from a cooled graduated pipet in 0.3-ml. portions at five-minute intervals, the condenser being kept cold by fresh additions of Dry Ice. After several hours, the flask was immersed in an ice-bath and stirring continued overnight. The ice-bath was then removed, fresh Dry Ice added to the condenser, and stirring continued at room temperature for a further ten hours. The total reaction time was thirty hours.

About 40 ml. of ether was added to the mixture, and the unreacted potassamide decomposed by the cautious addition of water from a dropping funnel. The ether layer was separated, extracted thoroughly with dilute hydrochloric acid, and the acid extract combined with the acidified aqueous portion of the reaction mixture. The combined solutions were repeatedly extracted with ether to remove non-basic impurities, alkalized with sodium hydroxide, and again extracted with ether. This second extract was dried with potassium carbonate, the ether removed by distillation and the residue vacuum distilled in a Vigreux–Claisen flask. The product was a water-white oil with a penetrating odor reminiscent of oil of aniseed, b. p. 60–61° (0.7 mm.). The yield was 2.6 g. (22%), 67% of the starting material being recovered.

The analysis results were slightly low, presumably due to the presence of unchanged 5-methoxy-2-methylpyridine, so the product of several runs was carefully fractionated at about 1 mm. pressure in a column (23 cm. long and 1 cm. dia.) packed with wire gauze, and equipped with a heated jacket and Whitmore and Lux still-head.[12] Two sharp fractions were obtained at 37–40° and 60–62°, corresponding to unchanged starting material and the desired product, respectively.

Anal. Calcd. for $C_9H_{13}ON$: C, 71.48; H, 8.66. Found: C, 71.45, 71.48, 71.50; H, 8.87, 8.76, 8.63; $n^{25}D$ 1.5012.

Treatment with the theoretical amount of picric acid in methanol gave a picrate in pale greenish-yellow needles, m. p. 113–114°.

Anal. Calcd. for $C_9H_{13}ON \cdot C_6H_3O_7N_3$: C, 47.37; H, 4.24. Found: C, 47.47, 47.67; H, 4.24, 4.30.

5-Hydroxy-2-propylpyridine (V).—For the demethylation, 4.30 g. (0.028 mole) of 5-methoxy-2-propylpyridine was refluxed for ninety hours with 200 ml. of glacial acetic acid containing 90 ml. of 48% hydrobromic acid. After cooling, the solution was diluted with its own volume of water and extracted four times with twice its own volume of ether. It was then basified with sodium hydroxide pellets and extracted with ether again. This extract yielded 0.13 g. of starting material (3%).

The aqueous solution was made just acid with concentrated hydrochloric acid, then basified with excess ammonium hydroxide, and the solution extracted continuously overnight with ether. The extract was dried with Drierite and concentrated to 10 ml. on the steam-bath. A white crystalline solid separated on cooling, and a further quantity could be obtained from the mother liquors by slow and repeated addition of petroleum ether (b. p. 50–60°). The product was readily purified by crystallization from ether–petroleum ether, being obtained as a white crystalline solid m. p. 93–93.5°. It is much more soluble in ether than 5-hydroxy-2-methylpyridine, and like the latter gives a deep red color with aqueous ferric chloride.

(12) F. C. Whitmore and A. R. Lux, THIS JOURNAL, **54**, 3448 (1932).

Anal. Calcd. for $C_8H_{11}ON$: C, 70.06; H, 8.08. Found: C, 70.01, 70.20; H, 7.84, 7.93.

The final yield was 2.60 g. (66%).

5-Hydroxy-2-propylpiperidine (VI).—One gram (0.0073 mole) of 5-hydroxy-2-propylpyridine was hydrogenated at 44 lb. pressure in 50 ml. of glacial acetic acid containing 250 mg. of Adams catalyst, the reaction time being sixteen hours. The solution was diluted with its own volume of water, filtered from the catalyst, acidified with 5 ml. of concentrated hydrochloric acid, and most of the acetic acid removed by ether extraction. The solution was basified with sodium hydroxide and extracted continuously overnight with ether. The extract was dried with potassium carbonate, and the ether removed by distillation, leaving a yellow oil which partially crystallized on cooling. The mixture had a pleasant sweetish smell reminiscent of crushed leaves. Yield was 1.008 g. (96%).

***dl*-Pseudoconhydrine.**—A bulb was blown in the end of a 30-cm. length of 12 mm. Pyrex tubing, and an ether solution of 1 g. of 5-hydroxy-2-propylpiperidine introduced into it. The ether was removed at the water-pump, and the residue slowly vacuum distilled from an air-bath, the portion of the tube outside the bath being wrapped with asbestos to provide a temperature gradient. The compound distilled at 70–75° (0.1 mm.) giving white crystals in the hotter part of the tube, and a colorless oil in the cooler part, the two being separated by breaking the tube between the fractions. The solid could be crystallized from ethyl acetate–petroleum ether in fine felted needles, but still had a diffuse melting point, probably due to hydrate formation. It was again sublimed *in vacuo*, being obtained in feathery white needles, m. p. 91.5–92°. It gave no color with aqueous ferric chloride, and depressed the melting point of 5-hydroxy-2-propylpyridine by over 50°.

Anal. Calcd. for $C_8H_{17}ON$: C, 67.11; H, 11.96. Found: C, 67.30, 67.24; H, 11.71, 11.76.

***l*- and *d*-Pseudoconhydrine.**—For the resolution, 0.685 g. of the racemic base was treated with 1.590 g. of *d*-6,6′-dinitro-2,2′-diphenic acid in 30 ml. of hot water. On cooling, 0.854 g. of yellow crystals separated. These were recrystallized from water nine times, giving 0.132 g. of salt, m. p. 238–240° (dec.).

Anal. Calcd. for $C_8H_{17}ON \cdot C_{14}H_8O_8N_2$: C, 55.56; H, 5.30. Found: C, 55.49, 55.35; H, 5.06, 5.14.

The free base was liberated and distilled at 70° (0.05 mm.) being obtained in feathery white crystals m. p. 105–106° (in vacuum tube); $[\alpha]^{26}D$ −10.75° (c = 1.675 in absolute ethanol). The hydrochloride was prepared and crystallized from methanol–acetone in silvery-white needles, m. p. 214–215°.

The free base was recovered from the mother liquors of the above resolution and treated with *l*-6,6′-dinitro-2,2′-diphenic acid. The same treatment as above yielded *d*-pseudoconhydrine m. p. 105–106°; $[\alpha]^{23}D$ +11.09° (c = 1.715 in absolute ethanol).

Treatment with 1 mole of benzoyl chloride in ether solution yielded the N-benzoyl derivative, which was recrystallized from ether in white nodules, m. p. 131–132°.

Summary

1. The structure assigned to pseudoconhydrine has been confirmed by a total synthesis of the alkaloid from α-picoline.

2. The 5-hydroxy-2-propylpiperidine so obtained has been separated by fractional distillation into two racemic diastereomers, of which the solid isomer has been resolved into its optical antipodes by means of its salts with the optically active 6,6′-dinitro-2,2′-diphenic acids.

OTTAWA, CANADA

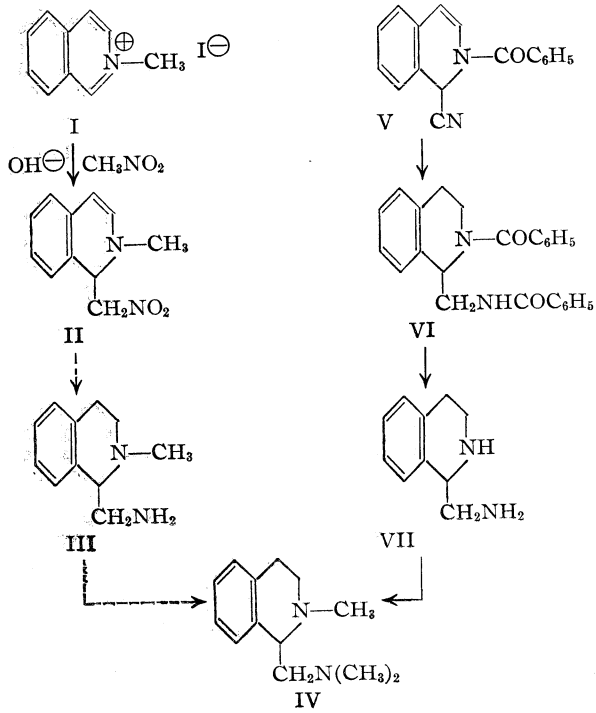
RECEIVED MAY 23, 1949

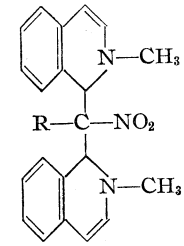
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Reactions of Nitroparaffins with Isoquinolinium Compounds

BY NELSON J. LEONARD AND GERHARD W. LEUBNER[1,2]

One method for the synthesis of substituted 1-aminomethyltetrahydroisoquinolines (*e. g.*, III, IV), which are of pharmacological interest,[3] would appear to be the condensation of nitroparaffins with isoquinolinium salts in the presence of alkali, followed by stages of reduction and alkylation. For example, the mono-condensation product (II) of nitromethane with 2-methylisoquinolinium iodide (I) should be convertible to 1-dimethylaminomethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV). Positive comparison of this product with that obtained (VI → VII → IV)[4] from Reissert's isoquinoline compound (V)[5] would serve to establish the structure of the compounds in the nitroparaffin series. Surprising results were encountered in the proposed synthesis of II in that *2-nitronaphthalene* (XV) was obtained from the reaction of nitromethane with 2-methylisoquinolinium iodide in the presence of alkali. In addition, the alkaline condensation of nitromethane with I furnished some disubstituted nitroparaffin to which has been assigned the structure VIIIa. The alkaline condensation of nitroethane and 1-nitropropane with I yielded VIIIb and VIIIc.





VIII (a, R = H; b, R = CH_3; c, R = C_2H_5)

The condensation of nitromethane with 2-methylisoquinolinium iodide in the presence of two molecular equivalents of potassium hydroxide has been described in the patent literature.[6] Kaufmann reported a product melting at 99°, but further characterization was lacking. In our hands, the same condensation in the presence of varying amounts of alkali invariably led to a non-homogeneous product, the components of which were difficult to separate. Recrystallization, sublimation, distillation and chromatographic adsorption of the crude reaction product were investigated. A single, pure chemical individual was isolated (in about 9% yield) by the methods of sublimation and chromatography. The pale yellow crystalline solid, m. p. 78–79°, thus obtained possessed a melting point and an analytical composition which were suggestive of 2-nitronaphthalene (XV); indeed, the product was found to be identical with an authentic sample of 2-nitronaphthalene. Moreover, it was converted by reduction and acetylation to acet-2-naphthalide, identical with an authentic sample of this compound.

Since the transformation of an isoquinoline ring system to a naphthalene ring system is unusual, it is interesting to speculate on the method whereby 2-nitronaphthalene is produced. A plausible series of reactions can be written in which the first step supposes the formation of 1-nitromethyl-2-methyl-1,2-dihydroisoquinoline (II) from 2-methylisoquinolinium hydroxide and nitromethane. Compound II has a Mannich base structure so that its conversion to the open chain nitroölefin (IX) might be expected to occur.[7] Hope and Robinson[8] have reported the isolation of a similar type of compound from the reaction of methyl iodide with anhydrocotarninenitromethane. The 1,3-shift of hydrogen corresponding to the conversion of a vinyl secondary amine (IX) to a Schiff

(1) Eli Lilly and Company Fellow, 1946–1948.

(2) Present address: Eastman Kodak Company, Rochester, New York.

(3) (a) Magidson and Gorbovizkii, *Ber.*, **68**, 656 (1935); (b) Dey and Kantam, *J. Indian Chem. Soc.*, **14**, 91 (1937); (c) Takase and Sato, *J. Pharm. Soc. Japan*, **49**, 1096 (1929).

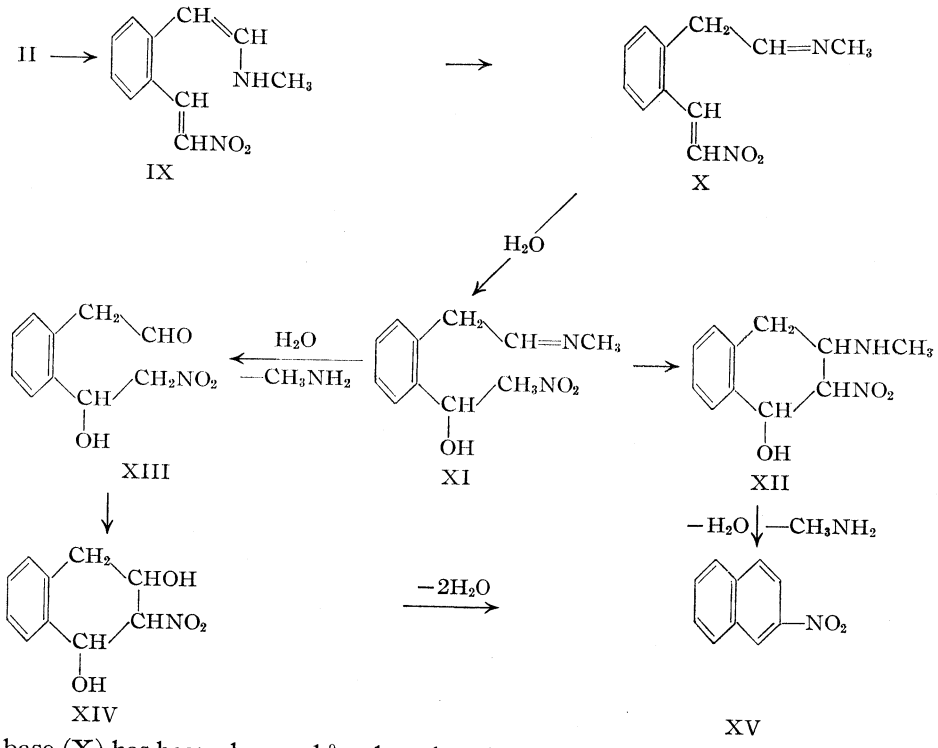
(4) Rupe and Frey, *Helv. Chim. Acta*, **22**, 673 (1939).

(5) Reissert, *Ber.*, **38**, 3415 (1905).

(6) Kaufmann, German Patent 250,154, July 15, 1912; *Frdl.*, **10**, 1317 (1910–1912).

(7) Blicke, in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. I, p. 318.

(8) Hope and Robinson, *J. Chem. Soc.*, **99**, 2114 (1911).



base (X) has been observed,[9] as has the addition of water (X → XI) to a nitroölefin.[10,11] The sequence of these and subsequent reactions is not to be considered inflexible. The conversion of the Schiff-base hydrolysis product (XIII) to XIV represents a common reaction of aldehydes with nitroparaffins[11] and the conversion of XI to XII represents a known reaction of nitroparaffins with imines.[12] The transformation of both XIV and XII to 2-nitronaphthalene (XV) would be expected to occur readily. Further study is planned to determine the scope and course of the over-all transformation.

Also obtained from the reaction of nitromethane and 2-methylisoquinolinium iodide in the presence of alkali was a compound, isolated as the monohydrochloride and monopicrate, which had a composition represented by the structure VIIIa. An analogous product was isolated as the free base (in 44% yield) from the condensation of nitroethane with two moles of 2-methylisoquinolinium iodide and potassium hydroxide and was assigned the structure, 1,1-bis-[1′-2′-methyl-1′,2′-dihydroisoquinolyl)]-nitroethane (VIIIb), on the basis of analysis and infrared absorption spectrum. A similar product, 1,1-bis-[1′-(2′-methyl-1′,2′-dihydroisoquinolyl)]-1-nitropropane (VIIIc) was obtained in a 21% yield using 1-nitropropane. Previously reported examples of the reaction of nitroparaffins with isoquinolinium compounds have never disclosed the formation of dicondensation products.[3b,6,8,13,14,15,16]

In the preparation of IV from Reissert's isoquinoline compound,[5] with certain modifications of the method of Rupe and Frey,[4] the intermediates VI and VII were isolated. The anhydrous hydrochloride of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (VII) was obtained, rather than the hydrated salt, and the dipicrate of 1-dimethylaminomethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV) was formed from IV, rather than the monopicrate, as observed by Rupe and Frey.

Experimental[17]

Reaction of Nitromethane with 2-Methylisoquinolinium Hydroxide.—Fifty grams (0.185 mole) of 2-methylisoquinolinium iodide, m. p. 161–162°, and 33.8 g. (0.554 mole) of freshly distilled nitromethane[18] were dissolved in 250 ml. of hot absolute ethanol. To this was added a hot solution of 25 g. (0.38 mole) of potassium hydroxide pellets (85% KOH) in 100 ml. of absolute ethanol. The color of the solution changed immediately from yellow to red, and potassium iodide began to precipitate. After allowing the solution to stand for ten minutes, 250 ml. of water was added. The solution was cooled in an ice-bath and was acidified slowly with approximately 300 ml. of 5% aqueous acetic acid, with rapid stirring. The light brown solid which formed was allowed to settle and the supernatant liquid was decanted. The solid was stirred with water and the supernatant liquid was again decanted. After the washing process was repeated three times, the solid was collected and air-dried (25 g.). The wide melting range of the solid was not improved by recrystallization (ethanol, methanol, petroleum ether). In one run, a picrate was made from a filtered ether solution of the solid and an ethereal solution of picric acid. Four recrystallizations from ethylene dichloride–ethanol gave tiny yellow needles, which decomposed at 200° and were found to have an elementary composition corresponding to the **monopicrate of bis-[1-(2-methyl-1,2-dihydroisoquinolyl)]-nitromethane (VIIIa).**

Anal. Calcd. for $C_{27}H_{24}N_6O_9$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.28; H, 4.10; N, 14.16.

In a second run, using 1.1 moles of potassium hydroxide per mole of nitromethane and 2-methylisoquinolinium iodide, the crude dry product (1 g.) was dissolved in 100 ml. of ether and treated with anhydrous hydrogen chlo-

(9) Marz, Diss. Techn. Hochsch., München, 1913; see Adams and Mahan, THIS JOURNAL, **64**, 2588 (1942).
(10) Lambert, *J. Chem. Soc.*, 1474 (1947).
(11) Levy and Rose, *Quarterly Reviews*, **1**, 358 (1948).
(12) Mayer, *Bull. soc. chim. France*, [3] **33**, 395 (1905).
(13) Dey and Srinivasan, *J. Indian Chem. Soc.*, **12**, 526 (1935).
(14) Haworth, Perkin and Rankin, *J. Chem. Soc.*, **127**, 1444 (1925).
(15) Malan and Robinson, *ibid.*, 2653 (1927).
(16) Robinson and Robinson, *ibid.*, **111**, 958 (1917).
(17) All melting points are corrected. The authors are indebted to Mrs. James L. Johnson for determination of the infrared absorption spectra.
(18) Freund and Bode, *Ber.*, **42**, 1746 (1909).

ride. The precipitated salt was recrystallized four times from absolute ethanol to yield 0.33 g. of colorless prisms, which decomposed at 184° after initial sintering and darkening at 170°. In elementary composition the compound corresponded to the **monohydrochloride of bis-[1-(2-methyl-1,2-dihydroisoquinolyl)]-nitromethane.**

Anal. Calcd. for $C_{21}H_{22}ClN_3O_2$: C, 65.70; H, 5.78; N, 10.95. Found: C, 65.74; H, 6.13; N, 11.00.

The **picrate** prepared from this hydrochloride salt was identical with that described above.

In a duplicate of the original run (two moles of potassium hydroxide per mole of nitromethane and 2-methylisoquinolinium iodide) the crude condensation product was dissolved in benzene and chromatographed on a column of Harshaw 2-350 aluminum oxide. The chromatogram was developed with benzene to give successive canary yellow, lighter yellow, and brown bands. The lowest yellow band was eluted with benzene and the benzene solution was evaporated to dryness. The light yellow crystalline solid, after purification by sublimation and recrystallization from water (as needles), melted at 78–79°. The analytical composition corresponded to the empirical formula $C_{10}H_7NO_2$.

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.70; H, 4.10; N, 7.72.

Analysis and melting point were suggestive of 2-nitronaphthalene.[19] An authentic sample of 2-nitronaphthalene, m. p. 78–79°, was prepared by the method of Hodgson, Birtwell and Marsden[19] from 2-nitro-1-naphthylamine. Mixtures of the two samples gave no depression in melting point. The $C_{10}H_7NO_2$ product was reduced by means of iron powder in acetic acid and acetic anhydride to give a product, m. p. 131–132°, which separated as colorless plates from aqueous ethanol. This product gave no depression in melting point when mixed with an authentic sample, m. p. 131–132°, of acet-2-naphthalide.[20] The amount of 2-nitronaphthalene isolated by means of chromatography corresponded to a yield of 9% based on the 2-methylisoquinolinium iodide used. Approximately the same yield of 2-nitronaphthalene, similarly characterized, was realized by sublimation of the crude condensation product of 2-methylisoquinolinium hydroxide and nitromethane. The sublimation was carried out in the range of 80–150° and 0.01–0.5 mm. No other pure compounds could be isolated by chromatography and sublimation methods. It is probable that the yield of 2-nitronaphthalene can be raised by further examination of the conditions of the reaction.

1,1-bis-[1′-(2′-Methyl-1′,2′-dihydroisoquinolyl)]-nitroethane (VIIIb).—To a hot solution of 75 g. (0.28 mole) of 2-methylisoquinolinium iodide, 62 g. (0.83 mole) of nitroethane and 30 ml. of methanol was added a heated solution of 27.4 g. (0.42 mole) of potassium hydroxide in 100 ml. of methanol. The solution was allowed to stand one-half hour and was then evaporated at 25° with a stream of dry air. After the crystalline material began to separate, evaporation was aided by mechanical stirring. A thick paste of crystals and dark red oil resulted. The oil was removed by repeated washing with cold methanol, and potassium iodide was removed by water washing. The colorless organic solid (22 g., 44% yield) crystallized as prisms from acetone; m. p. 210–212°.

Anal. Calcd. for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.14; H, 6.55; N, 11.72.

The infrared absorption spectrum agreed well with the structure assigned on the basis of analysis. The strong characteristic nitro absorption band was observed at 1535 cm.$^{-1}$, and the bands at 741 and 751 cm.$^{-1}$ were characteristic of the *o*-substituted phenyl grouping.

1,1-bis-[1′-(2′-Methyl-1′,2′-dihydroisoquinolyl)]-1-nitropropane (VIIIc).—The reaction between 1-nitropropane and 2-methylisoquinolinium iodide was carried out in the same manner as that described for nitroethane. When the reaction mixture was allowed to stand for several days at 25°, crystalline material separated. The solid (21% yield) was obtained as colorless prisms upon recrystallization from acetone; m. p. 201.5–202°.

Anal. Calcd. for $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19. Found: C, 73.58; H, 6.87; N, 10.99.

The infrared absorption spectrum was very similar to that observed for the lower homolog (VIIIb).

1-Aminomethyl-1,2,3,4-tetrahydroisoquinoline (VII) Hydrochloride.—The preparation of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline (V) was effected by the method of Reissert[5] with some modifications. Hydrogenation of V in ethanol over Raney nickel catalyst at 150 atm. and 100° gave 1-benzoylaminomethyl-1,2,3,4-tetrahydroisoquinoline as an oil which was converted to solid 1-benzoylaminomethyl-2-acetyl-1,2,3,4-tetrahydroisoquinoline (VI), m. p. 196–197.5° (reported, 201°).[4] Hydrolysis of VI to 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (VII), b. p. 154–159° (15 mm.), $n^{20}D$ 1.5779, was effected with 20% hydrochloric acid. To a cooled solution of 11.5 g. (0.071 mole) of VII in 20 ml. of absolute ethanol was added slowly with stirring 6.8 ml. of absolute ethanol containing 2.6 g. (0.071 mole) of hydrogen chloride. The mixture containing some crystalline solid was heated, 25 ml. additional of absolute ethanol was added, and the material was allowed to crystallize. The monohydrochloride was obtained as colorless plates which darkened at 171° and melted at 179–184°. Recrystallization from absolute ethanol failed to improve the melting point.

Anal. Calcd. for $C_{10}H_{15}ClN_2$: C, 60.44; H, 7.61; N, 14.10. Found: C, 60.39; H, 7.37; N, 13.92.

Rupe and Frey[4] prepared the monohydrochloride in absolute ether and recrystallized from ethanol containing a small amount of water to obtain a dihydrate of the salt, m. p. 281° (dec.).

1-Dimethylaminomethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV).—The formaldehyde–formic acid method of methylation[21] was adapted to the conversion of VII to IV, rather than the methyl iodide–potassium hydroxide method of Rupe and Frey.[4] Twenty-one grams (0.13 mole) of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (VII) was dissolved with cooling in 51.1 g. (0.97 mole) of 87.5% formic acid and to this was added 34.7 g. (0.43 mole of formaldehyde) of formalin. After a short period of heating on the steam-bath, the initially vigorous evolution of carbon dioxide subsided in fifteen minutes. Heating on the steam-bath was continued for eight hours, 23 ml. of 12 *N* hydrochloric acid was added, and the solution was then evaporated to dryness under reduced pressure. The sirup which remained was dissolved in water, and the cold aqueous solution was made strongly alkaline with sodium hydroxide. The alkaline mixture was extracted with ether, the ethereal solution was dried, and the ether was removed. Fractional distillation of the residue *in vacuo* gave 12.6 g. (48%) of colorless oil, b. p. 143–146° (16 mm.) (reported, b. p. 135° (12 mm.)[4]); $n^{20}D$ 1.5331.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.72. Found: C, 76.23; H, 9.78; N, 14.07.

The methiodide, recrystallized from ethanol, melted at 196–197° (reported, 199°).[4] Two new derivatives of 1-dimethylaminomethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline were formed. The **dihydrobromide monohydrate** was prepared by the slow addition of 12.2 g. (0.072 mole of HBr) of 48% hydrobromic acid with stirring to an ice-cold solution of 7.4 g. (0.036 mole) of IV in 15 ml. of absolute ethanol. During the addition the crystalline salt began to separate. The mixture was heated and additional absolute ethanol was added to bring about solution. After filtration and cooling, 11.7 g. (88%) of colorless elongated prisms separated. Recrystallization from ethanol plus a small amount of water gave a 94% recovery of material which began sintering at 138° and melted with decomposition at 152–153°.

Anal. Calcd. for $C_{13}H_{24}Br_2N_2O$: C, 40.64; H, 6.30; N, 7.29. Found: C, 40.46; H, 6.48; N, 6.90.

(19) Hodgson, Birtwell and Marsden, *J. Chem. Soc.*, 112 (1944).

(20) Leonard and Hyson, *J. Org. Chem.*, **13**, 164 (1948).

(21) "Organic Syntheses," **25**, 89 (1945).

A small sample was well crushed and dried in an Abderhalden apparatus over phosphorus pentoxide at 110° for ten hours. The melting point of the anhydrous **dihydrobromide** was 216–220°.

Anal. Calcd. for $C_{13}H_{22}Br_2N_2$: C, 42.64; H, 6.06. Found: C, 42.76; H, 6.31.

We were unable to isolate the monopicrate, m. p. 202°, described by Rupe and Frey,[4] but we obtained a **dipicrate** when the amine in ethanol was treated with a large excess of ethanolic picric acid. Recrystallization from acetone–ethanol gave yellow crystals which softened at 158° and melted at 171–174°.

Anal. Calcd. for $C_{25}H_{26}N_8O_{14}$: C, 45.32; H, 3.96; N, 16.91. Found: C, 45.56; H, 4.18; N, 17.17.

Summary

It has been established that 2-nitronaphthalene is produced from the condensation of 2-methylisoquinolinium iodide with nitromethane in the presence of potassium hydroxide, and a plausible series of reactions has been suggested to account for this unusual transformation. The alkaline condensation of 2-methyliosquinolium iodide with nitromethane also produced some bis-[1-(2-methyl - 1,2 - dihydroisoquinolyl)]-nitromethane, that with nitroethane produced 1,1-bis-[1′-(2′-methyl - 1′,2′ - dihydroisoquinolyl)]-nitroethane, and that with 1-nitropropane gave 1,1-bis-[1′-(2′-methyl-1′,2′-dihydroisoquinolyl)]-1-nitropropane.

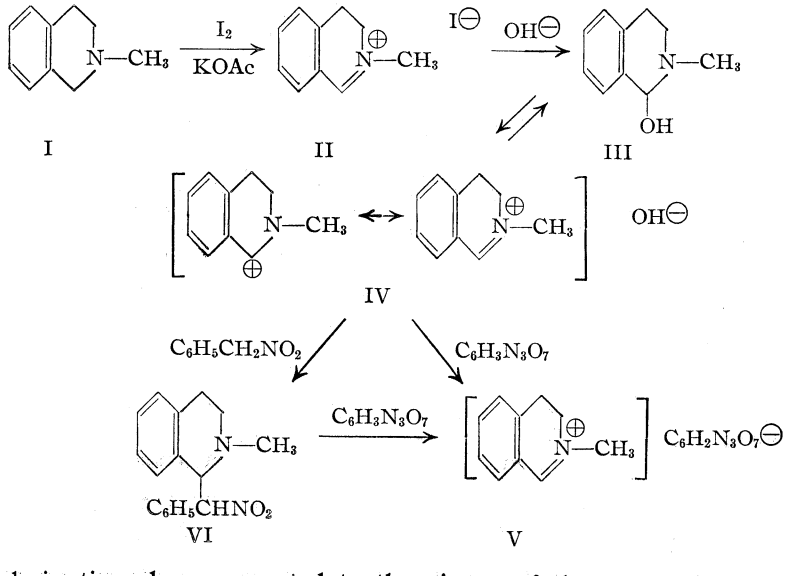
URBANA, ILLINOIS RECEIVED APRIL 28, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Reactions of Nitroparaffins with Pseudo Bases Related to Dihydroisoquinolinium Hydroxide

BY NELSON J. LEONARD AND GERHARD W. LEUBNER[1,2]

In an investigation[3] of the reaction of nitroparaffins with a pseudo base of type III,[4] the attempted characterization of the nitromethane product (analogous to VI) by picrate formation gave an unusual result. The supposed picrate derivative always reverted to the picrate of the pseudo base (V)! This observed elimination of nitromethane prompted a reëxamination of the picrate derivatives of anhydrocotarninenitromethane (VIII) and anhydrohydrastininenitromethane (VIII without methoxyl) reported by Hope and Robinson.[5] It has now been found that these reported derivatives are, in fact, cotarnine picrate (IX) and hydrastinine picrate (IX without methoxyl), both products of nitromethane elimination.



The method of synthesis of the pseudo base III required the initial preparation of 2-methyl-1,2,3,4-tetrahydroisoquinoline (I). The previously described directions for obtaining I by the reduction of 2-methylisoquinolinium iodide with tin and hydrochloric acid[6] or with sodium and ethanol[7] were less convenient than the formaldehyde–formic acid methylation[8] of 1,2,3,4-tetrahydroisoquinoline. 2-Methyl-1,2,3,4-tetrahydroisoquinoline (I) was oxidized to 2-methyl - 3,4 - dihydroisoquinolinium iodide (II) by means of iodine and potassium acetate. Compound II had been prepared previously, but by a degradation process.[9] The conversion of tetrahydro- to dihydro-compounds by iodine oxidation had been realized previously with several highly substituted tetrahydroisoquinolines,[10,11,12] but Schmidt had reported that iodine oxidation of tetrahydroisoquinoline itself gave iso-

(1) Eli Lilly and Company Fellow, 1946–1948.

(2) Present address: Eastman Kodak Company, Rochester, N. Y.

(3) For previous paper, see Leonard and Leubner, THIS JOURNAL, **71**, 3405 (1949).

(4) Compound III results from alkali treatment of a 3,4-dihydroisoquinolinium salt (II).

(5) Hope and Robinson, *J. Chem. Soc.*, **99**, 2114 (1911).

(6) Wedekind and Oechslen, *Ber.*, **34**, 3986 (1901).

(7) Emde, *Ann.*, **391**, 88 (1912).

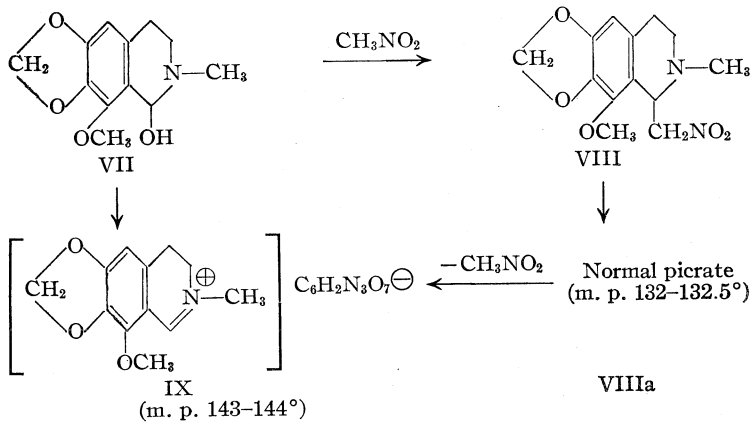
(8) "Organic Syntheses," **25**, 89 (1945).

(9) Pyman, *J. Chem. Soc.*, **95**, 1738 (1909).

(10) Haworth, Perkin and Rankin, *ibid.*, **127**, 1444 (1925).

(11) Haworth and Perkin, *ibid.*, **127**, 1434 (1925).

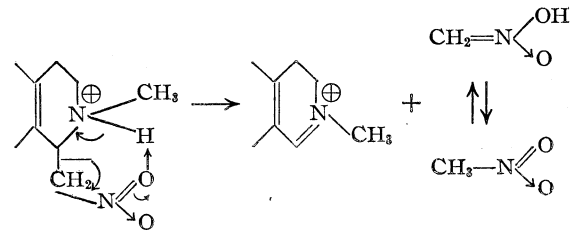
(12) German Patent 267,272, Jan. 19, 1913; *Frdl.*, **11**, 1004 (1912–1914).



quinoline.[13] The conversion of I to II was found to proceed in satisfactory yield. Since the reaction of II with nitromethane in the presence of alkali did not produce any pure chemical individual, attention was turned to the pseudo base III, obtained from II by treatment with sodium hydroxide.

The combination of 1-hydroxy-2-methyl-1,2,3,-4-tetrahydroisoquinoline (III) with nitromethane in methanol led to the liberation of heat, but not to the formation of any crystallizable or distillable condensation product. Although the liberation of heat was indicative at a reaction between III and the nitroparaffin, as was the separation of water when the two were mixed in the absence of a solvent or in benzene, a picrate prepared from the reaction mixture was identified as 2-methyl-3,4-dihydroisoquinolinium picrate (V). The same picrate was prepared directly from the pseudo base (III) without the intervening nitromethane treatment. From these results it appeared that a transient nitromethane condensation product with III was produced, but that this product lost nitromethane readily at some stage. Further information was gained through the reaction of the pseudo base (III) with phenylnitromethane, since this combination produced a readily isolable solid product. The reaction is considered to proceed by combination of the carbonium species IV with the phenylnitromethane carbanion. An eighty-seven per cent. yield of 2-methyl-1-(α-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (VI) was obtained merely by bringing the reactants together in methanol at 25°. When a picrate derivative was prepared from crystalline VI, the picrate was non-homogeneous as first precipitated, but heating in ethanol provided pure 2-methyl-3,4-dihydroisoquinolinium picrate (V). Phenylnitromethane must have been eliminated—and as a result of the picric acid.

The observed probable elimination of nitromethane and certain elimination of phenylnitromethane in these attempts to form picrates of condensation products of type VI suggested a re-examination of analogous derivatives of some of the isoquinoline alkaloids. Cotarnine (VII) forms a picrate (IX), m. p. 143–144°,[14] and a solid condensation product with nitromethane, called anhydrocotarninenitromethane (VIII).[5] The picrate of VIII prepared by Hope and Robinson[5] was described as melting at 136–137°, but no analysis was reported. It appeared from these close melting points that the nitromethane condensation product might have lost some nitromethane upon or after picric acid treatment. Following the procedure of Hope and Robinson, a picrate was prepared from anhydrocotarninenitromethane in aqueous acetic acid. This picrate melted at 134–136° when heated rapidly, and sintered at 140° and melted at 142–144° when heated slowly. The melting point of a mixture with authentic cotarnine picrate (IX) was 143–144°. Recrystallized "anhydrocotarninenitromethane picrate"[5] was definitely cotarnine picrate. When the picrate of VIII was prepared in anhydrous ether solution, a different picrate was obtained, m. p. 132–132.5°. This derivative, which was not recrystallized but was merely washed with ether as a means of purification, had the correct analysis for the normal picrate of anhydrocotarninenitromethane (VIIIa). Picrate VIIIa reverted to cotarnine picrate (IX), with elimination of nitromethane, when heated in acetone for recrystallization. The loss of nitroparaffin is parallel to that observed with 2-methyl-1-nitromethyl-1,2,3,4-tetrahydroisoquinoline and 2-methyl-1-(α-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (VI). That the elimination of nitroparaffin is acid-catalyzed (X → XI) follows from the sensitivity of these pseudo base–nitroparaffin condensation products to acetic acid and to picric acid (especially in warm solution)



X XI

The alkaloid hydrastinine (VII without methoxyl) forms a picrate, m. p. 173°,[15] and a condensation product with nitromethane, called anhydrohydrastininenitromethane.[5] A picrate of anhydrohydrastininenitromethane was described by Hope and Robinson[5] as melting at 173–174°, but no analysis was reported. Because of the suggestive proximity of these melting points and by

(13) Schmidt, *Arch. Pharm.*, **237**, 561 (1899).

(14) Heilbron, "Dictionary of Organic Compounds," Vol. I, 1934, p. 356.

(15) Decker, *Ann.*, **395**, 321 (1913).

analogy to the three cases of nitroparaffin elimination described herein, we conclude that the derivative described as "anhydrohydrastinenitromethane picrate" is actually hydrastinine picrate.

Experimental[16]

2-Methyl-1,2,3,4-tetrahydroisoquinoline (I).—Hydrogenation of isoquinoline in absolute ethanol at 200 atm. and 200° over copper chromite catalyst gave a 98% yield of 1,2,3,4-tetrahydroisoquinoline. Methylation of 1,2,3,-4-tetrahydroisoquinoline by means of formaldehyde and formic acid[8] gave a 79% yield of 2-methyl-1,2,3,4-tetrahydroisoquinoline,[6,7] b. p. 84–85° (4 mm.), 103–105° (14 mm.), 223–224° (745 mm.); $n^{20}D$ 1.5422.

2-Methyl-3,4-dihydroisoquinolinium Iodide (II).—A solution of 73.5 g. (0.5 mole) of 2-methyl-1,2,3,4-tetrahydroisoquinoline and 54 g. (0.55 mole) of anhydrous potassium acetate (freshly fused) in 500 ml. of absolute ethanol was heated to refluxing, and to the solution was added slowly (four hours) with stirring a solution of 127 g. (0.5 mole) of iodine in 1.2 l. of absolute ethanol. When the addition was complete, the solution was refluxed for three hours. Ethanol (1.5 l.) was distilled from the reaction mixture and the residue was allowed to cool to room temperature. Potassium iodide was removed by filtration and the filtrate and washings were concentrated. After removal of the second crop of potassium iodide, the remaining ethanol and acetic acid were removed under reduced pressure on the steam-bath. The dark viscous residue was dissolved with heating in 125 ml. of acetone and 20 ml. of absolute ethanol. Cooling induced the separation of 54 g. (40%) of yellow prisms which were recrystallized from the same mixed solvent; m. p. 124–125° (reported, 125–128°).[9] Similar runs using smaller amounts (3 g.) invariably gave better yields (65–80%).

Anal. Calcd. for $C_{10}H_{12}IN$: C, 43.97; H, 4.43; N, 5.13. Found: C, 44.10; H, 4.36; N, 5.06.

1-Hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (III).—Fifty-four grams (0.2 mole) of crude 2-methyl-3,4-dihydroisoquinolinium iodide, m. p. 118–124°, was stirred with 90 ml. of water. After removal of the insoluble material (1.2 g.) by filtration, the orange solution was cooled to 0° and a cold solution of 32 g. (0.8 mole) of sodium hydroxide in 50 ml. of water was added slowly with stirring. An orange solid separated. The mixture was extracted with three 250-ml. portions of ether, the ethereal solution was concentrated by distillation and was finally allowed to evaporate at room temperature. The residue, which consisted of a mixture of red oil and beautiful elongated prisms, was stirred and crushed with cold acetone. The insoluble solid was collected and washed with cold acetone; yield, 14.2 g. (45%). Recrystallization from acetone gave colorless prisms, m. p. 101–103° (reported, 110–111°).[9,17]

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.48; H, 8.28; N, 8.46.

In an infrared spectrum determination no carbonyl absorption was observed, but a band (3093 $cm.^{-1}$) was found at the low frequency characteristic of strongly bonded O–H. Absorption bands at 1607 and 1491 $cm.^{-1}$ were characteristic of the phenyl group and that at 745 $cm.^{-1}$, of *o*-substituted phenyl.

2-Methyl-3,4-dihydroisoquinolinium Picrate (V).—Prepared in absolute ethanol from 1-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline and picric acid and recrystallized from absolute ethanol, the picrate was obtained as yellow elongated prisms, m. p. 147–148° (reported, 145°).[9]

Reaction of 1-Hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline with Nitromethane.—The reaction of 2-methyl-3,4-dihydroisoquinolinium iodide with nitromethane in the presence of alkali led to non-homogeneous material from which neither a pure product nor a derivative could be isolated. There was apparently a reaction between nitromethane (0.56 g., 0.09 mole) and 1-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.50 g., 0.03 mole) in methanol (1 ml.) since heat was liberated upon addition of the nitromethane. The solution was allowed to evaporate at room temperature. The light yellow oily residue could not be distilled or induced to crystallize. A picrate prepared in ethanol solution sintered at 103° and melted at 106–145°. Two recrystallizations from absolute ethanol gave yellow elongated prisms, m. p. 147–148°, which gave no depression when mixed with 2-methyl-3,4-dihydroisoquinolinium picrate.

Anal. Calcd. for $C_{16}H_{14}N_4O_7$: C, 51.34; H, 3.77. Found: C, 51.54; H, 3.89.

When the reaction between 1-hydroxy-2-methyl-1,2,3,-4-tetrahydroisoquinoline and nitromethane was run in the absence of a solvent or in benzene, water separated from the solution, thus indicating initial condensation before picrate formation. In a run employing 6 g. of pseudo base (III) with excess nitromethane, the theoretical quantity of water was collected by distillation after condensation.

Reaction of 1-Hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline with Phenylnitromethane.—A solution of 0.5 g. (0.03 mole) of 1-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline in 1 ml. of methanol was treated with 1.23 g. (0.09 mole) of purified[18] phenylnitromethane. After one-half hour crystals began to separate, and the mixture was allowed to stand at 25° for twelve hours. After cooling, filtering and drying operations, 0.75 g. (87%) of colorless prisms were collected; m. p. 118–119°. Several recrystallizations from methanol did not alter the melting point of the product, 2-methyl-1-(α-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (VI).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.42; N, 9.92. Found: C, 72.02; H, 6.75; N, 9.81.

The picrate prepared in ether solution melted over a range 135–145°. When this derivative was heated in ethanol solution for recrystallization, it was converted to a pure compound, isolated as yellow elongated prisms, m. p. 147–148°, and identified as 2-methyl-3,4-dihydroisoquinolinium picrate.

Cotarnine Picrate (IX).—Prepared in and recrystallized from absolute ethanol, cotarnine picrate was obtained as delicate yellow needles, m. p. 143–144°.[14]

Anhydrocotarninenitromethane (VIII).—To a hot solution of 1.0 g. (0.004 mole) of cotarnine chloride (Merck Stypticin) and 0.72 g. (0.012 mole) of nitromethane in 3 ml. of absolute ethanol was added a hot solution of 0.52 g. (0.008 mole) of potassium hydroxide in ethanol. The mixture was filtered hot to remove the by-product potassium chloride. From the cooled filtrate, 0.76 g. (69%) of anhydrocotarninenitromethane separated as colorless prisms, m. p. 125–126° (reported, 129°).[5]

The infrared absorption spectrum showed strong bands at 1549 and 1321 $cm.^{-1}$, characteristic of the nitro group. The strong band observed at 1620 $cm.^{-1}$ was due partially, at least, to the phenyl group, which also accounted for the band at 1498 $cm.^{-1}$. The strong absorption bands at 1123, 1095, 1077, 1061, 1050, 1033 and 1026 $cm.^{-1}$ were in the C–O vibration region.

Anhydrocotarninenitromethane Picrate (VIIIa).—The picrate was made by treating a saturated solution of anhydrocotarninenitromethane in ether with anhydrous picric acid in ether. The precipitated yellow prisms were collected and washed with ether; m. p. 132–132.5°.

Anal. Calcd. for $C_{19}H_{19}N_5O_{12}$: C, 44.80; H, 3.76; N, 13.75. Found: C, 45.19; H, 3.90; N, 13.52.

When heated in ethanol or acetone for recrystallization, this picrate was converted to cotarnine picrate, yellow needles, m. p. 143–144°, as established by mixed melting point.

(16) All melting points are corrected. The authors are indebted to Mr. Roger E. Beyler for assistance and to Mrs. James L. Johnson for determination of the infrared absorption spectra.

(17) Avenarius and Pschorr, *Ber.*, **62**, 321 (1929).

(18) Fieser and Gates, THIS JOURNAL, **68**, 2249 (1946).

Following Hope and Robinson's directions[5] for the preparation of anhydrocotarninenitromethane picrate, anhydrocotarninenitromethane was dissolved in aqueous acetic acid and an aqueous solution of picric acid was added. A solid picrate resulted which melted at 134–136°, when the melting point was taken with rapid heating, and sintered at 140° with melting at 142–144°, when the temperature was raised slowly. When mixed with cotarnine picrate, the melting point was 143–144°. A sample was submitted for analysis after two recrystallizations from absolute ethanol; yellow needles, m. p. 143–144°.

Anal. Calcd. for cotarnine picrate, $C_{18}H_{16}N_4O_{10}$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.35; H, 3.66; N, 12.14.

Summary

The elimination of nitromethane from 2-methyl-1-nitromethyl-1,2,3,4-tetrahydroisoquinoline and anhydrocotarninenitromethane and of phenylnitromethane from 2-methyl-1-(α-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline has been observed in the presence of picric acid.

URBANA, ILLINOIS RECEIVED MAY 6, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, FACULTY OF SCIENCE, TOKYO UNIVERSITY]

Equilibrium Ratio of Rotational Isomers of *n*-Pentane: with Special Reference to its Difference from that of 1,2-Dichloroethane

BY SAN-ICHIRO MIZUSHIMA AND HIROATSU OKAZAKI

As shown in our preceding papers on the Raman effect, infrared absorption, dipole moment, and electron diffraction,[1] the molecules of 1,2-dichloroethane $ClH_2C–CH_2Cl$ in the gaseous and liquid states consist of the *trans* and the gauche forms, where the former is the configuration in which the two chlorine atoms are at the farthest distance apart and the latter differs from the former in an internal rotation by $\pm 120°$ about the C–C bond as axis.

We determined also the equilibrium ratio of these two "rotational isomers" in the gaseous state by the measurement of dielectric constant and of the intensity ratio of two Raman lines or of two infrared absorption lines, one assigned to the *trans* form and the other to the gauche form.[1] From this equilibrium ratio the energy of the gauche molecule was found to be greater than that of the *trans* molecule by an amount of $\Delta E = 1.20$ kcal./mole. The intensity measurement made for the liquid spectra tells us that the situation is quite different in the liquid state. The relative number of molecules in the gauche form was found much larger than was expected from the value of ΔE stated above.[1a] This was explained[2] as due to the electrostatic interaction between the molecules in the liquid state: *i. e.*—while the *trans* molecule has no dipole moment, the gauche molecule has a considerable one and in consequence the energy of the gauche molecule is lowered by the electrostatic interaction to approach to that of the *trans* molecule.[3] If this explanation be appropriate, we expect for a non-polar substance that the value of ΔE in the liquid state will not be much different from that in the gaseous state. It would, therefore, be very interesting to measure the intensity change of the Raman spectrum of a non-polar liquid with temperature. With this object in view we have measured the Raman spectrum of *n*-pentane at 32° and at −72°.

For *n*-pentane there can be considered three rotational isomers of skeleton: the first one corresponding to the planar, zigzag form (four consecutive carbon atoms forming the *trans* configuration), the second one containing one gauche structure, and the third one containing two gauche structures. Of these three forms the first one is the most stable and the third one the most unstable, since in the first form all the movable groups (*i. e.*, CH_3– or CH_2–groups) are at the farthest distance apart.

The identification of the Raman lines to be assigned to the first form can at once be made from

(1) The former part of this series of researches is summarized in: Mizushima and Morino, *Bull. Chem. Soc. Japan*, **17**, 94 (1942), (see also Mizushima, Morino and Takeda, *J. Chem. Phys.*, **9**, 826 (1941)) and the latter part is published in Mizushima, Morino, Watanabe, Simanouti, Yamaguchi, *etc.*, *Sci. Papers Inst. Phys. Chem. Research, Tokyo*, **39**, 387, 396, 401 (1942), **40**, 87, 100, 417, 425, 467 (1943), **42**, *Chem.*, 1, 5, 27 (1944), **42**, *Chem.*, 51 (1946).

(1a) *Cf.* Gerding and Meerman, *Rec. trav. chim. pays-bas*, **61**, 523 (1942). This paper is not available to the authors.

(2) Watanabe, Mizushima, and Masiko, *Sci. Papers Inst. Phys. Chem. Research, Tokyo*, **40**, 425 (1943).

(3) If we assume the same model of dielectrics as that of Onsager (THIS JOURNAL, **58**, 1486 (1936)) and consider a small cavity of radius a in the continuous medium of dielectric constant ϵ, a dipole of moment μ situated at the center of this spherical cavity will cause dielectric polarization in the continuous medium, which in turn exerts a field R (reaction field) upon the original dipole.

$$R = \frac{2(\epsilon - 1)}{2\epsilon + 1}\frac{\mu}{a^3}$$

Let us further assume that the gauche molecule can be represented by a sphere of radius a, at whose center the total permanent moment is located. The gauche molecule in the liquid state will then acquire an excess of electrostatic energy by an amount of

$$\Delta E' = \int_0^{\mu} -R\mathrm{d}\mu = -\frac{(\epsilon - 1)}{2\epsilon + 1}\frac{\mu^2}{a^3}$$

as compared with that in the gaseous state (*i. e.*, of the free molecule). The corresponding energy change of the *trans* molecule with no moment is negligible. Introducing the moment value of the gauche molecule (2.55 *D*) into μ of the above equation, we see that the value of $\Delta E'$ is almost equal to the value of ΔE, and therefore, the energy of the gauche molecule approaches to that of the *trans* molecule in the liquid state (see footnote (2)).

our previous observation[4] on the change of Raman spectrum on solidification, since the solid consists only of the molecules of the first form. Thus the Raman line observed at 865 cm.$^{-1}$ is assigned to the first form and that observed at 838 cm.$^{-1}$ to the second form or to the third. The intensity ratio of these two lines was obtained from the microphotometer tracings of the Raman spectra photographed at the two temperatures, and was found as

$$I(838)/I(865) = 1.21 \text{ at } 305°\text{K.}$$
$$= 0.77 \text{ at } 201°\text{K.}$$

Then the energy difference ΔE between the first form and another can at once be calculated from:[4a]

$$\frac{1.21}{0.77} = e^{-\frac{\Delta E}{R}\left(\frac{1}{305} - \frac{1}{201}\right)}$$

and we have

$$\Delta E = 0.53 \text{ kcal./mole}^{4b}$$

Similarly from a pair of lines at 865 and at 764 cm.$^{-1}$ we obtain a value of $\Delta E = 0.70$ kcal./mole which is somewhat larger than the preceding one. The difference may merely be due to the experimental error, but we cannot deny the possibility that the line at 764 cm.$^{-1}$ belongs to the rotational isomer different from what we stated above with regard to the line at 838 cm.$^{-1}$: *i. e.*, we may assign the line at 764 cm.$^{-1}$ to the third molecular form which is more unstable than the second one. We are not, however, sure whether this assignment is appropriate, since the number of lines seems to be too small to account for the coexistence of three molecular forms.[5]

TABLE I

OBSERVED INTENSITY RATIO OF PAIRS OF LINES AT ν AND 865 CM.$^{-1}$

ν	$I(\nu)/I(865)$ at 201° K.	at 305° K.	ΔE kcal./mole
764	0.27	0.49	0.70
838	.77	1.21	.53

We have not yet observed the temperature dependence of the intensity ratio in the gaseous state, the accurate determination of which would be considerably difficult, but we have reason to believe that the values of ΔE obtained above are not much different from that of a free molecule, since these values are of the magnitude which would be expected from the steric repulsion between the moving groups about the C–C bond as axis.[6]

In any case we are sure that on liquefaction the energy difference between the rotational isomers of *n*-pentane does not change so much as in the case of dichloroethane and it is, therefore, reasonable that we explained the difference in the spectral intensity between the gaseous and liquid dichloroethane mainly by the electrostatic interaction between polar molecules.

Summary

The relative intensity of the Raman lines of *n*-pentane was measured at 32° and at −72° and from this experimental result the energy difference between the rotational isomers was calculated as 0.5 kcal./mole.

(4) Mizushima and Simanouti, THIS JOURNAL, **71**, 1320 (1949).

(4a) See Langseth and Bernstein, *J. Chem. Phys.*, **8**, 410 (1940).

(4b) After the manuscript was submitted to the Editorial Board, Sheppard and Szasz (*J. Chem. Phys.*, **17**, 86 (1949)) reported the value of ΔE in excellent agreement with ours.

(5) The number of Raman lines observed for *n*-pentane is not larger than that observed for *n*-butane (see footnote (4)). It seems, therefore, probable to consider the coexistence of only two molecular forms for *n*-pentane as for *n*-butane. However, some Raman lines of *n*-pentane may escape detection because of their weak intensity and, therefore, we cannot deny the possibility of the coexistence of three molecular forms.

(6) The value of ΔE obtained by Pitzer (0.8 kcal./mole) in his calculation of entropies of *n*-butane and *n*-heptane is not much different from that obtained in the present experiment; see Pitzer, *Chem. Rev.*, **27**, 39 (1940), *J. Chem. Phys.*, **8**, 711 (1940).

BUNKYOKU, TOKYO, JAPAN RECEIVED JANUARY 3, 1949

[CONTRIBUTION FROM (a) THE WELLCOME RESEARCH LABORATORIES AND (b) CHEMICAL INSTITUTE, UNIVERSITY OF MUNICH, GERMANY]

The Synthesis of Pterorhodin (Rhodopterin)[1,1a]

BY PETER B. RUSSELL,[a] ROBERT PURRMANN,[b] WERNER SCHMITT[b] AND GEORGE H. HITCHINGS[a]

Pterorhodin is a violet-red substance which is formed during autoxidation of acid solutions of crude butterfly wing pigments,[2] and xanthopterin[3] and erythropterin[3] of natural origin. Both Schöpf[5] and Hopkins[3] suggested that it was formed from erythropterin, but the proportion of pterorhodin obtainable from this source diminishes with increasing purity of the erythropterin.[6] Moreover, xanthopterin is not the precursor since synthetic xanthopterin fails to yield the substance.[4,7]

A structural formula for pterorhodin (I) was suggested by Purrmann and Maas[4] primarily on the basis of degradative experiments in which leucopterin (II) and xanthopterin-7-carboxylic acid (III) were obtained as the products of oxida-

(1) Presented in part at the 115th meeting of the American Chemical Society at San Francisco, California, March 30, 1949.

(1a) Pterorhodin has been named first lepidoporphyrin,[2] then rhodopterin[3] by Hopkins, but Purrmann's proposal,[4] pterorhodin, is perhaps preferable since the substance is not a primary butterfly wing pigment.

(2) Hopkins, *Trans. Roy. Soc. (London)*, **B186**, 661 (1895).

(3) Hopkins, *Proc. Roy. Soc. (London)*, **B130**, 359 (1942).

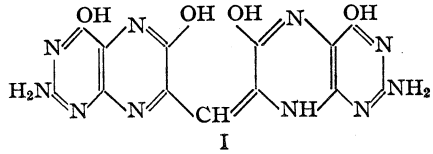
(4) Purrmann and Maas, *Ann.*, **556**, 186 (1944).

(5) Schöpf and Becker, *ibid.*, **507**, 266 (1933).

(6) Purrmann and Eulitz, *ibid.*, **559**, 169 (1948).

(7) A. R. Todd, personal communication.

tion. This formulation is in agreement with the analytical data, the reversible reduction to a tetrahydro derivative by sodium amalgam, the cleavage by chlorine water to oxalylguanidine and other properties.[4] However, an alternative formulation (IV) could not be excluded by these properties and reactions.



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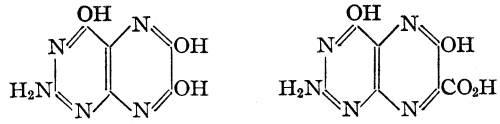
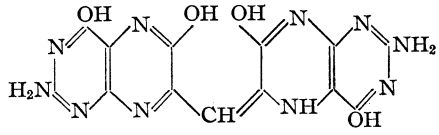
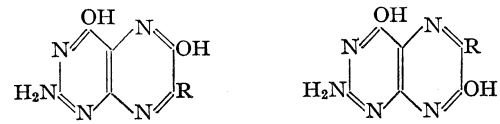


II III



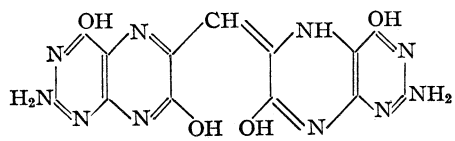
IV

The formulations (I) or (IV) for pterorhodin suggested a possible synthetic approach to the problem if the reactivities of the pyrazine moiety and attached methyl groups were sufficiently great to permit the oxidative condensation of xanthopterin (V) or iso-xanthopterin (VII) with the respective methyl derivatives (VI) (VIII).[8] Condensation of xanthopterin (V) with 7-methylxanthopterin (VI) would be expected to yield (I). Compound (IV) could be formed either from xanthopterin (V) and 6-methyl*iso*xanthopterin (VIII) or from iso-xanthopterin (VII) and 7-methylxanthopterin (VI), while a third isomer (IX) would be expected from the condensation of iso-xanthopterin (VII) and methyl*iso*xanthopterin (VIII). Pterorhodin, identical with that from natural



V R = H
VI R = CH_3

VII R = H
VIII R = CH_3

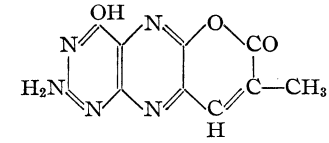


IX

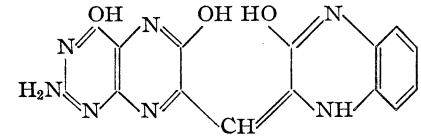
pterins of *C. argante* was in fact obtained by the condensation of xanthopterin with 7-methylxanthopterin. Moreover, iso-pterorhodin (IV) and *allo*-pterorhodin (IX) were obtained as predicted.

The formation of pterorhodin from xanthopterin may be carried out in a variety of ways. A mixture of xanthopterin and 7-methylxanthopterin in acid solution can be oxidized with air or with hydrogen peroxide, or 7-methylxanthopterin may be formed by the reaction of 2,4,5-triamino-6-hydroxypyrimidine with oxalacetic ester[9] and condensed with a further quantity of xanthopterin without isolation of the intermediate. Furthermore, appreciable quantities of pterorhodin are obtained when acid solutions of xanthopterin containing acetone or acetaldehyde are oxidized with hydrogen peroxide, and even during acetylation of xanthopterin with acetic anhydride.[10] Thus the methylene group of pterorhodin may have a variety of sources. However, in view of the close resemblance in properties of xanthopterin and 7-methylxanthopterin[8] it is highly probable that the latter is the precursor which is present in xanthopterin from natural sources.

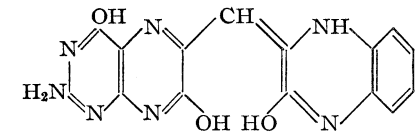
The reactivity of the methyl group which appears to be involved in these syntheses of pterorhodin (and its isomers) may be illustrated by other reactions of xanthopterin derivatives. In strongly acid solution, 2,4,5-triamino-6-hydroxypyrimidine and pyruvic acid give xanthopterin methacrylic acid lactone (X) which apparently arises through the condensation of the methyl group of 7-methyl-



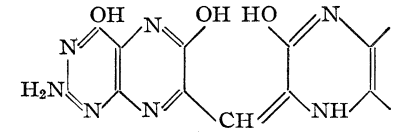
X



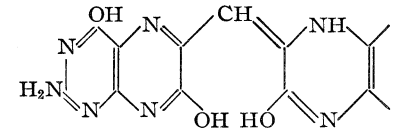
XI



XII



XIII



XIV

(8) Elion and Hitchings, THIS JOURNAL, **69**, 2553 (1947).

(9) The condensation of ethyloxalacetate with 4,5-diaminopyrimidines gives almost exclusively 6-hydroxy-7-methylpteridines in strong acid and 7-hydroxy-6-methylpteridines in acetic acid solution. The yields are superior to those obtainable with pyruvic acid (Elion, Russell and Hitchings, to be published).

(10) Purrmann, unpublished observations.

xanthopterin with a second molecule of pyruvic acid. Xanthopterin and iso-xanthopterin both condense oxidatively with 2-hydroxy-3-methylquinoxaline to give substances, XI and XII, respectively, similar to the pterorhodins. It is interesting in this connection that the absorption spectrum of XI (Fig. 1) has the general characteristics of that of pterorhodin (I) (Fig. 1) which thus seems to be correlated with the grouping (XIII). The spectrum of XII resembles that of

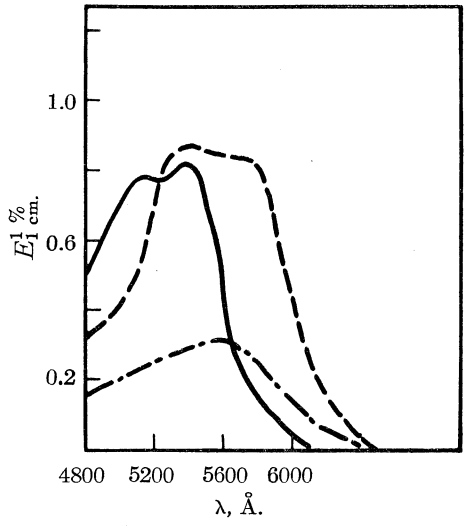


Fig. 1.—Absorption spectra of: isopterorhodin - - - - -; pterorhodin———; condensation product of xanthopterin and 3-methyl-2-quinoxalone —·—·— in concentrated sulfuric acid.

allo-pterorhodin (IX) (Fig. 2) and both substances contain the structure (XIV). Isopterorhodin (IV) which might be viewed as containing either or both of the structures XIII or XIV gives a spectrum more closely related to that of the pterorhodin series.

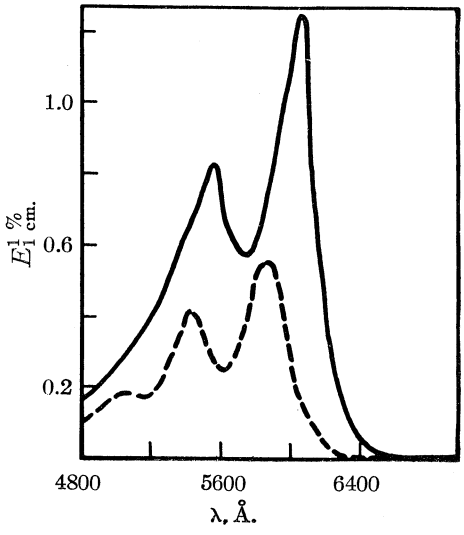


Fig. 2.—Absorption spectra of: *allo*-pterorhodin ——; the condensation product of iso-xanthopterin and 3-methyl-2-quinoxalone - - - - in conc. sulfuric acid.

The oxidative condensations of the xanthopterin derivatives perhaps are best viewed as (a) an acid catalyzed reversible addition of the active 7 (or 6) methyl group to the 7,8 (or 5,6) double bond to give aldol-like intermediates (A) followed by (b) dehydrogenation in the side-chain to give the products B. In the formation of pterorhodin from xanthopterin and acetone or acetaldehyde an intermediate carboxylic acid would be postulated (A or B, R = CO_2H) as arising from the carbonyl group by oxidation. Decarboxylation then would result in 7-methylxanthopterin (B, R = H). Some evidence for the formation of an intermediate of the postulated type was obtained. When xanthopterin and 7-methylxanthopterin are mixed in acid solution a rapid change in spectrum occurs after which an equilibrium state appears to be reached (Table I). At equilibrium the spectrum resembles that of a mixture of xanthopterin and dihydroxanthopterin and therefore approximates that which might be expected of a substance (A) containing isolated nuclei of this type.

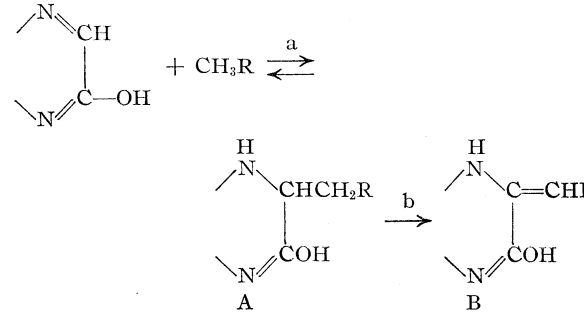


TABLE I

CHANGES IN ULTRAVIOLET ABSORPTION SPECTRUM DURING REACTION OF XANTHOPTERIN WITH 7-METHYLXANTHOPTERIN

	Substance	Reference spectra $E_{1\text{ cm.}}^{1\%}$ 305 mμ / $E_{1\text{ cm.}}^{1\%}$ 390 mμ	Time, min.	Reaction mixture[a] $E_{1\text{ cm.}}^{1\%}$ 305 mμ / $E_{1\text{ cm.}}^{1\%}$ 390 mμ
A	Xanthopterin	0.20	0	0.20
B	7-Methylxanthopterin	0.12	15	.51
C	β-Dihydroxanthopterin	∞	30	.61
			45	.63
	A + C	0.70	60	.63
	B + C	1.20	105	.70

[a] Equimolecular quantities of xanthopterin and 7-methylxanthopterin were dissolved in 2 *N* hydrochloric acid and the solutions were mixed. The optical densities of the mixtures were determined at 305 and 390 mμ immediately and after the indicated period at 60°.

This reaction mechanism appears to be consistent with the observed reactions. The resemblance of the pyrazine —C=N— (7,8 or 5,6) linkage, in the xanthopterin-type compound, to a carbonyl group[11] is brought out in the condensations, and

(11) Wieland and Purrmann, *Ann.*, **544**, 163 (1940).

also in the decarboxylations which occur both in the formation of the methylxanthopterins *via* oxalacetic ester and in the formation of pterorhodin from xanthopterin and acetaldehyde or acetone. In this respect isoxanthopterin and xanthopterin (6 and 7) acetic acids resemble β-keto acids. A parallel reaction has been observed in the quinoxaline field.[12]

The discovery that a synthetic 7,8-dihydroxanthopterin is not identical with the reduction product of xanthopterin[13] may or may not be inconsistent with this view of the potentialities of the pteridine —C=N— linkage. The reduction of xanthopterin may follow a course differing from that of the condensations, in fact, 1,4-addition (*i. e.*, addition at the 5,8-position) of hydrogen would appear probable. In any case, the two isomeric dihydroxanthopterins probably should be regarded as "stable tautomers"[13] and the significance of their existence will depend on further work on the fine structure of the reduction isomer. The existence of stable isomeric dihydropteridines differing in the position of the double bond in the pyrazine ring has been reported.[14]

Since the preparation of this manuscript Karrer and Schwyzer[15] have reported the synthesis of "methylpterin red" by the reaction of 2,4,5-triamino-6-hydroxypyrimidine and glyceric aldehyde. The published spectrum of this substance is very similar, but not identical, to that found for natural and synthetic pterorhodin (Fig. 3). A direct comparison of these substances appears to be desirable.

Experimental

Pterorhodin from Xanthopterin and 7-Methylxanthopterin. (a) **With Air.**—One-half gram of xanthopterin[16] was mixed with 0.5 g. of 7-methylxanthopterin[8] and the mixture dissolved in 200 ml. of *N* hydrochloric acid; the solution was filtered from a small amount of insoluble matter, heated to 90° in a water-bath and a stream of air passed through at a rate of about 200 bubbles per minute. After about one-half hour the solution began to redden and shortly thereafter a dark purple, almost black, solid began to separate. After two and one-half hours the solid was filtered off, washed with hot *N* hydrochloric acid and hot water. The solid was a mass of minute dark purple needles (sample I). Its absorption spectrum in concentrated sulfuric acid differed only slightly from that of an authentic sample of pterorhodin in the same solvent (Fig. 3). It appears likely that one or both samples contain trace impurities, which would account for the observed differences.

(b) **With Hydrogen Peroxide.**—One hundred and twenty milligrams each of the two reactants were dissolved in 100 ml. of 3 *N* hydrochloric acid. The solution was filtered and 10 ml. of a 15% hydrogen peroxide solution was added. On standing at room temperature a dark solid separated. After three and one-half hours it was filtered off (100 mg.). It proved to be amorphous but was identical with the above product in every other respect.

A portion was purified by solution in concentrated sulfuric acid and precipitated with water. It was dried at 150° *in vacuo* for analysis (sample IV). Several repetitions of the hydrogen peroxide oxidation, with or without added seeds, failed to produce pterorhodin in crystalline form.

On standing, the mother liquors from the above oxidation deposited some bright red needles. These could be recrystallized from 3 *N* hydrochloric acid but too little was obtained to allow further examination.

Pterorhodin by Oxidation of the Condensation Product of 2,4,5-Triamino-6-hydroxypyrimidine and Ethyl Oxalacetate with Xanthopterin.—A solution obtained by treating 2 g. of 2,4,5-triamino-6-hydroxypyrimidine with 4 g. of sodium ethyl oxalacetate in 200 ml. of boiling 2 *N* sulfuric acid for one and one-half hours followed by filtration was treated with 1.5 g. of xanthopterin in 8 l. of 0.1 *N* hydrochloric acid. The solution was warmed and allowed to stand for three days after which time 1.35 g. of fine violet needles was collected (47%). After purification by precipitation from concentrated sulfuric acid with water and drying at 150° *in vacuo* the substance was analyzed (sample II).

In another experiment the original sulfuric acid solution was diluted to 1 l., the xanthopterin added and the solution heated on a water-bath while air was drawn through. The yield of violet-black needles was 1.15 g. (40%). This was analyzed (sample III) after drying at 150° *in vacuo*.

Anal. Calcd. for $C_{13}H_{10}O_4N_{10}$: C, 42.2; H, 2.7; N, 37.8. Found: Sample I: C, 41.5; H, 3.1; N, 37.4. Sample II: C, 42.4; H, 3.0; N, 34.4. Sample III: C, 42.2; H, 2.5; N, 37.2. Sample IV: N, 37.3.

Pterorhodin by Oxidation of Xanthopterin with Acetaldehyde or Acetone.—Three hundred milligrams of xanthopterin was dissolved in 20 ml. of warm *N* sulfuric acid and the solution filtered. To this solution was added 0.04 ml. of acetaldehyde in 4 ml. of water followed by 0.3 ml. of a 30% solution of hydrogen peroxide. The mixture was warmed for five minutes in a boiling water-bath and set aside for twelve hours. At the end of this time 56 mg. of purple material had separated. This was shown to be identical with pterorhodin after purification by precipitation from sulfuric acid with water.

When a solution of xanthopterin in 3 *N* hydrochloric acid was treated with acetone and hydrogen peroxide in a similar manner pterorhodin was obtained in about 20–30% yield.

Pterorhodin Sulfate.—Synthetic pterorhodin (100 mg., sample I) was converted to the sulfate by the method of Purrmann and Maas.[4] The sulfate (66 mg.) formed red

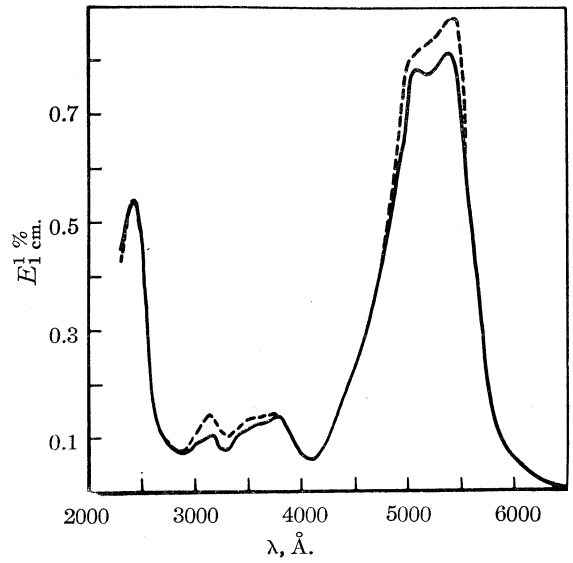


Fig. 3.—Absorption spectrum of pterorhodin in concd. sulfuric acid: natural – – – –; synthetic ——.

(12) Ruhemann and Stapleton, *J. Chem. Soc.*, **77**, 239 (1900).
(13) Hitchings and Elion, THIS JOURNAL, **71**, 467 (1949).
(14) Pesson, *Bull. soc. chim.*, [5] **15**, 963 (1948).
(15) Karrer and Schwyzer, *Helv. Chim. Acta*, **32**, 423 (1949).
(16) Elion, Light and Hitchings, THIS JOURNAL, **71**, 741 (1949).

plates identical in appearance to a sample prepared from authentic pterorhodin. It was dried at 120° *in vacuo*.

Anal. Calcd. for $C_{13}H_{10}O_4N_{10}\cdot 2H_2SO_4$: C, 27.6; H, 2.5; N, 24.7. Found: C, 27.8; H, 2.6; N, 24.3.

Tetrahydropterorhodin Perchlorate.—Synthetic pterorhodin (sample I) was reduced with sodium amalgam following Purrmann and Maas.[4] The colorless hydrochloride was converted to the perchlorate which separated from the solution in rhombic prisms. It was dried at 150° for analysis.

Anal. Calcd. for $C_{13}H_{14}O_4N_{10}\cdot 2HClO_4$: C, 27.1; H, 2.8. Found: C, 27.6; H, 2.6.

The solid perchlorate began to turn purple rapidly on exposure to air. The mother liquors of the hydrochloride and perchlorate on dilution and oxidation with air gave pterorhodin.

Isopterorhodin.—One hundred milligrams each of 7-methylxanthopterin and isoxanthopterin[17] were treated with 30 ml. of 5 *N* hydrochloric acid. The isoxanthopterin did not dissolve completely. Air was drawn through the solution as previously described. After six hours the red micro-crystalline powder was filtered (75 mg.). It was visibly contaminated with some white material. Seventy milligrams of the red powder was dissolved in 1 ml. of concentrated sulfuric acid, the deep purplish-red solution was filtered through a sintered glass plate and 3 ml. of water added cautiously. The almost black crystalline precipitate (50 mg.) was collected by centrifugation, washed twice with 40% sulfuric acid, six times with acetic acid and finally several times with ether. It was dried at 150° *in vacuo*.

Anal. Calcd. for $C_{13}H_{10}O_4N_{10}\cdot H_2SO_4\cdot H_2O$: C, 32.1; H, 2.9; N, 28.8. Found: C, 32.1; H, 3.1; N, 28.5.

When the above preparation was carried out with xanthopterin and 6-methylisoxanthopterin[8] the same product was obtained.

Allopterorhodin.—One hundred milligrams each of isoxanthopterin and 6-methylisoxanthopterin were suspended in 30 ml. of 5 *N* hydrochloric acid and the suspension oxidized as previously described. The oxidation was continued for two days and the product filtered off at the end of this time (103 mg.). It was converted to the sulfate by solution in 4 ml. of concentrated sulfuric acid and dilution with 6 ml. of water. The purple sulfate separated as a crystalline powder. It was centrifuged off, washed with dilute sulfuric acid, acetic acid and ether. It was dried at 150° *in vacuo*.

Anal. Calcd. for $C_{13}H_{10}O_4N_{10}\cdot H_2SO_4$: C, 33.4; H, 2.6; N, 30.0. Found: C, 33.9; H, 2.8; N, 30.3.

Ethyl 2-Quinoxalone-3-acetate.—To a solution of *o*-phenylenediamine (5 g.) in 300 ml. of 2 *N* acetic acid was added 10 g. of sodium ethyl oxalacetate. Almost at once a yellow solid separated. The solution was heated for two hours on a steam-bath and then cooled and filtered. The yellow solid (9.0 g., 85%) was recrystallized from ethanol. It formed yellow needles, m. p. 210° (after softening from 205°). Ruhemann and Stapleton[12] described this compound, obtained by the condensation of *o*-phenylenediamine and ethyl acetylenedicarboxylate, as melting at 210° with previous softening.

3-Methyl-2-quinoxalone.—This compound was obtained in 80% yield by hydrolysis of the above ester with potassium hydroxide.[12] The acid decarboxylated spontaneously on acidification. The quinoxalone melted at 247–248° (dec.).[12,18]

Oxidative Condensation of 3-Methyl-2-quinoxalone with Xanthopterin.—Two hundred milligrams of each of the components was dissolved in 50 ml. of 3 *N* hydrochloric acid. Solution took place at once with the formation of a red color. The solution was warmed to 90° and air passed through as before. After about one hour the purple solid began to separate; at the end of four hours 125 mg. was collected. The product was converted to its sulfate by solution in 2.5 ml. of concentrated sulfuric acid and dilution with 2.5 ml. of water. The sulfate was separated by centrifugation, washed ten times with acetic acid and finally with ether. The red microcrystalline product was dried at 150°.

Anal. Calcd. for $C_{15}H_{10}O_3N_7\cdot H_2SO_4$: N, 22.7. Found: N, 22.9.

The sulfuric acid mother liquors deposited more amorphous material on dilution with water.

Oxidative Condensation of 3-Methyl-2-quinoxalone with Isoxanthopterin.—The reaction was carried out as above with isoxanthopterin and 3-methyl-2-quinoxalone. Isoxanthopterin was not soluble to any great extent and as a consequence the reaction mixture appeared as a suspension which on oxidation changed from gray to a reddish-brown. After four hours the brown solid was filtered off and washed with hot dilute hydrochloric acid and with hot water. The condensation product gave a greenish-red solution in concentrated sulfuric acid, the color changing to violet on addition of only a drop of water. Further dilution gave a precipitate of the violet sulfate which, on standing or on further addition of water, changed to the brownish-red free base. For analysis the process was repeated twice and the product dried at 150°.

Anal. Calcd. for $C_{15}H_{10}O_3N_7$: N, 29.0. Found: N, 29.3.

Xanthopterin Methacrylic Acid Lactone.—Five hundred milligrams of 2,4,5-triamino-6-hydroxypyrimidine bisulfite was treated with 30 drops of concentrated sulfuric acid and then warmed with 6 ml. of pyruvic acid for twenty minutes on the water-bath. On cooling the crystalline material (370 mg., 55%) was filtered, washed with acetic acid and crystallized twice from 5 ml. of concentrated sulfuric acid by addition of 5 ml. of water.

Anal. Calcd. for $C_{10}H_7O_3N_5\cdot H_2SO_4$: C, 35.0; H, 2.6; N, 20.5; SO_4, 28.0. Found: C, 35.3; H, 2.5; N, 18.6; SO_4, 30.3.

The free lactone was prepared by heating the sulfate with water. The precipitate was filtered and washed with water.

Anal. Calcd. for $C_{10}H_7O_3N_5$: C, 49.0; H, 2.8; N, 28.6. Found: C, 49.0; H, 2.8; N, 29.0.

Acknowledgment.—Our thanks are due Samuel W. Blackman for microanalyses, and Gertrude B. Elion for the determination of absorption spectra. The invaluable assistance of Dr. B. K. Blount in effecting contact between the German and the American authors is gratefully acknowledged.

Summary

1. Pterorhodin (rhodopterin) has been synthesized by the oxidative condensation of xanthopterin and 7-methylxanthopterin. This suggests the presence of 7-methylxanthopterin as an hitherto undetected constituent of the pterins of butterfly wings.

2. Two isomeric substances, isopterorhodin and *allo*-pterorhodin have been prepared by similar means. Isopterorhodin has been synthesized from xanthopterin and 6-methylisoxanthopterin and from isoxanthopterin and 7-methylxanthopterin. *Allo*-pterorhodin was obtained by the condensation of the two isoxanthopterin derivatives.

3. Studies on the reactivity of the 7-position of xanthopterin (6-position of isoxanthopterin) and of the methyl groups attached to these positions are reported.

(17) Purrmann, *Ann.*, **548**, 290 (1941).

(18) Hinsberg, *ibid.*, **292**, 249 (1896).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE MUNICIPAL UNIVERSITY OF WICHITA]

Derivatives of 2-Amino-6-methoxybenzothiazole[1]

BY C. G. STUCKWISCH

p-Substituted anilines are readily converted to 2-amino-6-substituted benzothiazoles by reaction with alkali thiocyanates in the presence of bromine.[2] By modification of procedure we have obtained 2-amino-6-methoxybenzothiazole from *p*-anisidine in 87% yield.

In a search for types of compounds that might exhibit antimalarial activity several derivatives of 2-amino-6-methoxybenzothiazole were prepared.[3] Details are given in the experimental section.

Experimental

2-Amino-6-methoxybenzothiazole.—To a solution of 24.6 g. (0.2 mole) of *p*-anisidine and 77.6 g. (0.8 mole) of potassium thiocyanate in 360 ml. of 96% acetic acid was added dropwise, with stirring, 32 g. (0.2 mole) of bromine dissolved in 150 ml. of glacial acetic acid while the temperature was kept below 35°. After all the bromine solution had been added the mixture was stirred for ten hours and was then filtered and the residue washed with water. The combined filtrate and washings were neutralized with ammonium hydroxide. The precipitate was collected on a filter and dried. The yield of product melting at 158–161° was 31.5 g. or 87%. This material is pure enough for subsequent reactions. Larger runs do not affect the yield.

Further purification is most readily carried out by crystallization from a mixture composed of equal volumes of concentrated hydrochloric acid and 95% ethanol. The hydrochloride thus obtained is dissolved in water and the free base is precipitated with sodium carbonate. The recovery of 2-amino-6-methoxybenzothiazole, melting at 161–162°,[4] is nearly quantitative. An alternate method of purification is crystallization from benzene.

2-Chloro-6-methoxybenzothiazole.—A solution of 18 g. (0.1 mole) of 2-amino-6-methoxybenzothiazole in 50 ml. of formic acid, 20 ml. of glacial acetic acid and 40 ml. of concd. hydrochloric acid was cooled to −5° and then 7 g. of sodium nitrite in 10 ml. of water was added dropwise with stirring. After addition was complete, stirring was continued for fifteen minutes at 0°. The mixture was then added slowly to an ice-cold vigorously stirred solution of 0.13 mole of cuprous chloride in 59 ml. of hydrochloric acid (sp. gr. 1.14). After one-half hour the mixture was heated to 60° on a steam-bath. When evolution of nitrogen ceased, the mixture was diluted with water and the solid was filtered off and extracted with hot ethanol. The alcohol extract was poured into water and the precipitated material collected on a filter and dried. Crystallization from dilute methanol gave 6 g. or 30% of 2-chloro-6-methoxybenzothiazole, m. p. 43–44°.

Anal. Calcd. for C_8H_6ONClS: Cl, 17.8. Found: Cl, 17.7.

TABLE I

SOME 2-SUBSTITUTED-6-METHOXYBENZOTHIAZOLES

Substituent	M. p., °C.	Solvent	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1-Pyrryl[a]	117–118	Ethanol	28	62.6	62.4	4.25	4.39	12.17	12.00
2,5-Dimethyl-1-pyrryl[b]	125–126	Ethanol	40	65.1	65.0	5.42	5.52	10.85	10.78
Piperidino[c]	72–72.5	Methanol	66	62.9	62.6	6.41	6.49	11.29	11.34
Morpholino[c]	127.5–129	Methanol	58	57.6	57.7	5.61	5.70	11.21	11.27
Morpholinoacetylamino[d]	129–130	Ethanol	36	57.5	57.3	5.48	5.46	9.55	9.72
m-Nitrobenzoylamino[e]	235	Pyridine	76	54.7	54.8	3.34	3.41	12.77	12.62
m-Aminobenzoylamino[f]	147–148	Acetic acid	90	60.2	59.9	4.35	4.24	14.38	14.46
p-Dimethylaminophenylazo[g]	225–227	Acetic acid	44	61.5	61.3	5.13	5.18	17.95	17.77

[a] A mixture of 8 g. of mucic acid and 6 g. of 2-amino-6-methoxybenzothiazole was distilled from a 50-ml. Claisen flask evacuated to 2 mm. (Bell, *Ber.*, **10**, 1861 (1877)). [b] 2-Amino-6-methoxybenzothiazole and acetonylacetone were heated for five hours at 135°. [c] 2-Chloro-6-methoxybenzothiazole was refluxed with the requisite amine for two hours. [d] A mixture of 2-amino-6-methoxybenzothiazole, chloroacetyl chloride and dimethylaniline was heated on a steam-bath for an hour and was then poured into 500 ml. of dilute hydrochloric acid. The yellow precipitate was collected on a filter and dried. The crude material was heated with morpholine at 135° for four hours. [e] 2-Amino-6′-methoxybenzothiazole was condensed with *m*-nitrobenzoyl chloride in pyridine solution. [f] The corresponding nitro compound was reduced with tin and acetic acid. [g] 2-Amino-6-methoxybenzothiazole was diazotized as previously described and then coupled with N,N-dimethylaniline.

Summary

1. A procedure for the preparation of 2-amino-6-methoxybenzothiazole has been described.

2. Several derivatives of 2-amino-6-methoxybenzothiazole have been prepared.

WICHITA, KANSAS RECEIVED APRIL 12, 1949

(1) Presented before the Organic Division of the Fifteenth Midwest Regional Meeting of the American Chemical Society, Kansas City, Missouri, June, 1947.

(2) British Patent 295,295, March 30, 1927.

(3) A number of 2-amino-6-alkoxybenzothiazoles have been tested as antimalarials. *Cf.* "Survey of Antimalarial Drugs 1941–1945," Wiselogle, Editor, Edwards Bros., Ann Arbor, Mich., 1946, Vol. II, Part I, pp. 1938, *et seq.*

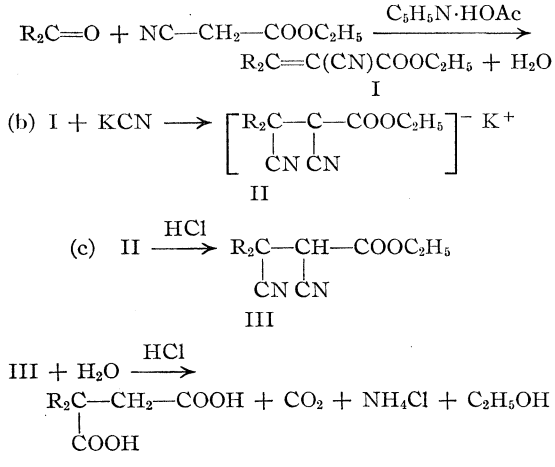
(4) Dyson, Hunter and Morris, *J. Chem. Soc.*, 186 (1927), report a melting point of 147°. Tubs and Fox, U. S. Patent 1,931,077 (1934), report a melting point of 161–162.5°.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

A Synthesis for Unsymmetrically Substituted Succinic Acids[1]

BY PETER A. S. SMITH AND JEROME P. HORWITZ[2]

A convenient and somewhat general procedure which we have developed for the synthesis of succinic acids of the type $HOOC-CR_2-CH_2-COOH$ is described here as applied to seven examples. The procedure, which consists of two laboratory steps, takes place according to the equations



Reaction (b) is combined with reaction (a), which is only partially complete at equilibrium, in order to draw reaction (a) more completely in the desired direction. This same effect was accomplished by Cope and Alexander,[3] who added hydrogen instead of potassium cyanide to the unsaturated ester (I). Reaction (a) may also be driven to completion by removal of the water by distillation.[4]

It is in the actual laboratory procedure that the method reported here represents an improvement over a stoichiometrically similar method described by Lapworth and McRae.[5]

Their procedure involves isolation of the alkylidene cyanoacetic ester before treatment with potassium cyanide. This gives from cyclohexanone and cyanoacetic ester, for example, a 53% yield of cyclohexylidenecyanoacetic ester; by the procedure reported in this paper, the corresponding hydrogen cyanide addition product is obtained in 75% yield from the same starting materials. The Lapworth and McRae procedure gives superior results, however, with aromatic aldehydes.

Our attention was directed toward this method when a need arose for a supply of α,α-dimethylsuccinic acid. The preparation of this acid according to Higson and Thorpe[6] by the condensation of acetone cyanohydrin with sodiocyanoacetic ester, followed by hydrolysis and decarboxylation of the α,α-dimethyl-β-carboethoxysuccinonitrile so produced, was found to be manipulatively inconvenient and sensitive to variations in conditions which are difficult to control. By the method described here we were able consistently to obtain α,α-dimethylsuccinic acid in two convenient steps in over-all yields above 50%. Because of this success, we were led to extend the method to the synthesis of some additional succinic acids. The satisfactory results with unhindered aliphatic ketones and aldehydes show that this procedure is of synthetic value for the preparation of alkyl- and α,α-dialkylsuccinic acids. The poor results with benzaldehyde and acetophenone, and the complete lack of reaction of diisopropyl ketone, are indicative of the probable limitations of the method.

Experimental

The condensation of the aldehydes and ketones with cyanoacetic ester and the hydrolysis and decarboxylation of the resulting dicyano ester was essentially the same in all the cases here reported. For this reason only the operations leading to α,α-dimethylsuccinic acid are described in detail; the results of the other preparations are given in the accompanying table. Analyses of new compounds are given in footnotes to the table.

Ethyl α,β-Dicyano-β-methylbutyrate.—A mixture of 58 g. (1 mole) of dry acetone, 113 g. (1 mole) of ethyl cyanoacetate, 79 g. (1 mole) of pyridine and 63 g. (1 mole) of glacial acetic acid was refluxed for one hour. Absolute ethyl alcohol (100 ml.) was then added, and as soon as active boiling subsided, 65 g. (1 mole) of potassium cyanide was added through the neck of the flask. The condenser was immediately replaced, and the refluxing which occurred because of the ensuing vigorous spontaneous reaction was continued by the application of heat when necessary for a total of one hour. It is important that the cyanide addition be made before the mixture has cooled appreciably below the temperature of active refluxing, for the reaction with the potassium cyanide cannot otherwise be made complete, and low yields and an impure product result.

The slurry which formed on cooling was then treated with 400 ml. of 1:3 hydrochloric acid, and swirled and gently warmed until all solid disappeared. The aqueous layer, after separation of the oil, was extracted with two 100-ml. portions of ether, and the combined organic layers were neutralized with sodium bicarbonate, dried over sodium sulfate, and distilled; yield 126 g. (70%), b. p. 136–141° (9 mm.).

α,α-Dimethylsuccinic Acid.—A mixture of 126 g. of ethyl α,β-dicyano-β-methylbutyrate and 600 ml. of concentrated hydrochloric acid was refluxed for five hours, after which 150 ml. more acid was added and the refluxing was continued three hours. Distillation to dryness under aspirator vacuum left a cake of α,α-dimethylsuccinic acid and ammonium chloride, from which the acid was extracted with several 100-ml. portions of boiling ether

(1) Taken from part of the doctoral thesis of Jerome P. Horwitz, (1949).

(2) Present address: Department of Chemistry, Northwestern University, Evanston, Illinois.

(3) A. C. Cope and E. R. Alexander, THIS JOURNAL, **66**, 886 (1944).

(4) A. C. Cope, C. M. Hoffman, C. Wyckoff and E. Hardenbergh, *ibid.*, **63**, 3452 (1941); A. C. Cope, *ibid.*, **59**, 2326 (1937).

(5) Lapworth and McRae, *J. Chem. Soc.*, **121**, 2741 (1922).

(6) A. Higson and J. F. Thorpe, *ibid.*, **89**, 1455 (1906).

TABLE I

α,β-DICYANO-ESTERS AND SUCCINIC ACIDS

Carbonyl compound	Yield, %	Dicyano-ester B. p., °C.	Mm.	Succinic acid	Yield, %	M. p., °C.
Acetone	70	136–141	9	α,α-Dimethylsuccinic acid	76	138–139
Methyl ethyl ketone	49	145–146	10	α-Methyl-α-ethylsuccinic acid[a]	73	101–102
Cyclohexanone	75	177–179	10	1-Carboxycyclohexylacetic acid[b]	75	131–132
Propionaldehyde	53	158–160	12	Ethylsuccinic acid[c]	60	98–100
Isobutyraldehyde	67	151–155	10	Isopropylsuccinic acid[d]	78	115–116
Acetophenone	17	140–145	0.1	α-Phenyl-α-methylsuccinic acid[e]	60	157–158
Benzaldehyde	[f]	145–158	0.1	Phenylsuccinic[f] acid and α-cyanocinnamic acid	12	

[a] Higson and Thorpe[6] report ethyl α,β-dicyano-β-methylvalerate, b. p. 162° (20 mm.), and α-ethyl-α-methylsuccinic acid, m. p. 102–103°. [b] Dickens, Horton and Thorpe, *J. Chem. Soc.*, 125 (1934), report ethyl 1-cyanocyclohexylcyanoacetate, b. p. 210–212° (22 mm.), and (1-carboxycyclohexyl)-acetic acid, m. p. 132°. [c] Ethyl α,β-dicyanovalerate: *Anal.* Calcd. for $C_9H_{12}O_2N_2$: N, 15.56. Found: N, 15.62.[7] [d] Ethyl α,β-dicyano-γ-methylvalerate: *Anal.* Calcd. for $C_{10}H_{14}O_2N_2$: N, 14.43. Found: N, 14.41.[7] Von Braun and Reinhardt, *Ber.*, **62**, 2585 (1929), report isopropylsuccinic acid, m. p. 116°. [e] α-Phenyl-α-methylsuccinic acid: *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.77; neut. equiv., 104. Found: C, 63.32; H, 5.82[6]; neut. equiv., 107. [f] The mixture of esters was hydrolyzed without separation to give phenylsuccinic acid and α-cyanocinnamic acid, which were separated by means of the solubility of the former in hot water, in 12% over-all yield each.

The product was obtained in a very pure state by evaporation to a volume of about 125 ml., heating to boiling with 1 l. of benzene, and allowing to stand until crystallization was complete (about one day); yield 77 g. (76%), m. p. 138–139° (lit. 139°[5]). The acid can also be recovered from the hydrolysis mixture more simply, but in lower yield (*ca.* 60%), by allowing crystallization to take place instead of distilling the mixture to dryness, and extracting the filtered solids with ether as described.

The hydrolyses of the other dicyano-esters reported in the table were essentially the same, except that 1-carboxycyclohexylacetic acid had to be precipitated from benzene solution by the addition of petroleum ether (60–75°), and α-phenyl-α-methylsuccinic acid was freed from ammonium chloride by crystallization from hot water.

(7) Analysis by Micro-Tech Laboratories, Skokie, Illinois.

Summary

A convenient synthesis for certain succinic acids is described which employs the condensation of aldehydes or ketones with cyanoacetic ester and potassium cyanide.

ANN ARBOR, MICHIGAN RECEIVED MAY 31, 1949

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Analogs of Oxytocic Drugs. II. β-Hydroxyphenethyl-β-alanine Esters[1]

BY RICHARD BALTZLY AND ARTHUR P. PHILLIPS

Oxytocic activity having been found in a family of phenethyl-β-alanine esters[2] the effect of introducing an hydroxyl group in the side-chain was studied. Data on the compounds prepared for this purpose and on new intermediates are presented in Table I.

Although the available methods of assay render any precise conclusions on the influence of the hydroxyl group questionable, its presence appears advantageous. While compounds IV and V were not clearly more active than the comparable substances without the hydroxyl group, compounds I–III are also of the same order of activity, whereas in the phenethyl series[2] maximum activity was observed only with two alkoxyl substituents on the aromatic ring.

The preferred method of synthesis was by the addition of the appropriate phenylalkanolamine to methyl acrylate

$$RCHOHCH_2NHMe + CH_2{=}CHCOOMe \longrightarrow RCHOHCH_2N(Me)CH_2CH_2COOMe$$

Under the conditions described in the experimental section this reaction appears to be quantitative. Compound I was prepared from *d,l*-ephedrine and ethyl-β-bromopropionate. Compound V was obtained from IV by ester exchange.[2]

The secondary amines required from compounds II–IV are known.[3,4] The intermediate for compound VI, N-methyl-β-hydroxy-β-(3,4-dimethoxyphenyl)-ethylamine (XI)[5] is less easily prepared than might be supposed. When the corresponding benzylmethylaminoketone hydrochloride (VIII) was hydrogenated with Adams catalyst in the expectation of obtaining XI, cleavage of the dimethoxyphenacyl group appeared to compete with debenzylation. A considerable quantity of neutral material less volatile than toluene was present in the reaction mixture and XI was iso-

(1) The work here reported is part of a joint program carried out in collaboration with a pharmacological group in these laboratories.

(2) Baltzly, Dvorkovitz and Phillips, THIS JOURNAL, **71**, 1162 (1949).

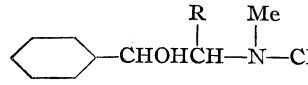
(3) Baltzly and Buck, *ibid.*, **62**, 164 (1940).

(4) Ardis, Baltzly and Schoen, *ibid.*, **68**, 591 (1946).

(5) Mannich, *Arch.*, **248**, 127 (1910), prepared the base but could not obtain crystalline salts.

TABLE I

HYDROCHLORIDES OF N-METHYL-N-(β-HYDROXY-β-PHENYLETHYL)-β-ALANINE ESTERS



Compound	Ring substituents	R	R′	M. p., °C.[a]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	None	Me	Et	129–130	$C_{15}H_{24}ClNO_3$	59.69	59.97	8.02	7.82
II	2-OH-5-Me	Me	Me	188.5–189	$C_{15}H_{24}ClNO_4$	56.67	56.93	7.61	7.88
III	2-OMe-5-Me	Me	Me	179–180	$C_{16}H_{26}ClNO_4$	57.88	57.71	7.90	8.29
IV	2,5-$(OMe)_2$	H	Me	156–156.5[b]	$C_{15}H_{24}ClNO_5$	53.95	54.20	7.25	7.66
V	2,5-$(OMe)_2$	H	Et	125–126	$C_{16}H_{26}ClNO_5$	55.22	55.43	7.54	7.27
VI	3,4-$(OMe)_2$	H	Me	127–128 (dec.[c])	$C_{17}H_{25}NO_9$[d]	52.69	52.66	6.51	6.66
				Intermediates					
VII	2,5-$(MeO)_2C_6H_3CHOHCH_2NMeBz\cdot HCl$[e]			165.5–167	$C_{18}H_{20}ClNO_3$	63.96	63.93	7.16	7.61
VIII	3,4-$(MeO)_2C_6H_3COCH_2NMeBz\cdot HCl$			186.5–187.5 (dec.)	$C_{18}H_{22}ClNO_3$	64.38	64.63	6.61	6.95
IX	3,4-$(MeO)_2C_6H_3COCH(CH_3)NMeBz\cdot HCl$			183–184	$C_{19}H_{24}ClNO_3$	65.20	65.48	6.92	7.40
X	3,4-$(MeO)_2C_6H_3CHOHCH_2NMeBz\cdot HCl$			196–198	$C_{18}H_{20}ClNO_3$	63.96	64.14	7.16	7.56
XI	3,4-$(MeO)_2C_6H_3CHOHCH_2NHMe\cdot HCl$			217.5–220[b] (dec.)	$C_{11}H_{18}ClNO_3$	53.31	53.18	7.33	7.39

[a] Melting points below 200° are corrected. [b] Needles. [c] Flattish prisms. [d] Acid oxalate. [e] Bz = Benzyl.

lated with difficulty and in poor yield. A preferable course was to reduce the tertiary amino ketone base with aluminum isopropoxide and debenzylate the resultant tertiary amino alcohol

$$RCOCH_2NMeBz \xrightarrow{Al(i\text{-}PrO)_3} RCHOHCH_2\cdot NMeBz \xrightarrow[H_2]{Pd\text{–}C} RCHOH\text{—}CH_2NHMe$$

This sequence was also employed in preparing larger quantities of IV and proceeded smoothly and without complications.

This lability of a phenacyl group toward hydrogenolysis was unexpected to us at the time. Subsequently one of us (A.P.P.) observed a hydrogenolytic cleavage of a phenacylpyridinium salt and these facts taken together with the unusual speed of dehalogenation of phenacyl chloride[6] suggest that dephenacylation may resemble debenzylation generally. Some phenomena reported from Adkins' laboratory[7] may also be related. Further investigation is planned.

Experimental[8]

β-(2,5-Dimethoxyphenyl)-β-hydroxyethylbenzylmethylamine Hydrochloride (VII).—Thirty-two gram of α-benzylmethylamino-2,5-dimethoxyacetophenone hydrochloride was dissolved in water, and alkali was added to liberate the base. The ethereal solution of the base was dried over potassium carbonate and evaporated. The base so obtained was refluxed in isopropyl alcohol containing 22 g. of aluminum isopropoxide for five hours, the acetone formed being fractionated off. The reduction mixture was cooled and made strongly alkaline with sodium hydroxide solution and extracted five times with ether. The combined ethereal extracts were dried over potassium carbonate and added to an excess of ethanolic hydrogen chloride solution. An oil separated that crystallized on scratching. The crystalline product weighed 28 g. (a 90% yield) and melted at 166–167°. Recrystallization did not raise the melting point. The starting amino ketone hydrochloride melts at 167.5°[3] but a mixture melted at 148–154°.

β-Hydroxy-β-(2,5-dimethoxyphenyl)-ethylmethylamine Hydrochloride.—Seventy millimoles (23.6 g.) of the tertiary aminoalcohol was dissolved in methanol and hydrogenated with palladized charcoal. The catalyst was filtered off, the methanol and toluene evaporated *in vacuo* and the residue was crystallized from an ethanol–ethylacetate–ether mixture. The product weighed 17 g. (calcd. 17.3 g.) and melted at 151.5°.[3]

N-Methyl-N-(β-hydroxy-β-2,5-dimethoxyphenyl)-ethyl-β-alanine Methyl Ester Hydrochloride.—The base was liberated from the previous preparation, taken into benzene, dried over potassium carbonate and added to 45 g. of methyl acrylate (Eastman Practical Grade). The reaction mixture was allowed to stand at room temperature three days and warmed to about 50° for three hours. On cooling, the solution was poured into about 200 cc. of acetone to which 10 g. of 39% (wt./wt.) methanolic hydrogen chloride had been added. The solution was diluted with ether to the point of turbidity and seeded. The crystalline product weighed 21 g. and melted at 154.5–155°. After one recrystallization from methanol–acetone–ether mixture the m. p. was 156–156.5°, yield 20.5 g. The over-all yield in the last two operations was 90%.

The tertiary aminoketones VIII and IX were prepared by the reaction of 2 mols. of benzylmethylamine with one mol. of bromoacetoveratrone and α-brompropioveratrone, respectively. Compound IX was not employed in further syntheses.

All the compounds reported in Table I have the type of solubilities usual with amine hydrochlorides. The intermediates VII–XI were crystallized from ethanol–ether mixtures, sometimes with addition of ethyl acetate. The β-alanine esters, I–VI, were crystallized by solution in the esterifying alcohol and addition of acetone (or ethyl acetate with I and V) and ether to the point of turbidity.

Acknowledgment.—The authors wish to express their gratitude to Messrs. Walter S. Ide and Samuel Blackman for the microanalyses.

Summary

The preparation of some N-β-hydroxyphenethyl-N-methyl-β-alanine esters with oxytocic action is described.

TUCKAHOE 7, N. Y. RECEIVED MAY 17, 1949

(6) Baltzly and Phillips, THIS JOURNAL **68**, 261 (1946).

(7) Sprague and Adkins, *ibid.*, **56**, 2669 (1934); Kuick and Adkins, *ibid.*, **57**, 143 (1935).

(8) The reactions of the secondary aralkanolamines with methyl acrylate were all run in the same manner. One sequence of procedures is described.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Analogs of Oxytocic Drugs. III. Homologs of the Phenethyl β-Alanine Type[1]

BY RICHARD BALTZLY AND ARTHUR P. PHILLIPS

Oxytocic activity having been observed in certain N-phenethyl-β-alanine esters[2] it seemed desirable to examine the effect of varying the length of the chains (a) between the ring and the amino nitrogen, and (b) between the amino group and the ester grouping. To this end were first prepared four phenethyl derivatives of glycine and α-alanine, Compounds I–IV, none of which proved of physiological interest. The β-alanine homolog of IV is quite active wherefore it is apparent that at least two carbons must intervene between the amino and carbalkoxyl groups.

The reverse operation, increase of the distance between amino and ester functions, produced no comparable change in physiological activity. Compounds VIII and IX were not significantly less potent than their β-alanine equivalents. Evidently there is no critical upper limit in this distance.

The variation of chain length between the amino groups and the ring was not studied in comparable detail since amines with more than two carbons in this chain were less accessible. Three substituted benzyl β-alanine esters, V–VII, were prepared and found to be inactive. At the same time alterations in the nitrogen substituent were made without affecting this result.

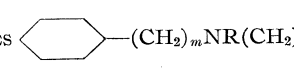
The compounds prepared and their analytical data are presented in Table I. Compounds V–VII were formed from the appropriate secondary amines and methyl acrylate as described in the first paper of this series.[2] The other amino esters were obtained by reaction of the required secondary amine with the appropriate halo ester. The yields by this method were in the range of 30–50% based on pure product. Compound II was prepared by heating I with ethanolamine.

Experimental[2a]

N-Methyl-N-homoveratryl Glycine Ethyl Ester (IV).—Nine grams of ethyl chloroacetate and 14.5 g. of N-methylhomoveratrylamine were refluxed together in absolute ethanol for five hours and the alcohol was then evaporated *in vacuo*. The residual sirup was dissolved in water, basified with sodium carbonate and the bases were taken into ether. After drying over potassium carbonate the bases were distilled at 11 mm. a fraction (4.3 g.) boiling at 192° being selected for further examination. This was dissolved in absolute ethanol, acidified with ethanolic hydrogen chloride and crystallized by addition of ether.

N-Methyl-N-(ξ-carbethoxyhexyl)-homoveratrylamine (IX).—Six hundredths mole of N-methylhomoveratrylamine (12.5 g.) was refluxed in 40 cc. of ethanol with 15 g. of ethyl ξ-bromoheptoate[3] for sixty hours. The alcohol was evaporated and the residual material was dissolved in water. The solution was basified with sodium hydroxide solution and the liberated bases were taken into ether and dried over potassium carbonate. The dry ethereal solution was then treated with portions (1–2 g.) of phenyl isocyanate until the odor of that substance persisted. The excess isocyanate was destroyed with alcohol, the urea filtered off, and the tertiary amine taken into water by extraction with dilute hydrochloric acid. The base was then liberated again, taken into ether, dried and precipitated by addition of ethanolic hydrogen chloride.

TABLE I

SALTS OF PHENALKYLAMINO ACID DERIVATIVES 

Compound	Ring substituents	m	R	n	R′	HX	M. p., °C.[a]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	None	2	CH_3	1	OEt	HCl	219–220[f]	$C_{13}H_{20}ClNO_2$	60.56	60.58	7.83	7.76
II	None	2	CH_3	1	$NHCH_2CH_2OH$	HCl	106–107[b]	$C_{13}H_{21}ClN_2O_2$	57.23	57.47	7.77	7.93
III	None	2	CH_3	1[c]	OEt	HBr	120	$C_{14}H_{22}BrNO_2$	53.13	52.75	7.01	7.16
IV	3,4-$(MeO)_2$	2	CH_3	1	OEt	HCl	164.5	$C_{15}H_{24}ClNO_4$	56.65	56.40	7.61	7.59
V	4-MeO-3-Br	1	C_2H_5	2	OMe	$(COOH)_2$	126–127	$C_{16}H_{22}BrNO_7$	45.69	45.57	5.28	5.43
VI	3,4-$(MeO)_2$	1	CH_3	2	OMe	HCl	136.5[b]	$C_{14}H_{22}ClNO_4$	55.34	55.18	7.31	7.66
VII	3,4-$(MeO)_2$	1	n-C_4H_9	2	OMe	$(COOH)_2$	126–127	$C_{19}H_{29}NO_8$	57.11	57.00	7.32	7.26
VIII	2,5-$(MeO)_2$	2	CH_3	3	OMe	HCl	105–108	$C_{16}H_{26}ClNO_4$	57.89	57.94	7.90	8.22
IX	3,4-$(MeO)_2$	2	CH_3	6	OEt	HCl	118–120	$C_{20}H_{34}ClNO_4$	61.89	61.54	8.84	8.97
						Intermediates						
X	4-MeO-$C_6H_4CH_2NHC_2H_5$·HCl						180–180.5[d]	$C_{10}H_{16}ClNO$	59.53	59.61	8.00	7.93
XI	4-MeO-3-Br-$C_6H_3CH_2NHC_2H_5$·HBr						214[d]	$C_{10}H_{15}Br_2NO$	36.93	37.36	4.66	4.90
XII	3,4-$(MeO)_2C_6H_3CH_2NHCH_3$·HCl						207[d]	$C_{10}H_{16}ClNO_2$	55.15	54.82	7.41	7.56
XIII	3,4-$(MeO)_2C_6H_3CH_2NHC_4H_9$-$n$·HCl						128–129[e]	$C_{13}H_{22}ClNO_2$	60.08	60.19	8.54	8.61

[a] Melting points below 200° are corrected. [b] Needles. [c] $(CH_2)_n$ = —CH(CH_3)—. [d] Plates. [e] Fine felted needles. This compound comes down as very minute crystals, almost as a gel. [f] v. Braun and Wirz, *Ber.*, **60**, 102 (1927), prepared the base and described the hydrochloride as oily.

N-Methyl-N-phenethylglycine Ethanolamide (II).—Eleven grams (0.05 mole) of N-methyl-N-phenethyl glycine ethyl ester and 30 g. (0.5 mole) of ethanolamine was

(1) The work here reported is part of a program carried out in collaboration with a pharmacological group in these laboratories.

(2) Baltzly, Dvorkovitz and Phillips, THIS JOURNAL, **71**, 1162 (1949).

(2a) Since the preparations fall into definite classes and were fairly uniform, a few type procedures are given.

(3) Barger, Robinson and Smith, *J. Chem. Soc.*, 718 (1937).

heated under reflux with a thermometer in the liquid. Heating was applied by a metal-bath. The material, at first in layers, became homogeneous at about 90°. The temperature of the liquid when it began to boil was 154° (b. p. of ethanolamine, 172°) and this temperature fell during twenty minutes to 144° where it remained during forty-five minutes more of gentle refluxing. The contents of the flask was then distilled at 16 mm.; 22 g. of ethanolamine came over at 82°. The residue, which was not extracted from aqueous solution by ether, was acidified with hydrochloric acid (12 cc. of concentrated acid), iced and treated with 10 g. of sodium nitrite and 5 cc. more of concentrated hydrochloric acid. After standing an hour, the solution was evaporated *in vacuo*, dissolved in a minimum of water and basified with 20% sodium hydroxide solution. Repeated extraction with ether removed a sirupy base leaving most of the color behind. The ethereal extracts were dried over potassium carbonate and poured into an excess of ethanolic hydrogen chloride solution. A sirupy layer separated and crystallized slowly. The yield of purified material was 7 g.

The salts described in Table I had no unusual solubilities but the lower melting members were most advantageously recrystallized from acetone with a trace of the esterifying alcohol and with addition of sufficient ether to saturate the solution to the liquid phase. The acid oxalates, V and VII, were prepared because the hydrochlorides could not be induced to crystallize. The hydrobromide III was obtained directly from the reaction mixture in which it was formed.

Intermediates.—The secondary amines leading to compounds I, III, IV and IX, phenethylmethylamine and homoveratrylmethylamine are familiar. The precursor of VIII, N-methyl-2,5-dimethoxyphenethylamine was described by Buck.[4] The intermediates for compounds V–VII are shown in Table I. Veratrylmethylamine (XII),[5] veratrylbutylamine (XIII) and anisylethylamine (X) were prepared by hydrogenation of the corresponding Schiff bases in acetic acid with Adams catalyst; the yields were 75–80%. N-Methyl-4-methoxy-3-bromobenzylamine (XI) was prepared by brominating X in aqueous solution as its hydrobromide; the yield of recrystallized hydrobromide was 76%.

Acknowledgment.—The microanalyses here reported were performed by Messrs. Walter S. Ide and Samuel Blackman to whom we wish to express our gratitude.

Summary

A group of N-phenethyl glycine and N-benzyl-β-alanine derivatives as well as two higher homologs have been prepared for study of their oxytocic properties.

(4) Buck, THIS JOURNAL, **54**, 3661 (1932).

(5) Tiffeneau, *Bull. soc. chim.*, [4] **9**, 930 (1911), has characterized the base and its hydroiodide.

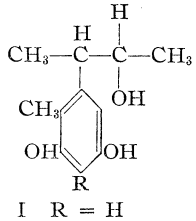
TUCKAHOE 7, NEW YORK RECEIVED MAY 17, 1949

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

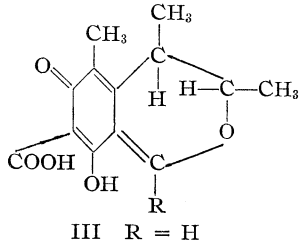
The Synthesis of Dihydrocitrinin and Citrinin

BY H. H. WARREN, GREGG DOUGHERTY AND EVERETT S. WALLIS

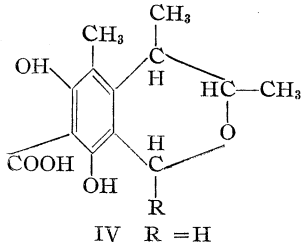
The synthesis of citrinin by Cartwright, *et al.*,[1] from the phenolic degradation product A (I), and the synthesis of the racemic form of A corroborates the structure, III, for citrinin advanced by Brown and co-workers.[2] In this Laboratory we have accomplished the synthesis of dihydrocitrinin (IV) from I by the cyclization of the carboxylic acid derivative, II, with methylal. The dihydrocitrinin thus prepared (m. p. 169.5–170.5° dec.) was readily converted to citrinin by oxidation with bromine in accordance with a method essentially the same as that recently published by Schwenk, Schubert and Stahl.[3]



I R = H
II R = COOH



III R = H



IV R = H

Preliminary observations from investigations now in progress on the synthesis of homologs and analogs of dihydrocitrinin and of citrinin for the purpose of determining the effect of variation in structure on physiological activity indicate that the cyclization is of general applicability for the preparation of derivatives of III and IV where R is methyl, ethyl, benzyl, etc., or substituted radicals of various structures. The results of these experiments will be described in a later paper.

Experimental Part

Compound A.—Citrinin was hydrolyzed with ammonium hydroxide according to the method of Schwenk.[3] Compound A was obtained in excellent yields. Recrystallization from hot chloroform gave a pure product of m. p. 128–130°.

Carboxylic Acid Derivative of Compound A.—The method used was similar to that described by Cartwright.[1] A mixture of 0.50 g. of compound A, 1.00 g. of potassium bicarbonate and 1.00 g. of glycerol was heated under an atmosphere of carbon dioxide in an oil-bath at 150° for five hours. After cooling, the material was dissolved in twice its volume of water and was extracted four times with ether to remove glycerol. Careful acidification of the

(1) Cartwright, Robertson and Whalley, *Nature*, **163**, 94 (1949).

(2) Brown, Cartwright, Robertson and Whalley, *ibid.*, **162**, 72 (1948); see also Frye, Wallis and Dougherty, *J. Org. Chem.*, **14**, 397 (1949).

(3) Schwenk, Schubert and Stahl, *Arch. Biochem.*, **20**, 220 (1949).

cold aqueous solution with dilute sulfuric acid yielded 0.38 g. of white crystalline material which, after three recrystallizations from ether and chloroform, melted at 178.3–179.8 (dec.).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.97; H, 6.71. Found: C, 59.70; H, 6.80.

Dihydrocitrinin.—A suspension of 0.20 g. of the carboxylic acid derivative of compound A in a solution of 0.40 g. of methylal and 4.0 ml. of benzene saturated with dry hydrogen chloride at room temperature was heated in a sealed tube at 60° for six hours. After standing overnight the tube was opened and the clear, slightly yellow liquid was decanted from a very small amount of oil, decolorized with Darco and evaporated nearly to dryness in a stream of nitrogen. Petroleum ether was added dropwise until a tarry precipitate started to form. The clear solution was decanted from the tar and upon further addition of petroleum ether a white crystalline material separated. Four recrystallizations from hot carbon tetrachloride and cyclohexane yielded a product which melted at 169.5–170.5 (dec.).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.87; H, 6.39. Found: C, 61.54; H, 6.15.

Citrinin.—To a solution of 0.030 g. of dihydrocitrinin in one-half ml. of chloroform was added dropwise a molar solution of bromine in chloroform until the bromine color persisted. After standing for ten minutes the solvent was evaporated at low temperature, yielding a dark orange tar which was dissolved in a minimum amount of ethanol. Addition of hot water initiated the formation of a lemon-yellow crystalline material, which after cooling was filtered and recrystallized. Crystals were obtained which melted at 175.8–176.3° (dec.). No depression of the melting point was observed when a sample of this material was admixed with an authentic sample of citrinin.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.24; H, 5.47.

Acknowledgment.—We wish to take this opportunity to express our thanks to The Schering Corporation, Bloomfield, N. J., for the citrinin used in the preparation of Compound A, and to Merck and Company, Inc., Rahway, N. J., for the analyses published in this paper. We also wish to express our appreciation to The Standard Brands Corporation, New York City, N. Y. for a grant-in-aid which made this work possible.

Summary

A synthesis of dihydrocitrinin and of citrinin has been described.

Preliminary observations indicate that the synthesis is applicable to homologs and analogs and to other derivatives of similar structure.

PRINCETON, NEW JERSEY RECEIVED APRIL 20, 1949

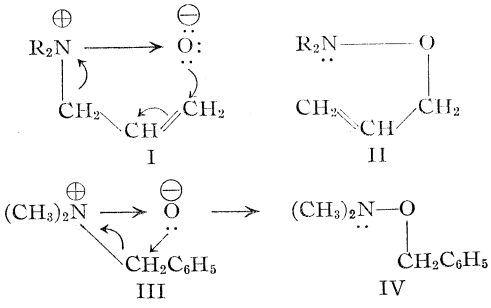
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Rearrangement of Allyldialkylamine Oxides and Benzyldimethylamine Oxide[1]

BY ARTHUR C. COPE AND PHILIP H. TOWLE

Meisenheimer has shown that allylmethylaniline oxide and allylethylaniline oxide rearrange to O-allyl-N-alkyl-N-phenylhydroxylamines on heating with aqueous sodium hydroxide, and that benzylmethylaniline oxide rearranges to O-benzyl-N-methyl-N-phenylhydroxylamine under the same conditions.[2,3] These reactions have been interpreted as intramolecular, thermal rearrangements, because crotylmethylaniline was observed to rearrange with inversion of the crotyl group, yielding O-methylvinylcarbinyl-N-methyl-N-phenylhydroxylamine.[4] The fact that the rearrangement products are formed in high yield in the presence of sodium hydroxide indicates that the oxygen–carbon bond is formed essentially at the same time that the nitrogen–carbon bond is broken, for otherwise appreciable amounts of allyl alcohol and benzyl alcohol should be formed by reaction of the migrating groups (if momentarily free as carbonium ions) with hydroxyl ions. According to this interpretation, the sodium hydroxide has no function in the rearrangement other than to liberate the amine oxides from their salts.

Meisenheimer[3] reported that allyldimethylamine oxide and allyldiethylamine oxide did not rearrange on heating with aqueous sodium hydroxide, but were recovered unchanged except for small amounts which were cleaved into dimethylamine and diethylamine, respectively, and unidentified decomposition products. If the driving force for the rearrangement is a nucleophilic attack of an unshared electron pair of oxygen on the allyl or benzyl group, or the attraction of the positively charged nitrogen of the amine oxide for the electron pair attaching it to the allyl or benzyl group, the rearrangement would be expected to proceed in the aliphatic series as indicated:



A possible explanation for the difference in behavior of allyldialkylamine oxides and allylalkylaniline oxides on heating is the greater tendency of aliphatic amine oxides to hydrate,[5] since combina-

(1) Presented at the St. Louis meeting of the American Chemical Society, Division of Organic Chemistry, Sept. 7, 1948.

(2) Meisenheimer, *Ber.*, **52**, 1667 (1919).

(3) Meisenheimer, Greeske and Willmersdorf, *ibid.*, **55**, 513 (1922).

(4) Kleinschmidt and Cope, THIS JOURNAL, **66**, 1929 (1944).

(5) Sidgwick, "The Organic Chemistry of Nitrogen," revised by Taylor and Baker, University Press, Oxford, 1942, p. 167.

TABLE I

TERTIARY AMINES[a]

Amine	Yield, %	B. p., °C.	$n^{25}D$	d^{25}_4	Formula	Molecular refraction Calcd.	Molecular refraction Found	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Allyldimethyl[b]	39–43	64	1.3981	0.7094	$C_5H_{11}N$	28.76	28.98	70.53	70.12	13.02	12.87	16.45	16.45
Allyldiethyl[c]	79–84	111	1.4170	.7477	$C_7H_{15}N$	38.00	38.07	74.27	74.19	13.36	13.36	12.37	12.18
Allyldi-*n*-propyl[d]	76–80	153.5	1.4239	.7633	$C_9H_{19}N$	47.24	47.26	76.52	76.67	13.56	13.78	9.92	9.98
Allyldiisopropyl	57–60	147.5	1.4258	.7697	$C_9H_{19}N$	47.24	47.00	76.52	76.38	13.56	13.51	9.92	9.67
Allyldi-*n*-hexyl[e]	57–68	126 (8 mm.)	1.4411	.7935	$C_{15}H_{31}N$	74.94	75.03	79.92	80.36	13.86	13.71	6.22	6.19

[a] The secondary amines from which these compounds were prepared were obtained from Sharples Chemicals, Inc., except for dimethylamine, which was obtained from Rohm and Haas. [b] Previously described in ref. 8. [c] Previously described by Rinne, *Ann.*, **168**, 265 (1873); Liebermann and Paal, *Ber.*, **16**, 526 (1883); Kharasch and Fuchs, *J. Org. Chem.*, **10**, 159 (1945). [d] Previously described by Liebermann and Paal, *Ber.*, **16**, 527 (1883). [e] In the preparation of this compound extraction with hydrochloric acid was omitted because the amine hydrochlorides were relatively insoluble in water. The benzene suspension of amine hydrobromides was treated with an excess of aqueous sodium hydroxide, and the benzene solution of the amines (allyldi-*n*-hexylamine and di-*n*-hexylamine) was dried over potassium hydroxide and fractionated through an adiabatic, total condensation, variable take-off type column with a 1.2 × 40 cm. Vigreux section.

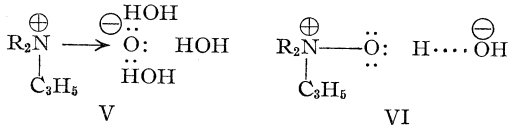
TABLE II

TERTIARY AMINE DERIVATIVES

Derivative	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Allyldimethylamine picrate[a]	116.2–116.8	$C_{11}H_{14}N_4O_7$	42.04	42.25	4.49	4.79	17.83	17.91
Allyldiethylamine picrate[b]	91.2–91.4	$C_{13}H_{18}N_4O_7$	45.61	45.55	5.30	5.36	16.37	16.14
Allyldi-*n*-propylamine picrate	86.8–87.4	$C_{15}H_{22}N_4O_7$	48.64	48.78	5.99	5.97	15.13	15.21
Allyldiisopropylamine picrate	113–113.6	$C_{15}H_{22}N_4O_7$	48.64	48.84	5.99	6.28	15.13	14.93
Allyldi-*n*-hexylamine picrylsulfonate[c]	116.8–117.3	$C_{21}H_{34}N_4O_9S$	48.64	48.74	6.61	6.59	10.80	10.88

[a] Ref. 3 and Knorr and Roth, *Ber.*, **39**, 1428 (1906), report m. p. 95° for allyldimethylamine picrate (possibly a lower melting dimorphous form). [b] Ref. 3 reports m. p. 94–95.5° for allyldiethylamine picrate. [c] The picrate separated as an oil which failed to crystallize.

tion with water as hydrates such as V or hydroxides (VI) would be expected to reduce the reactivity of the unshared electron pairs of the amine oxide oxygen and interfere with the rearrangements if they proceed in the manner indicated in the equations.



V VI

Accordingly a number of aliphatic allyldialkylamine oxides (I) and benzyldimethylamine oxide (III) were investigated in order to determine whether they would rearrange under appropriate conditions to yield O-allyl-N,N-dialkylhydroxylamines (II) and O-benzyl-N,N-dimethylhydroxylamine (IV), respectively.

In beginning this work, Meisenheimer's observation[3] concerning the stability of allyldimethylamine oxide in alkaline aqueous solution was confirmed. After the amine oxide had been heated at the reflux temperature with approximately 25% aqueous sodium hydroxide for six and one-half hours, 7.4% decomposition to dimethylamine had occurred, as determined by titration of the volatile base formed and isolation of dimethylamine picrate, and 64% of the allyldimethylamine oxide was recovered from the alkaline aqueous solution as the crystalline picrate. The susceptibility of allyldimethylamine oxide to rearrangement then was determined under conditions less favorable for hydration. Allyldimethylamine was converted into the oxide by treatment with 10% aqueous hydrogen peroxide. The excess hydrogen peroxide was decomposed in the presence of platinum foil, and the allyldimethylamine oxide solution was concentrated to a viscous sirup, which was heated at 105–110° for one-half hour. During this period a water-insoluble, volatile product formed. Further heating and distillation completed the isomerization of the amine oxide, and after redistillation the rearrangement product, O-allyl-N,N-dimethylhydroxylamine (II, R = CH_3), was isolated in 51% yield. Its structure was established by analysis, analysis of its picrate and methiodide, and direct comparison (m. p. and mixed m. p.) of these solid derivatives with corresponding derivatives of an authentic sample of O-allyl-N,N-dimethylhydroxylamine prepared by methylation of O-allylhydroxylamine with dimethyl sulfate.

In order to determine whether other allyldialkylamine oxides rearranged in a similar manner, the tertiary amines listed in Table I were first prepared and characterized as solid derivatives (Table II). These amines and benzyldimethylamine were converted to the oxides by treatment with hydrogen peroxide. The use of concentrated aqueous hydrogen peroxide or an organic solvent, to produce homogeneous reaction mixtures, was required for the oxidation of the higher molecular weight amines. Allyldiethylamine was oxidized by 10% aqueous hydrogen peroxide, and allyldi-*n*-propylamine, allyldiisopropylamine and benzyldimethylamine were oxidized with 35% aqueous hydrogen peroxide. Allyldi-*n*-hexylamine re-

TABLE III

AMINE OXIDE DERIVATIVES

Derivative	Yield, %[f]	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Allyldimethylamine oxide picrate[a]	94	135.5–136.6	$C_{11}H_{14}N_4O_8$	40.00	40.22	4.27	4.47	16.97	16.96
Allyldiethylamine oxide picrate[b]	89	138.5–138.8	$C_{13}H_{18}N_4O_8$	43.58	43.65	5.06	5.36	15.64	15.54
Allyldi-*n*-propylamine oxide picrate[c]	95	97.2–97.6	$C_{15}H_{22}N_4O_8$	46.63	46.42	5.74	5.73	14.50	14.85
Allyldiisopropylamine oxide picrate[c]	92	149.6–150.4	$C_{15}H_{22}N_4O_8$	46.63	46.87	5.74	5.97	14.50	14.71
Allyldi-*n*-hexylamine oxide picrylsulfonate[d]	..	88.8–89.6	$C_{21}H_{34}N_4O_{10}S$	47.18	46.99	6.41	6.45	10.48	10.62
Benzyldimethylamine oxide picrate[e]	96	159.4–160.0	$C_{15}H_{16}N_4O_8$	47.37	47.17	4.24	4.31	14.73	14.72

[a] Recrystallized from a mixture of absolute alcohol and dry ether. Ref. 3 reports m. p. 136°. [b] Recrystallized from absolute alcohol. Ref. 3 reports m. p. 138°. [c] Recrystallized from 95% alcohol. [d] Semicrystalline, solvated material which separated from alcohol was washed five times with pentane in a centrifuge tube to remove alcohol and triturated repeatedly with ether until the ether remained colorless. [e] Recrystallized from 80% alcohol. [f] Over-all yield from the amines to the amine oxide derivatives listed.

quired treatment with 35% aqueous hydrogen peroxide in acetone[6] or oxidation with perbenzoic acid for conversion to the amine oxide. All but one of the amine oxides were obtained in high yield, as indicated by the yields of their picrates (Table III). The yield of allyldi-*n*-hexylamine oxide could not be determined in this manner because its picrate failed to crystallize and its picrylsulfonate was crystallized with difficulty and consequent loss of material.

When the amine oxides were concentrated and heated under reduced pressure at temperatures of 80–165°, rearrangement to trialkylhydroxylamines occurred in each case. It was important to remove the excess hydrogen peroxide rather completely by treatment with platinum before the amine oxide solutions were concentrated. If substantial quantities of hydrogen peroxide remained in the solutions, explosive decomposition occurred in some cases when the residues were heated. The lower molecular weight amine oxides rearranged only after almost all of the water had been removed from their aqueous solutions, while the higher homologs rearranged in the presence of water during the distillation. The trialkylhydroxylamines which were formed were isolated in yields of 51 to 80%, and were differentiated easily from the isomeric, non-volatile amine oxides from which they were prepared by their physical properties (including volatility), and by preparation of solid derivatives.

From these results it is concluded that the rearrangement of allyl and benzyldialkylamine oxides is not essentially different from the rearrangement of allyl and benzylalkylaniline oxides.[2,3,4] It has been shown that the rearrangement takes place readily in the absence of alkali. The fact that removal of most of the water from the alkyldialkylamine oxides facilitates their rearrangement may be interpreted as indicating that hydration (represented in formulas V and VI) interferes with the rearrangement either sterically or by an effect on the dipole moment of the amine oxide or the dielectric constant of the solution. An alternate, less likely explanation which is not consistent with the case of rearrangement with inversion observed previously[4] would be isomerization by a bimolecular process, which would proceed more rapidly at higher concentrations, rather than by an intramolecular route.

(6) Bruson and McCleary, U. S. Patent 2,220,835 (Nov. 5, 1940); *C. A.*, **35** 1550 (1941).

Experimental[7]

Tertiary Amines (Table I).—Allyldimethylamine was prepared by a method similar to one described by Weston, Ruddy and Suter.[8] A 25% aqueous solution of dimethylamine (112 g.) and allyl chloride (38.3 g.) was weighed into each of six 8-oz. pressure bottles. To each bottle was added a solution of 4.8 g. of sodium hydroxide in 6 ml. of water. The bottles were capped and shaken with a mechanical shaker for eighteen hours. The mixtures became warm initially and cooled to room temperature within two hours. They were combined in a separatory funnel, and the amine layer was separated and combined with an additional quantity which separated when a solution of 60 g. of potassium hydroxide in 60 ml. of water was added to the aqueous phase. The aqueous solution was distilled, and the material boiling below 85° was added to the amine fraction, which was then distilled through an adiabatic, total condensation, variable take-off type column with a 1.1 × 30 cm. section packed with glass helices.

Allyldiethylamine was prepared by an adaptation of a procedure described by Menschutkin for similar preparations.[9] Allyl bromide (165 g., 1.37 moles) was added slowly with stirring to a solution of diethylamine (200 g., 2.74 moles) in 240 ml. of dry benzene in a 1-l. three-necked flask fitted with a stirrer, dropping funnel, reflux condenser and a thermometer dipping into the liquid. The flask was cooled intermittently to keep the reaction temperature from rising above 45–50°. After the addition was completed, the mixture was heated under reflux in a bath at 80° for two hours. After cooling, 150 ml. of concentrated hydrochloric acid and 100 ml. of water were added. The layers were separated, the benzene layer was extracted with two 50-ml. portions of 10% hydrochloric acid, and the combined acid extracts and aqueous phase were extracted with 50 ml. of benzene. The aqueous solution was made alkaline by adding a solution of 200 g. of sodium hydroxide in 500 ml. of water, and the non-aqueous phase was separated and combined with two 50-

(7) Melting points are corrected and boiling points are uncorrected. In calculation of molecular refractions the Eisenlohr values were used (Eisenlohr, *Z. physik. Chem.*, **75**, 605 (1911)), and 2.48 for nitrogen in the hydroxylamine derivatives (Bruhl, *Ber.*, **26**, 2508 (1893)). We are indebted to Mr. S. M. Nagy and Mrs. Louise W. Spencer for analyses.

(8) Weston, Ruddy and Suter, THIS JOURNAL, **65**, 674 (1943).

(9) Menschutkin, *J. Russ. Phys. Chem. Soc.*, **31**, 43 (1899); *Chem. Zentr.*, **70**. I, 1067 (1899).

ml. ether extracts of the water solution. The combined amine and ether extracts were dried over solid potassium hydroxide and fractionated through a 1.1 × 30 cm. helix-packed column. Other allyldialkylamines listed in Table I were prepared in essentially the same manner as allyldiethylamine. Benzyldimethylamine was obtained in 83% yield by methylation of benzylamine with formaldehyde and formic acid.[10]

Solid derivatives which were prepared from the tertiary amines are listed in Table II. They were made by heating the reactants briefly in 95% alcohol, and were recrystallized from absolute alcohol.

Amine Oxides.—The tertiary amines were converted to the oxides by reaction with hydrogen peroxide according to the following procedures. Small-scale preparations or aliquot portions of larger scale oxidations were treated with picric acid or picrylsulfonic acid in order to characterize the amine oxides which were formed, and to determine their yields by the weights of solid derivatives which were isolated (Table III).

Allyldimethylamine (20 g.) was added slowly to 171 g. (about 100% molar excess) of 10% aqueous hydrogen peroxide in a 500-ml. flask fitted with a stirrer, dropping funnel, thermometer and reflux condenser. During the addition the temperature of the mixture was maintained at 8–10° by cooling with an ice-bath. The turbid mixture became homogeneous after two hours, and was allowed to warm to room temperature and stirred for twelve hours. The solution was extracted with three 50-ml. portions of ether to remove any amine still present. Approximately 12 sq. cm. of platinum foil (cleaned by treatment with boiling dilute nitric acid, heated to redness in a flame, and cooled) was added to the solution to catalyze the decomposition of the excess hydrogen peroxide. The rate of evolution of oxygen decreased after one and one-half hours, and the decomposition was allowed to continue for twenty-four hours at room temperature. The solution was decanted from the platinum into a solution of 53.8 g. (0.24 mole) of picric acid in 1570 ml. of water at 80°. The solution was heated at 70–80° for fifteen minutes, cooled slowly, and after crystallization started was placed in an ice-bath and stirred until the crystallization appeared to be complete. The yield of allyldimethylamine oxide picrate, m. p. 135–136°, was 72.7 g. (94%). Allyldiethylamine oxide picrate was prepared in the same way. Allyldiisopropylamine (41.2 g.) was added to 35% hydrogen peroxide (82.4 g., about 200% molar excess) with stirring but without cooling. After nineteen hours the aqueous layer was separated and the amine was returned to the flask and again stirred with 80 g. of 35% hydrogen peroxide for twenty-one hours. The process was repeated a third time, and after five hours a homogeneous solution was obtained. The excess hydrogen peroxide in the combined aqueous solutions was decomposed by adding platinum foil at 0° and allowing the solution to stand, initially at 0° and finally at room temperature, until the oxygen evolution became very slow. An aliquot portion of the solution was used for the preparation of allyldiisopropylamine oxide picrate by the procedure described above. Allyldi-*n*-propylamine was oxidized in the same manner as its isomer, except that one treatment with 35% hydrogen peroxide proved to be sufficient to complete the oxidation, as evidenced by formation of a homogeneous solution. Allyldi-*n*-propylamine also was converted to the oxide (isolated as the picrate in 89% yield) by treatment with a 7% solution of hydrogen peroxide in *t*-butyl alcohol[11] for two days at room temperature. Allyldi-*n*-hexylamine (5.1 g.) in 21 ml. of acetone was oxidized by heating under reflux with 5 ml. of 35% aqueous hydrogen peroxide for five hours. The solution was cooled, platinum foil was added, and after oxygen evolution became slow the acetone was removed under reduced pressure. Water (15 ml.) was added to the residue, and the mixture (which formed two layers) was extracted with 10 ml. of pentane, which formed a third layer, to remove any allyldi-*n*-hexylamine which might be present. Allyldi-*n*-hexylamine oxide picrylsulfonate was prepared by adding picrylsulfonic acid in acetone, but it was isolated in poor yield, probably because of difficulties encountered in its crystallization. Allyldi-*n*-hexylamine oxide also was prepared by oxidation of the amine with perbenzoic acid in chloroform solution, and isolated in poor yield as the picrylsulfonate. Benzyldimethylamine (25 g.) was stirred with 35 g. of 35% aqueous hydrogen peroxide at room temperature. The mixture became homogeneous after one hour, and was stirred overnight. Excess hydrogen peroxide was decomposed by adding clean platinum foil and allowing the solution to stand until oxygen evolution became slow, and an aliquot portion of the solution was used for the preparation of benzyldimethylamine oxide picrate.

Stability of Allyldimethylamine Oxide in Alkaline Aqueous Solution.—Allyldimethylamine oxide hydrochloride was prepared from the picrate by a method used by Meisenheimer for similar conversions.[12] Allyldimethylamine oxide picrate (30 g., 90.9 millimoles) was shaken with 70 ml. of nitrobenzene, 70 ml. of ether and 15 ml. of concentrated hydrochloric acid until the picrate dissolved. Water (1 ml.) was added to facilitate separation of the layers, and the acid layer was withdrawn and combined with three successive 3-ml. portions of concentrated hydrochloric acid used to extract the ether–nitrobenzene solution. The acid solution was extracted with three 25-ml. portions of ether and diluted to 250 ml. with water. A Kjeldahl determination on an aliquot of this solution showed the presence of 1.080 g. of nitrogen (equivalent to 77.1 millimoles) in the solution (85% yield of allyldimethylamine oxide hydrochloride from the picrate). The allyldimethylamine oxide hydrochloride solution was placed in a 500-ml. round-bottomed flask, which was attached to a reflux condenser connected to two receivers in series containing standard hydrochloric acid. The inlet tubes to these receivers dipped below the surface of the acid, so that any base distilled into them would be absorbed. A solution of 120 g. of sodium hydroxide in 150 ml. of water was added to the allyldimethylamine oxide hydrochloride solution and the mixture was heated under reflux for six hours. After this period steam was passed through the reflux condenser while the basic solution was boiled for thirty minutes, so that any volatile bases would distil into the standard acid. The standard acid in the first receiver was diluted to 250 ml. Titration of aliquots showed that 5.6 millimoles of a volatile base had been neutralized, and Kjeldahl determinations on aliquots showed the presence of 0.081 g. of nitrogen (equivalent to 5.8 millimoles), in agreement with the acidimetric titration. The standard acid in the second receiver was found to have absorbed a negligible amount of volatile base, and was discarded. The volatile base was liberated by adding a solution of 30 g. of sodium hydroxide in 100 ml. of water to the acid solution (combined with the titrated samples), and steam distilled with about 40 ml. of water into a solution of 1.33 g. of picric acid in 26 ml. of alcohol. Dimethylamine picrate (1.5 g.) was obtained after concentration, and after recrystallization weighed 1.42 g. (5.2 millimoles), m. p. and mixed m. p. with a known sample 156–157°.

The original alkaline solution remaining after the period of reflux and distillation of the volatile base was neutralized with concentrated hydrochloric acid, concentrated to a volume of less than 1 l., and diluted to 1 l. with water. A Kjeldahl determination on an aliquot showed the presence of 0.985 g. of nitrogen (equivalent to 70.3 millimoles). After preliminary experiments on methods of isolating allyldimethylamine oxide picrate from small aliquots of the solution, the remainder was concentrated to dryness under reduced pressure, yielding sodium chloride containing some organic material. This residue was dried by refluxing with benzene and removing the water in the condensate with a continuous separator, and the benzene was then removed under reduced pressure. The residue

(10) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(11) Milas and Sussman, *ibid.*, **58**, 1302 (1936).

(12) Meisenheimer, *Ann.*, **385**, 120 (1911).

was extracted thoroughly with absolute alcohol, which was concentrated, leaving a residue which was dried with benzene as before and re-extracted with 50 ml. of absolute alcohol. The alcohol solution was concentrated to 10 ml., diluted with 50 ml. of water, and warmed with 14.5 g. of freshly precipitated silver oxide. The silver chloride which was formed and excess silver oxide were removed by filtration, and a solution of 15.9 g. of picric acid in 325 ml. of water at 80° was added to the filtrate. The allyldimethylamine oxide picrate which separated was recrystallized from alcohol; yield 14.8 g., m. p. 135.2–136.2°, which was not depressed by a known sample. This yield amounted to 64% of the amount of allyldimethylamine oxide hydrochloride employed, taking into account the aliquots removed for analyses and preliminary experiments.

Rearrangement of Allyldimethylamine Oxide to O-Allyl-N,N-dimethylhydroxylamine.—An aqueous solution of allyldimethylamine oxide prepared by oxidizing 20 g. (0.24 mole) of allyldimethylamine with 10% aqueous hydrogen peroxide, followed by decomposition of the excess hydrogen peroxide in the presence of platinum, was concentrated to a thick sirup under reduced pressure at a bath temperature of 60–65°. Two 50-ml. portions of absolute alcohol, three 50-ml. portions of benzene and finally 50 ml. of absolute alcohol were added and distilled under reduced pressure in order to remove water from the residue. The resulting pale yellow, viscous sirup was heated in a nitrogen atmosphere under a reflux condenser at a bath temperature of 105–110° for thirty minutes. The liquid became dark yellow and separated into two layers. The condenser was set for distillation, and the liquid was distilled by gradually raising the bath temperature to 140° during a period of four hours. The distillate, which collected in two layers, was separated, and the aqueous layer was extracted with 10 ml. of ether. The organic layer and the ether extract were combined, dried over potassium hydroxide and distilled through an adiabatic, total condensation, variable take-off type column with a 1.5 × 15 cm. section packed with glass helices. The yield of O-allyl-N,N-dimethylhydroxylamine was 12.2 g. (51%), b. p. 83°; $n^{25}D$ 1.3982; d^{25}_4 0.7939; M_D calcd. 30.05, found 30.77.

Anal. Calcd. for $C_5H_{11}NO$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.15; H, 10.73; N, 13.98.

O-Allyl-N,N-dimethylhydroxylamine picrate was prepared by heating the reactants in alcohol solution and was recrystallized from a mixture of alcohol and ether; m. p. 92.5–93.5°.

Anal. Calcd. for $C_{11}H_{14}N_4O_8$: C, 40.00; H, 4.27; N, 16.97. Found: C, 39.80; H, 4.26; N, 17.07.

O-Allyl-N,N-dimethylhydroxylamine (1 g.) and methyl iodide (1.4 g.) reacted to give a white, crystalline methiodide. The mixture was allowed to stand in a refrigerator for twenty-four hours, the solid was pressed dry on a suction filter, and recrystallized from a mixture of absolute alcohol and dry ether; m. p. 129° (dec.).

Anal. Calcd. for $C_6H_{14}NOI$: C, 29.64; H, 5.81; N, 5.76; I, 52.21. Found: C, 29.25; H, 5.95; N, 5.62; I, 53.00.

Synthesis of O-Allyl-N,N-dimethylhydroxylamine for Comparison with the Rearrangement Product.—Hydroxyurethan was prepared according to the method of Jones[13] and alkylated with allyl bromide under conditions similar to those employed previously.[4,13,14] It was found to be important to use moderately dilute solutions in the alkylation in order to obtain a high proportion of O-allylhydroxyurethan in the product; in concentrated solution the yield of this compound was less than 5% and O,N-diallylhydroxyurethan was the principal product. Hydroxyurethan (159 g.) in 330 ml. of absolute alcohol was converted into the potassium salt with a solution of 86.8 g. of potassium hydroxide in 330 ml. of absolute alcohol. Allyl bromide (195.5 g.) was added with cooling at room temperature, and the mixture was heated under reflux for two hours. After separation of the two products with 10% sodium hydroxide[4] the acidic fraction yielded 134.2 g. (61%) of O-allylhydroxyurethan, b. p. 107° (12.5 mm.), $n^{25}D$ 1.4429, and the neutral fraction yielded 25.2 g. of O,N-diallylhydroxyurethan, b. p. 91–92° (8.5 mm.), $n^{25}D$ 1.4436. O-Allylhydroxyurethan (134 g.) was hydrolyzed to O-allylhydroxylamine by heating with a solution of 120 g. of potassium hydroxide in 280 ml. of water for two hours under reflux. The product was steam distilled into dilute hydrochloric acid, and O-allylhydroxylamine hydrochloride was isolated by concentration under reduced pressure. After twice adding absolute alcohol and removing it under reduced pressure the yield was 91 g. (90%), m. p. 169–170°. After recrystallization from absolute alcohol and dry ether the m. p. was 170.6–170.8°.[4,15]

Freshly distilled dimethyl sulfate (52 g.) was added slowly with stirring and cooling to O-allylhydroxylamine hydrochloride (22.5 g.) in 200 ml. of 10% aqueous sodium hydroxide. The solution became turbid and two layers separated within three-quarters of an hour. An additional 5.2 g. of dimethyl sulfate and 40 ml. of 10% sodium hydroxide was added, and the mixture was heated under reflux for one-half hour and stirred at room temperature for twelve hours. The solution was extracted with 50- and 25-ml. portions of ether, which were dried over sodium sulfate and distilled. The O-allyl-N,N-dimethylhydroxylamine was converted into solid derivatives for comparison with derivatives prepared from O-allyl-N,N-dimethylhydroxylamine obtained by rearrangement. O-Allyl-N,N-dimethylhydroxylamine picrate was recrystallized from absolute alcohol; m. p. 92.6–93°, which was not depressed by mixture with the picrate obtained from the rearrangement product.

Anal. Calcd. for $C_{11}H_{14}N_4O_8$: C, 40.00; H, 4.27; N, 16.97. Found: C, 39.81; H, 4.23; N, 17.36.

Another sample of the O-allyl-N,N-dimethylhydroxylamine prepared by this synthesis was converted to the methiodide, which was recrystallized from a mixture of absolute alcohol and dry ether; m. p. and mixed m. p. with the methiodide prepared from the rearrangement product 129° (dec.).

Anal. Calcd. for $C_6H_{14}NOI$: C, 29.64; H, 5.81; N, 5.76; I, 52.21. Found: C, 29.60; H, 5.84; N, 5.66; I, 52.11.

Both samples of the methiodide decomposed suddenly within fifteen seconds when placed in a melting-point bath heated to 128–129°. If placed in the bath at a temperature below 120°, they darkened slowly and charred between 200 and 250°. If placed in the bath at temperatures between 120 and 128° they decomposed, but not within fifteen seconds and not always at the same temperature.

O-Allyl-N,N-diethylhydroxylamine.—An aqueous solution prepared by oxidizing 50 g. of allyldiethylamine with 10% aqueous hydrogen peroxide was treated with platinum to decompose the excess hydrogen peroxide and concentrated to a thick pale yellow sirup. The flask containing the sirup was attached to a condenser set for distillation, nitrogen was introduced through a capillary, and the flask was immersed in a bath at 125°. O-Allyl-N,N-diethylhydroxylamine began to distil along with water remaining in the amine oxide sirup within fifteen minutes, and the distillation was continued by raising the bath temperature as necessary until only a small dark residue remained. The product was separated, combined with two 15-ml. ether extracts of the aqueous layer, and dried over magnesium sulfate. The solution was distilled through a total condensation type column with a 1.5 × 15 cm. section packed with glass helices. The yield of O-allyl-N,N-diethylhydroxylamine was 33.9 g. (59%), b. p. 126°; $n^{25}D$ 1.4118; d^{25}_4 0.8018; M_D calcd. 39.28, found 40.07.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.09; H, 11.70; N, 10.84. Found: C, 65.18; H, 11.60; N, 10.66.

O-Allyl-N,N-diethylhydroxylamine picrate was pre-

(13) Jones, *Am. Chem. J.*, **20**, 40 (1898).

(14) Hecker, *ibid.*, **50**, 444 (1913).

(15) Brady and Peakin, *J. Chem. Soc.*, 226 (1930).

pared as a derivative and recrystallized from absolute alcohol; m. p. 78.8–79.4°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.58; H, 5.06; N, 15.64. Found: C, 43.22; H, 5.13; N, 15.42.

In two preparations, the rearrangement was conducted by concentrating the aqueous solution of allyldiethylamine oxide at atmospheric pressure. The solution was added from a dropping funnel to a distilling flask immersed in a bath at 150–155° as rapidly as water distilled from the solution. The O-allyl-N,N-diethylhydroxylamine distilled with steam after most of the water had distilled. The distillate was extracted with ether, which was dried over magnesium sulfate and fractionated. The yields were poorer (42 and 44%) than in the preparations in which the amine oxide was concentrated under reduced pressure before rearrangement.

O-Allyl-N,N-diisopropylhydroxylamine.—The aqueous solution of allyldiisopropylamine oxide (277 ml.) described under the preparation of the picrate was divided, 25 ml. being used for preparation of the picrate and the remainder for rearrangement according to the following procedure. The solution was heated in an oil-bath at 125° for twenty minutes, and then distilled rapidly at a pressure of 75 mm. The organic layer was separated from the distillate and combined with two 25-ml. extracts of the aqueous layer. After drying over magnesium sulfate the product was distilled through the total condensation type column with a 1.5 × 16 cm. section packed with glass helices. The yield of O-allyl-N,N-diisopropylhydroxylamine was 27.5 g. (67%), b. p. 92–93° (100 mm.); $n^{25}D$ 1.4248; d^{25}_4 0.8223; M_D calcd. 48.52, found 48.88.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.58; H, 12.23; N, 9.16.

O-Allyl-N,N-diisopropylhydroxylamine picrate decomposed on attempted recrystallization but was analytically pure as it crystallized on preparation in 95% alcohol; m. p. 86.4–87.2°.

Anal. Calcd. for $C_{15}H_{22}N_4O_8$: C, 46.63; H, 5.74; N, 14.50. Found: C, 46.41; H, 6.01; N, 14.59.

O-Allyl-N,N-di-*n*-propylhydroxylamine.—An aqueous solution of allyldi-*n*-propylamine oxide was prepared by oxidizing 50 g. of allyldi-*n*-propylamine with 35% hydrogen peroxide, treated with platinum to decompose hydrogen peroxide, and rearranged under the conditions described for preparation of O-allyl-N,N-diisopropylhydroxylamine. The yield of O-allyl-N,N-di-*n*-propylhydroxylamine was 44.5 g. (80%), b. p. 100–101° (100 mm.); $n^{25}D$ 1.4209; d^{25}_4 0.8125; M_D calcd. 48.52, found 49.07.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.78; H, 12.24; N, 9.05.

O-Allyl-N,N-di-*n*-propylhydroxylamine picrylsulfonate was prepared by heating the reactants in 95% alcohol and was recrystallized from the same solvent; m. p. 106.8–107.7°.

Anal. Calcd. for $C_{15}H_{22}N_4O_{10}S$: C, 40.00; H, 4.92; N, 12.44. Found: C, 40.27; H, 4.96; N, 12.47.

O-Allyl-N,N-di-*n*-hexylhydroxylamine.—Allyldi-*n*-hexylamine (5.1 g.) was oxidized with hydrogen peroxide in acetone by the procedure described under preparation of the amine oxide picrate. An aqueous suspension (two layers) of the amine oxide was concentrated under reduced pressure, with much difficulty because of foaming. The residue was heated with an electric heating mantle and distilled at 1 mm., also with foaming. The organic layer of the distillate was separated, combined with ether extracts of the aqueous layer, and redistilled through a short Vigreux column at 0.5 mm. Foaming interfered with the distillation, which was accomplished by heating the liquid as little as possible and directing an infrared lamp at its surface. The yield of O-allyl-N,N-di-*n*-hexylhydroxylamine was 3.73 g. (68%), b. p. 77–81° (0.5 mm.). A redistilled analytical sample had b. p. 93–94° (1 mm.); $n^{25}D$ 1.4381; d^{25}_4 0.8245; M_D calcd. 76.23, found 76.79.

Anal. Calcd. for $C_{15}H_{31}NO$: C, 74.62; H, 12.94; N, 5.80. Found: C, 74.93; H, 12.87; N, 5.70.

Unsuccessful attempts were made to prepare the following derivatives of O-allyl-N,N-di-*n*-hexylhydroxylamine in crystalline form: picrate, picrylsulfonate, perchlorate, diliturate, styphnate, methiodide and methyl *p*-toluenesulfonate.

O-Benzyl-N,N-dimethylhydroxylamine.—Benzyldimethylamine (25 g.) was oxidized by stirring with 35 g. of 35% aqueous hydrogen peroxide for five hours, while the mixture was immersed in a water-bath at room temperature to dissipate the heat of reaction. The solution was diluted with 25 ml. of water and stirred in the presence of platinum foil for two days. The aqueous solution was extracted with 10 ml. of pentane and concentrated under reduced pressure with a bath temperature of 45°. The residual sirup was dried by adding three successive 25-ml. portions of benzene and removing them under reduced pressure. The residue was distilled at a bath temperature of 85–165° and 15–10 mm. The organic layer was separated from the distillate, combined with ether extracts of the aqueous layer, and distilled through an adiabatic, total condensation type column with a 1.5 × 15 cm. Vigreux section. The yield of O-benzyl-N,N-dimethylhydroxylamine was 17 g. (61%), b. p. 79–80° (15 mm.); $n^{25}D$ 1.4920; d^{25}_4 0.9474; M_D calcd. 45.38; found 46.30.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.81; H, 8.76; N, 9.16.

O-Benzyl-N,N-dimethylhydroxylamine picrate was prepared by heating the reactants in 95% alcohol and was recrystallized from the same solvent; m. p. 111.6–112.4°.

Anal. Calcd. for $C_{15}H_{16}N_4O_8$: C, 47.37; H, 4.24; N, 14.73. Found: C, 47.10; H, 4.45; N, 14.96.

Summary

Allyldialkylamine oxides rearrange on heating, yielding O-allyl-N,N-dialkylhydroxylamines. Allyldimethylamine oxide does not undergo the rearrangement in alkaline aqueous solution, but does rearrange on heating after most of the water has been removed from its aqueous solution by distillation. Benzyldimethylamine oxide rearranges in a similar manner to yield O-benzyl-N,N-dimethylhydroxylamine. The rearrangement provides a satisfactory synthetic route for the preparation of O-allyl-N,N-dialkylhydroxylamines and O-benzyl-N,N-dimethylhydroxylamine.

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Reaction of Chloroalkyl Sulfides with Sodium[1]

BY CHARLES D. HURD AND KENNETH WILKINSON

The present problem deals with the behavior of several chloroalkyl sulfides with sodium and other metals. Simple alkyl halides are known to react[2] with sodium, giving first the alkylsodium, RNa, then the paraffin, R–R. Some α,ω-dihalides behave similarly, the products of reaction[3] of 1,10-dichlorodecane in ether with sodium being decane, eicosane, triacontane, and so on up to heptacontane, $C_{70}H_{142}$. The only chloroalkyl sulfide whose behavior toward sodium has been reported is 2-chloroethyl sulfide or mustard gas. Like 1,10-dichlorodecane, it also is an α,ω-dihalide, but it is reported to be inert toward sodium either in ether[4] or in refluxing xylene.[5]

Mustard gas was reinvestigated in the present work along with several other chloro sulfides. The list includes sulfides of the general formula $RS(CH_2)_nCl$ wherein R was phenyl, ethyl, *n*-, *s*-, and *t*-butyl, 2-chloroethyl and 3-chloropropyl; and *n* was 1, 2, 3 or 4. These compounds were generally synthesized by reaction of thionyl chloride on the corresponding hydroxy sulfide. Three of the chlorides were new: *s*-butyl 2-chloroethyl sulfide, *t*-butyl 2-chloroethyl sulfide and *n*-butyl 4-chlorobutyl sulfide. The hydroxyalkyl sulfides from which these three compounds were made were new also. They were synthesized from the sodium alkyl sulfide by reaction with either ethylene chlorohydrin or tetramethylene chlorohydrin.

The yield of *t*-butyl 2-chloroethyl sulfide was considerably lower than that for the *n*- and *s*-butyl isomers, pointing to extensive cleavage at the C–S bond. Supporting this statement is the fact that a 25% yield of *t*-butyl chloride was isolated as a by-product.

Reaction of the alkyl (or aryl) 2-chloroethyl sulfides with sodium wire in refluxing toluene was rapid. A purple color formed on the surface of sodium and a gas was evolved, namely, ethylene. The non-volatile reaction products included sodium chloride, sodium alkyl (or aryl) sulfide, and 1,2-bis-(alkylthio)-ethane, $RSCH_2CH_2SR$. None of the 1,4-bis-(alkylthio)-butane, $RSCH_2CH_2CH_2CH_2SR$, was obtained, showing that no Wurtz reaction was involved. The following three equations provide an explanation for the four major products isolated.

$$RSCH_2CH_2Cl + 2Na \longrightarrow RSNa + C_2H_4 + NaCl \quad (1)$$

$$RSNa + RSCH_2CH_2Cl \longrightarrow RSCH_2CH_2SR + NaCl \quad (2)$$

$$RSCH_2CH_2SR + 2Na \longrightarrow 2RSNa + C_2H_4 \quad (3)$$

A transient alkylsodium, $RSCH_2CH_2Na$, may be an intermediate step in equation 1 but, if so, its decomposition into $RSNa + C_2H_4$ took precedence over a tendency for a reaction of the Wurtz type.

The rapidity of these reactions is portrayed graphically in Fig. 1, all experiments being carried out in refluxing toluene. No curve for the *t*-butyl analog is included in Fig. 1, since it was impracticable, because of the vigor of the reaction, to add the sulfide all at once as was done with the others. After the initial rapid spurt of gas, the *t*-butyl compound also gave a slow, prolonged evolution of ethylene.

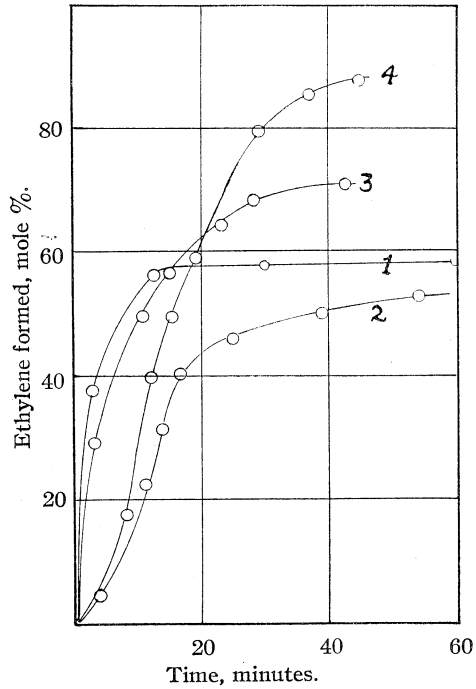

Fig. 1.—Effect of R on the reaction of $RSCH_2CH_2Cl$ with sodium: 1, R, ethyl; 2, R, butyl; 3, R, *s*-butyl; 4, R, phenyl.

All the curves in Fig. 1 depict experiments employing a mole ratio of sodium to the chloro sulfide of about 4:1. Lessening this ratio of 1.5:1 slackened the rate of evolution of ethylene from phenyl 2-chloroethyl sulfide below that of curve 2 for the first thirty-five minutes, passing curve 1 at fifty minutes, finally reaching 71 mole % of ethylene in two hours. This is considerably below the 90% mark reached in one hour when the ratio was 4.3:1.

(1) This paper consists of a report of work done under contract with the Technical Command, Chemical Corps, Department of the Army.

(2) Morton and Hechenbleikner, THIS JOURNAL, **58**, 1697, 2599 (1936).

(3) Carothers, Hill, Kirby and Jackson, *ibid.*, **52**, 5279 (1930).

(4) Helfrich and Reid, *ibid.*, **42**, 1229 (1920).

(5) Davies, *J. Chem. Soc.*, **117**, 298 (1920).

Support for equation 3 was obtained by treating 1,2-bis-(phenylthio)-ethane with sodium, again in hot toluene. Ethylene was evolved steadily, though slowly; about 27 mole per cent. was collected the first hour and 62% after five hours.

Correlation may be drawn between the formation of ethylene in equation 1 and the last step of the well-known Swallen–Boord synthesis of olefins by reaction of ethyl 2-bromoalkyl ethers with zinc

$$BrCH_2CHROEt + Zn \longrightarrow CH_2{=}CHR + BrZnOEt$$

Zinc dust and zinc amalgam both were found capable of liberating ethylene from phenyl 2-chloroethyl sulfide. Magnesium did not react. As with sodium, the isolated products were ethylene, sodium phenyl sulfide, sodium chloride and 1,2-bis-(phenylthio)-ethane. The yield of ethylene, however, was low. Only 30–37 mole per cent. appeared during the first hour, and only 39–45% after five hours. Thiophenol was not found. This suggests that equation 2 consumed all the thiophenol derivative formed in equation 1, with no cleavage by zinc according to equation 3.

In studying the effect of the distance of halogen from sulfur in $RS(CH_2)_nCl$, butyl chloromethyl sulfide was selected for $n = 1$. This was the only example found where any Wurtz product was obtained, but even here only a trace of 1,2-bis-(butylthio)-ethane was found. The chief product was the mercaptal, bisbutylthiomethane. Lesser quantities of mercaptan and gas appeared also. Butylene was the major gaseous product, ethylene and paraffins being lesser products.

The reaction of 3-chloropropyl compounds with sodium produced cyclopropane, not propylene. Ethyl 3-chloropropyl sulfide, for example, gave rise to sodium chloride, cyclopropane, sodium ethyl sulfide and 1,3-bis-(ethylthio)-propane. Phenyl 3-chloropropyl sulfide yielded cyclopropane, sodium phenyl sulfide and bis-(phenylthio)-propane. There was no formation of Wurtz products. These reaction products are well summarized by an extension of equations 1–3.

The reaction of sodium with phenyl 4-chlorobutyl sulfide was less clear cut. Although the phenyl compound is more stable than the dialkyl analogs,[6] it tends to undergo ring closure, forming a sulfonium chloride. In its reaction with sodium, the chief gas evolved was *n*-butane (not cyclobutane). Appreciable quantities of ethylene and 1-butene were formed also. Other identified products of the reaction were sodium phenyl sulfide, 1,4-bis-(phenylthio)-butane, and sodium chloride. To show that the butane did not arise by hydrogen transfer from an aromatic hydrocarbon, the reaction of butyl 4-chlorobutyl sulfide with sodium in butyl ether also produced butane. This formation of butane resembles the formation of decane[3] from 1,10-dichlorodecane.

Two symmetrical chloroalkyl sulfides were studied also, namely, 2-chloroethyl sulfide and 3-chloropropyl sulfide. This work is of interest in view of the reported non-reaction of sodium and mustard gas. We have confirmed Helfrich and Reid's observation[4] of non-reaction in ethyl ether if strictly anhydrous ether was used, but reaction was initiated by using ether which contained only 0.2% of ethanol. Reaction in benzene, toluene or butyl ether at temperatures of 80–110° was slower than with the alkyl 2-chloroethyl sulfides but so definite that it is difficult to understand the reported non-reaction in hot xylene.[5] About twelve hours was necessary to complete the reaction in hot toluene, whereas it took one week in ethyl ether at 25°.

In refluxing toluene, ethylene was evolved to the extent of 148 mole per cent. in twelve hours. The sodium wire assumed a brilliant purple color which did not change color on treatment with alcohol but did change in water to a pale yellow, very insoluble solid melting at 158–160°. It contained no chlorine. Here again, there was no evidence for a product of the Wurtz type. The latter would demand a product with a carbon–sulfur ratio of 4:1, whereas a 2:1 ratio was found.

Equation 1 evidently holds for 2-chloroethyl sulfide as well as for the unsymmetrical analogs. If but one of the chloroethyl groups reacts with sodium, the products would be ethylene and sodium 2-chloroethyl sulfide (A), $ClCH_2CH_2SNa$, whereas if both groups participate, it would lead to sodium sulfide. Actually, some sodium sulfide was formed. The chief solid product, however, was the solid mentioned earlier. It was a polymer with this recurring unit, $(-CH_2CH_2S-)_n$. This might result by reaction of A with itself or with 2-chloroethyl sulfide (equation 2). The extent of equation 3 cannot be estimated but probably some chain-splitting at the C–S bonds occurred.

Oxidation of the polymer by nitric acid yielded a water-soluble polysulfoxide, with apparently a sulfonic acid end group. Oxidation by hydrogen peroxide gave rise to a water-insoluble substance which was believed to be a polysulfone.

Bennett[7] has described a polymer, $(C_2H_4S)_n$, of m. p. 177–180°, made by reaction of 2-hydroxy-1-ethanethiol with hydrochloric acid. Our repetition of Bennett's synthesis yielded a substance of m. p. 158–165°. Apparently, therefore, the polymers from the two sources are similar, although they may not be identical.

3-Chloropropyl sulfide also evolved a gas (cyclopropane) and produced a polymer by reacting with sodium in hot toluene. Gas evolution was complete in less than one hour.

$$(ClCH_2CH_2CH_2)_2S \xrightarrow{Na} [RSCH_2CH_2CH_2Na] \longrightarrow RSNa + \begin{matrix} CH_2{-}CH_2 \\ \diagdown\ \diagup \\ CH_2 \end{matrix}$$

The polymer differed from that from 2-chloroethyl sulfide in melting lower (56°) and in being

(6) Bennett, Heathcoat and Mosses, *J. Chem. Soc.*, 2567 (1929).

(7) Bennett, *ibid.*, **121**, 2139 (1922).

soluble in hydrocarbon solvents. This polymer contained the recurring unit $(-CH_2CH_2CH_2S-)_n$.

Preliminary experiments with 2-chloroethyl ether (not sulfide) revealed that its reaction with sodium also liberates ethylene. Reaction was faster than with the sulfur analog. When 0.077 mole of this ether reacted with 0.165 mole of sodium wire in boiling toluene there was formed 0.060 mole of ethylene in two hours. A polymeric substance was formed which was soluble in water, alcohol or acetone.

Experimental Part

Preparation of Chloro Sulfides.—These compounds were prepared as described in the literature: 2-chloroethyl sulfide,[9] ethyl 3-chloropropyl sulfide,[8] butyl chloromethyl sulfide,[11] phenyl 3-chloropropyl sulfide,[14] phenyl 4-chlorobutyl sulfide,[6] 3-chloropropyl sulfide.[12] Supplementary information as shown was obtained for ethyl 2-chloroethyl sulfide[15] (60% yield, b. p. 69–73° (37 mm.)), butyl 2-chloroethyl sulfide[10] (74% yield, b. p. 98–100° (26 mm.)), phenyl 2-chloroethyl sulfide[13] (97% yield, b. p. 127–129° (6 mm.)).

Alkyl Hydroxyalkyl Sulfides.—Sodium was dissolved in a sevenfold weight of absolute alcohol. An equivalent portion of mercaptan (RSH: R = *s*-Bu, *t*-Bu, *n*-Bu) was added, followed by gradual addition of 1.1 equivalents of the chlorohydrin ($ClCH_2CH_2OH$ or $Cl(CH_2)_4OH$). After refluxing up to one hour, the solution was filtered and distilled. These products were obtained:

I. ***s*-Butyl 2-hydroxyethyl sulfide**, yield 44%, b. p. 105–108° (42 mm.).

II. ***t*-Butyl 2-hydroxyethyl sulfide**, yield 85%, b. p. 111–114° (45 mm.).

Anal. Calcd. for $C_6H_{14}OS$: C, 53.50; H, 10.58. Found: C, 53.73; H, 10.46.

III. **Butyl 4-hydroxybutyl sulfide**, yield 60%, b. p. 129–130° (6 mm.).

Anal. Calcd. for $C_8H_{18}OS$: C, 59.26; H, 11.18. Found: C, 60.02; H, 11.15.

Halogenation.—A small excess of thionyl chloride was added to the above hydroxy compounds. It was added directly, dropwise, to I and II. The product from I was distilled after thirty minutes of refluxing; yield 58%, b. p. 98–100° (40 mm.). That from II was allowed to stand overnight, distilled, and redistilled; yield, 30%, b. p. 85–88° (32 mm.). There was much higher boiling residue. Eight grams of *t*-butyl chloride from 39 g. of II was found in the cold trap.

III was diluted with 1.6 volumes each of carbon tetrachloride and dimethylaniline before addition of thionyl chloride; after refluxing the mixture for thirty minutes, it was acidified (hydrochloric acid) and the non-aqueous layer distilled. A 20% yield of crude butyl 4-chlorobutyl sulfide was collected at 120–124° (10 mm.). Purity was only 70% by halogen analysis. This instability compares with that of ethyl 4-chlorobutyl sulfide,[6] which immediately isomerized to the sulfonium chloride and could not be distilled without decomposition. When our hydroxy sulfide was treated with concd. hydrochloric acid as in the synthesis of mustard gas, reaction was rapid. There was formed a water-soluble sulfonium chloride which gave a characteristic yellow precipitate with picric acid.

Anal. Butyl 2-chloroethyl sulfides. *s*-Butyl. Calcd. for $C_6H_{13}ClS$: C, 47.20; H, 8.51. Found: C, 46.26; H, 8.72. *t*-Butyl. Found: C, 47.12; H, 8.95.

Reaction of Chloro Sulfides.—The reaction of the various chloro sulfides with sodium (or zinc) was carried out in a closed system consisting of a reaction flask (100-ml.) attached to a reflux condenser at the top of which was a dropping funnel and a delivery tube leading to a 10-ml. trap at −78°. In turn, this trap was connected to an Orsat gas analyzer. The cold trap was omitted in the experiments involving the 3-chloropropyl and 4-chlorobutyl compounds. The gas evolved was collected over mercury. A controlled rate of heating of the reaction flask by an electrically controlled oil-bath permitted an accurate measurement of the gas evolved. The volume of gas was plotted against time to indicate the speed of the reaction. Whenever the off gas had a volume larger than 100 ml., it was flushed into a collection bulb over water and retained for analytical purposes.

A typical example for the reaction of butyl 2-chloroethyl sulfide with sodium indicates the general technique. A mixture of 50 ml. of dry toluene and 2.3 g. of sodium wire was refluxed until there was no volume change in the gas collection bulb (five minutes). As long as the refluxing was gentle, the sodium remained as a molten wire presenting a large surface. When 7.023 g. of butyl 2-chloroethyl sulfide was drawn into the reaction flask and washed in with three 1-ml. portions of toluene without the admission of air, a reaction started immediately and a gas (ethylene) was evolved at a moderate rate. A faint fleeting blue color developed on the surface of the sodium wire. Over a period of ninety-nine minutes 580 ml. (S. T. P.) of a gas was collected at a measured rate. The last portion of the evolved gas was identified as ethylene by its absorption in 15% fuming sulfuric acid but not in 88%; reaction of 100 cc. of gas with liquid bromine produced 1 ml. of ethylene bromide, b. p. 128–130°, $n^{23}D$ 1.5358 (lit. b. p. 131°, $n^{20}D$ 1.5379).

The toluene in the reaction flask was decanted from the solid as quantitatively as possible, the excess sodium destroyed with ethanol and combined with a water extract of the toluene. This aqueous solution of chloride and mercaptide ion was diluted volumetrically and aliquots titrated for quantitative data. In the chloride analysis an aliquot was warmed for ten minutes with 30% hydrogen peroxide to destroy the mercaptan, the solution acidified with nitric acid, zinc oxide added as a buffer, and the aliquot titrated with standard silver nitrate using dichlorofluorescein as indicator. Another aliquot was acidified with hydrochloric acid and titrated with standard iodine solution to determine the mercaptan content. The toluene layer was evaporated to 10 ml. on a steam-bath then in an oil-bath at 150°. The remaining crude material was shown to be bis-(butylthio)-ethane by its boiling point (160–161° at 20 mm.) and by oxidation in glacial acetic acid with 30% hydrogen peroxide to the disulfone, m. p. 179°; lit. m. p. 180°.

Table I indicates the products isolated by reactions carried out in refluxing toluene with a variety of chloro sulfides.

Identification of Gaseous Products. Ethylene.—This gas was uncondensed in the −78° trap. When diluted with an equal volume of air, it was insoluble in 88% sulfuric acid but dissolved completely after three passes into fuming (15%) sulfuric acid. It dissolved readily in liquid bromine, forming ethylene bromide; b. p. 129–130°, $n^{20}D$ 1.5374.

Cyclopropane.—A molecular weight determination on a sample of the gas gave a value of 42, which corresponds to C_3H_6. That it was cyclopropane and not propylene was confirmed by its reactivity toward sulfuric acid and its sluggishness toward bromine. When the gas was diluted with an equal volume of air, it dissolved rapidly in 88% sulfuric acid. Practically the entire sample dissolved in the first pass. Propylene, in contrast, requires several passes for complete solution. After twelve passes through 76% sulfuric acid, this gas was 92% absorbed, whereas a 1:1 propylene–air mixture was only 56% absorbed.

Cyclopropane also is known to react sluggishly with

(8) Dawson, THIS JOURNAL, **55**, 2070 (1933).
(9) Clarke, *J. Chem. Soc.*, **101**, 1585 (1912).
(10) Whitner and Reid, THIS JOURNAL, **43**, 636 (1921).
(11) Walter, Goodson and Fosbinder, *ibid.*, **67**, 655 (1945).
(12) Bennett and Hock, *J. Chem. Soc.*, **127**, 2671 (1925).
(13) Steinkopf, Herold and Stöhr, *Ber.*, **53**, 1012 (1920).
(14) Kirner and Richter, THIS JOURNAL, **51**, 3413 (1929).
(15) Demuth and Meyer, *Ann.*, **240**, 310 (1887).

TABLE I

CHLOROALKYL SULFIDES AND METALS

Sulfide	Mole	Metal, g.		Time, min.	Products isolated, moles			
					Gas	RSNa	Cl^-	$RS(CH_2)_nSR$
Ethyl 2-chloroethyl	0.0231	Sodium	1.2	60	Ethylene	0.0135	0.0034	0.0231	0.0047
Butyl 2-chloroethyl	.0460	Sodium	2.3	99	Ethylene	.0258	.0084	.0460	.0204
s-Butyl 2-chloroethyl	.0200	Sodium	1.5	43	Ethylene	.0141	.0084	.0200	.0058
t-Butyl 2-chloroethyl	.0336	Sodium	1.8	90	Ethylene	.0204	.0067	.0336	.0120
Phenyl 2-chloroethyl	.0197	Sodium	2.0	72	Ethylene	.0179	.0175	.0197	....
Phenyl 2-chloroethyl	.0197	Sodium	0.7	105	Ethylene	.0139	.0089	.0196	.0049
Butyl chloromethyl	.0480	Sodium	4.0	30	Ethylene	.0010	.0032	.0483	.016[a]
					Butene	.0025			
					Saturates	.0019			
Ethyl 3-chloropropyl	.0450	Sodium	3.1	35	Cyclopropane	.0293	.023	.044	.012
Phenyl 3-chloropropyl	.0228	Sodium	2.3	63	Cyclopropane	.0135	.0158	.0230	.0038
Phenyl 4-chlorobutyl	.0186	Sodium	2.0	85	Ethylene	.0009	.0089	.0190	.0057
					Butene	.0012			
					Butane	.0039			
Phenyl 2-chloroethyl	.015	Zinc	4.2	300	Ethylene	.0061	None	.0146	....
Phenyl 2-chloroethyl	.0393	Zinc amalgam	10.0	65	Ethylene	.0154	None	.0391	-
2-Chloroethyl	.0035	Sodium	1.8	720	Ethylene	.0052	....	....	[b]
3-Chloropropyl	.0094	Sodium	1.6	30	Cyclopropane	.0093	....	....	[c]

[a] Also found 0.0004 mole of bis-(butylthio)-ethane and 0.2 g. of high boiling hydrocarbon. [b] Mostly bis-(phenylthio)-ethane but also an unidentified solid. [c] Polymers.

bromine. This gas reacted slowly with bromine even when irradiated. The dibromide formed could not have been propylene bromide (b. p. 141°), since it boiled above 150°. 1,3-Dibromopropene boils at 167°. The quantity of dibromide at hand was not purified rigorously.

1-Butene from Butyl Chloromethyl Sulfide.—The gas which collected in the −78° trap boiled at −5.0 to −4.0° (745 mm.). A Siwoloboff micro method[16] was used in this determination, on an 80-cc. sample of material. The gas also was absorbed in 88% sulfuric acid and was absorbed readily by bromine to yield 1,2-dibromobutane.

Butane from Phenyl 4-Chlorobutyl Sulfide.—This gas was unabsorbed in fuming sulfuric acid. Its boiling point was −1.0 to −0.6° by the Siwoloboff micro method. The H:C ratio was determined by combustion analysis to be 0.206. That calculated for C_4H_{10} is 0.208, and for C_4H_8 is 0.166, thus confirming its identity as butane, not cyclobutane.

2-Chloroethyl Sulfide and Sodium.—When 1.8 g. of sodium wire and 40 ml. of toluene was heated to gentle boiling, the sodium formed a pliable, molten wire. A 0.5518-g. sample of 2-chloroethyl sulfide was introduced and rinsed into the flask with two 10-ml. portions of dry toluene. The sodium turned blue. About 115 cc. (S. T. P.) of ethylene was collected in twelve hours.

Similarly, from 18 g. of the sulfide, 10 g. of sodium wire and 150 ml. of butyl ether kept at 80° for eight hours, there was collected 1996 cc. (S. T. P.) of ethylene.

The solid product from these reactions was processed by decanting the solvent, adding alcohol if an excess of sodium was used, then washing with water. Alcohol did not change the blue color, but water decolorized it to pale yellow; m. p. 158–160°.

Several conditions were studied using ether as solvent. A typical run involved refluxing a mixture of 63 g. of 2-chloroethyl sulfide (14 g. recovered), 350 g. of absolute ether, 0.5 g. of ethanol and 20.5 g. of sodium sand for six days. The ethylene was not collected. After decanting the ether, water was added thereby turning the blue solid yellow. It was rinsed thoroughly with acetone, and dried; m. p. 158–160°; yield, 4.2 g. It contained no ash and was insoluble in all the common solvents to less than 0.1% at 100°. These solvents included alcohols, ethers, esters, hydrocarbons, alkyl or aryl chlorides, ketones, nitriles, aniline, nitromethane, nitrobenzene, but was soluble at 170° in aniline, nitrobenzene or camphor.

Anal. Calcd. for $(C_2H_4S)_n$: C, 39.96; H, 6.70; S, 53.33. Found: C, 40.31; H, 6.67; S, 52.35.

Oxidation by Nitric Acid.—A mixture of 3 ml. of concentrated nitric acid and 0.8 g. of this solid was heated on a steam-bath for twenty minutes. Oxides of nitrogen were evolved vigorously at first. Excess nitric acid was removed by adding alcohol. Alcohol caused separation of a yellow precipitate. It was dissolved in 10 ml. of hot water, and reprecipitated by 10 ml. of hot acetone; yield, 0.6 g., m. p. 168–169°. After drying at 100° (30 mm.), it was analyzed.

Anal. Calcd. for $(C_2H_4SO)_n$: C, 31.6; H, 5.28; S, 42.1. Found: C, 31.56; H, 5.27; S, 35.33; neut. equiv., 420, 475, 487.

A terminal sulfonic acid group is suggested by the neutral equivalent. The compound reacted in aqueous solution with aniline to form a salt, m. p. 180–181° dec., precipitated by acetone.

Oxidation by Hydrogen Peroxide.—No solution occurred when 1.17 g. of the solid (m. p. 158–160°), 10 g. of glacial acetic acid and 10 ml. of 30% hydrogen peroxide were heated together for a few minutes but the solid changed to 1.34 g. of a substance of m. p. 312°. It was insoluble in water, alcohol, furfural, acetone or benzene.

Anal. Calcd. for $(C_2H_4SO_2)_n$: C, 26.2; H, 4.35; S, 34.8. Found: C, 26.14; H, 4.94; S, 31.92.

3-Chloropropyl Sulfide.—Butyl ether or toluene were used as solvents. In a typical run, 3.6 g. of sodium wire, 50 ml. of toluene and 4.2 g. of 3-chloropropyl sulfide were heated to gentle refluxing for thirty minutes. The products included 390 cc. (S. T. P.) of cyclopropane, and 0.75 g. of a water-insoluble, benzene-soluble, halogen-free solid of m. p. 55–61°. It was purified by dissolving in chloroform, adding acetone, and partially evaporating; m. p. 56–57°.

Anal. Calcd. for $(C_3H_6S)_x$: C, 48.65; H, 8.10. Found: C, 48.69; H, 8.10; mol. wt. (ebullioscopically in benzene), 2020.

1,2-Bis-(phenylthio)-ethane.—A solution of 0.760 g. of this compound in 10 ml. of toluene was added to a boiling mixture of 50 ml. of toluene and 1.4 g. of sodium wire. The ethylene evolved during three and one-half hours was 41 cc. (S. T. P.). From the reaction flask, 0.21 g. of the

(16) Morton, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1938, p. 51.

starting material was recovered, and 0.42 g. of thiophenol was identified by titration with iodine. Thus one mole of ethylene was formed for each two of thiophenol.

Acknowledgments.—Combustion microanalyses for C, H or N were performed by Margaret Ledyard, Patricia Craig, Margaret Hines and Jean Gibbs. Assistance given by Lawrence Buckles of the Chemical Corps eased many of the difficulties.

Summary

The reaction of chloroalkyl sulfides with sodium in inert solvents has been shown to be a general reaction. Examples were studied where n in the formula $RS(CH_2)_nCl$ represented 1, 2, 3 and 4. Ethylene is evolved when $n = 2$, cyclopropane when $n = 3$, and n-butane together with ethylene and butene when $n = 4$. Mixed gases were formed also when $n = 1$. Mercaptans and bis-(alkylthio)-alkanes, $RS(CH_2)_nSR$ were formed but practically none of the products which would have been predicted by the Wurtz reaction. 2-Chloroethyl ether also evolves ethylene in reaction with sodium.

Polymers were important products from the reactions involving 2-chloroethyl sulfide and 3-chloropropyl sulfide. The statements in the literature regarding the non-reactivity of mustard gas towards sodium need revision.

Zinc and zinc amalgam also cause liberation of ethylene from the 2-chloroalkyl sulfides.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF THE UNIVERSITY OF FLORIDA]

Dimercaptols of Acetonylacetone. II[1]

BY EDWARD G. RIETZ, JAMES B. FERNANDEZ, LLOYD T. SNIDER AND THOMAS K. TODSEN

With four exceptions, the normal dimercaptols of acetonylacetone, methyl through n-dodecyl, have been recorded.[2,3] The present paper describes the properties of the remaining four: n-amyl, n-heptyl, n-nonyl, and n-undecyl, as well as the preparation and properties of the sulfone and the mercuric chloride addition product derived from each member of the series.

The four dimercaptols were prepared in approximately 75% yield by the interaction of acetonylacetone and the mercaptan under the influence of hydrogen chloride according to the directions previously described.[3] The properties and analyses of the products are shown in Table I, and the melting points of the series are plotted in Fig. 1. Two observations should be made with regard to the series: Lengthening of four chains has the same effect as the lengthening of one chain in an ordinary homologous series, and a reversal of alternation of melting point occurs at the nonyl dimercaptol.

TABLE I

MELTING POINTS AND ANALYSES OF THE DIMERCAPTOLS, $CH_3C(SR)_2CH_2CH_2C(SR)_2CH_3$

Mercaptol	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-Amyl[a]	6.5	$C_{26}H_{54}S_4$	63.09	62.90	11.00	11.00
n-Heptyl	31	$C_{34}H_{70}S_4$	67.26	67.26	11.62	11.64
n-Nonyl	50	$C_{42}H_{86}S_4$	69.16	69.05	11.88	11.56
n-Undecyl	61	$C_{50}H_{102}S_4$	72.20	71.83	12.37	12.27

[a] d^{25}_4 0.9572. $n^{25}D$ 1.5098. Calcd. M_{D_2} 154.2. Found: M_D 154.6.

Early attempts at the preparation of the sulfones were directed at the preparation of the sulfoxides as intermediates, but bromine oxidation failed to yield crystalline products. Hence the sulfones were prepared directly by use of permanganate or by acetic anhydride-catalyzed perhydrol oxidation. Yields of the sulfones were uniform and approximated 30%. The melting points and analyses of the sulfones are shown in Table II; the graph of the melting points in Fig. 2.

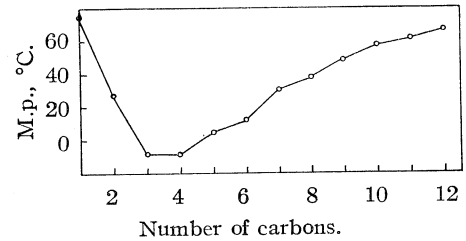

Fig. 1.—Melting points of the mercaptols plotted against the number of carbons in the alkyls.

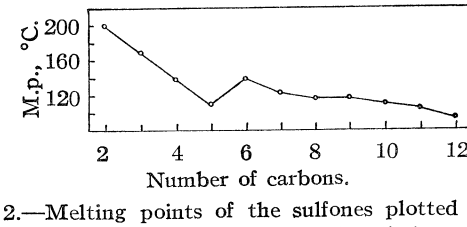

Fig. 2.—Melting points of the sulfones plotted against the number of carbons in the alkyls.

The mercuric chloride addition products were readily obtained by mixing diethylcarbitol solutions of the mercaptol and of mercuric chloride in molecular proportions 1:8, respectively.

The constitution of the mercuric chloride addition product is a function of the chain length. Maximum addition of eight mercuric chloride molecules per molecule of dimercaptol occurs with the

(1) Presented in part at the Southeastern Regional Meeting of the American Chemical Society, Oak Ridge, Tenn., June 11, 1949.

(2) Posner, *Ber.*, **33**, 2983–2993 (1900).

(3) Rietz, Chapman and Fernandez, THIS JOURNAL, **70**, 3486 (1948).

TABLE II

MELTING POINTS AND ANALYSES OF THE SULFONES, $CH_3C(SO_2R)_2CH_2CH_2(SO_2R)_2CH_3$, AND OF THE MERCURIC CHLORIDE ADDITION PRODUCTS OF THE DIMERCAPTOLS, $CH_3C(SR)_2CH_2CH_2C(SR)_2CH_3$

	Sulfones					Addition products						
R	M. p., °C.	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	M. p., °C., dec.	X	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl	230[a]	$C_{10}H_{22}O_8$	30.14	30.13	5.56	5.54	dec.	8.0	$C_{10}H_{22}S_4 \cdot 8HgCl_2$	4.91	5.06	0.91	1.27
Ethyl	...	.....	...	...	...	...	dec.	6.0	$C_{14}H_{30}S_4 \cdot 6HgCl_2$	8.59	8.25	1.54	1.91
n-Propyl	169	$C_{18}H_{38}S_4O_8$	42.32	42.47	7.50	7.56	182–183	5.0	$C_{18}H_{38}S_4 \cdot 5HgCl_2$	12.42	12.48	2.20	2.73
n-Butyl	140	$C_{22}H_{46}S_4O_8$	46.61	46.22	8.13	8.09	180–181	4.5[b]	$C_{22}H_{46}S_4 \cdot 4.5HgCl_2$	15.91	16.14	2.79	3.16
n-Amyl	114	$C_{26}H_{54}S_4O_8$	49.33	49.21	8.60	8.21	184–185	5.0	$C_{26}H_{54}S_4 \cdot 5HgCl_2$	16.86	17.11	2.93	3.36
n-Hexyl	140	$C_{30}H_{62}S_4O_8$	53.07	53.34	9.26	9.19	173–175	4.5[c]	$C_{30}H_{62}S_4 \cdot 4.5HgCl_2$	20.32	20.29	3.53	3.91
n-Heptyl	125	$C_{34}H_{70}S_4O_8$	55.54	55.71	9.60	9.33	161–163	4.0	$C_{34}H_{70}S_4 \cdot 4HgCl_2$	22.77	23.07	3.93	3.93
n-Octyl	118	$C_{38}H_{78}S_4O_8$	57.68	57.64	9.93	10.09	159–160	4.0	$C_{38}H_{78}S_4 \cdot 4HgCl_2$	26.09	25.76	4.49	4.49
n-Nonyl	110	$C_{42}H_{86}S_4O_8$	59.53	60.09	10.23	10.43	157–158	4.0	$C_{42}H_{86}S_4 \cdot 4HgCl_2$	27.94	27.72	4.80	5.15
n-Decyl	110	$C_{46}H_{94}S_4O_8$	61.15	60.85	10.49	10.40	155–156	4.0	$C_{46}H_{94}S_4 \cdot 4HgCl_2$	29.67	29.55	5.08	5.30
n-Undecyl	105	$C_{50}H_{102}S_4O_8$	62.58	62.57	10.71	10.92	154–155	4.0	$C_{50}H_{102}S_4 \cdot 4HgCl_2$	31.31	31.35	5.36	5.52
n-Dodecyl	93	$C_{54}H_{110}S_4O_8$	63.85	63.81	10.91	10.73	153–154	4.0	$C_{54}H_{110}S_4 \cdot 4HgCl_2$	32.85	32.36	5.61	5.76

[a] Dec. [b] After washing with alcoholic HCl: C, 16.59; H, 3.34. [c] After washing with alcoholic HCl: C, 20.95; H, 4.00.

methyl dimercaptol. This value decreases until it reaches the limiting value of four for the heptyl and subsequent dimercaptols.

The products derived from the butyl and hexyl dimercaptols were anomalous. Analysis of the compounds after washing with diethylcarbitol indicated an apparent coördination of 4.5 molecules of mercuric chloride per molecule, but treatment with alcoholic hydrochloric acid caused this value to become intermediate between 4.0 and 4.5. In view of the indefiniteness of the data, the authors can offer only a provisional statement regarding the constitution of these compounds The analyses and melting points of the addition compounds are collected in Table II.

Acknowledgment.—The authors are indebted to Dr. E. Emmet Reid for his advice and to Mr. Max Gergel of the Columbia Organic Chemicals Co., Columbia, S. C., for mercaptans used in the preparation of the dimercaptols.

Experimental

Tetrasulfones.—All tetrasulfones of this article may be prepared in approximately 30% yield by permanganate oxidation or by the use of acetic anhydride-catalyzed perhydrol. If the latter method is to be used, the directions described below should be followed rigorously. Simple addition of the reactants results in a violent reaction after an induction period of about thirty minutes.

2,2,5,5-Tetra-decylsulfonyl Hexane.—A 2.0-g. sample of *n*-decyl dimercaptol was mixed in a separatory funnel with 200 ml. of 4% $KMnO_4$, 3 ml. of 9 *M* H_2SO_4 and 5 ml. of glacial acetic acid. After heating to 60° on a water-bath the mixture was shaken vigorously for five minutes. On cooling, solid sodium bisulfite was added until the solution became clear. The product was extracted with three 50-ml. portions of chloroform and the solvent evaporated on the steam-bath. A repetition of the oxidation, extraction and evaporation followed by crystallization of the residue from ethanol yielded 0.6 g. of the tetrasulfone, m. p. 109–110°, yield, 26%.

2,2,5,5-Tetra-octylsulfonyl Hexane.—A mixture of 15 ml. of 30% perhydrol and 5 ml. of acetic anhydride was allowed to react until the temperature returned to 30°. A 1.8-g. sample of *n*-octyl dimercaptol was added under stirring whereupon the temperature rose gradually to 40°. This temperature was maintained by cooling until the initial reaction was completed. The solution was then warmed to 45° for ten minutes. On cooling, the solid was removed by filtration and crystallized from a 1:1 acetone–methanol solution; yield of product 0.6 g., or 28%; m. p. 117–118°.

This general procedure was modified for the members following the octyl dimercaptol. After the initial reaction had been completed, the mixture was warmed to 55° for completion of the reaction. At ten-minute intervals, the mixture was warmed to melt the products and reactants and was then permitted to cool to 55°. When successive heatings produced no change in melting point, the reaction was complete.

Mercuric Chloride Addition Compounds.—All dimercaptol mercuric chloride salts were prepared by the general method described below.

A 1.5-g. sample of *n*-octyl dimercaptol in 25 ml. of diethylcarbitol was mixed with a solution of 5 g. of mercuric chloride in 20 ml. of diethylcarbitol at 50°. The mixture was heated to effect solution of the initial precipitate and cooled. Filtration, followed by washing with two 5-ml. portions each of diethylcarbitol and ethanol resulted in 2.0 g. of product, m. p. 159–160°. Recrystallization from diethylcarbitol did not alter the melting point.

Great difficulty was encountered in attempts to crystallize the first six dimercaptol salts of the series. In these instances, the elevated temperatures necessary for solution resulted in decomposition. Hence occluded mercuric chloride was removed by washing with 30 ml. of 0.05 *M* hydrochloric acid in ethanol. Such treatment resulted in compounds of composition corresponding to integral numbers of mercuric chloride molecules per molecule of dimercaptol except for the butyl and hexyl dimercaptols.

Summary

1. The acetonylacetone dimercaptols of *n*-amyl, *n*-heptyl, *n*-nonyl and *n*-undecyl mercaptans have been prepared and characterized. These are new to the literature.

2. The tetrasulfones of the normal acetonylacetone dimercaptols, methyl through dodecyl, have been prepared and characterized. With the exception of the ethyl derivative, these are new to the literature.

3. Mercuric chloride forms coördination compounds with acetonylacetone dimercaptols. The extent of such addition is a function of the chain length.

GAINESVILLE, FLORIDA RECEIVED JUNE 3, 1949

[CONTRIBUTION NO. 261 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND COMPANY]

The Structure of Neoprene. III.[1] The Molecular Weight Distribution of Neoprene Type CG

BY W. E. MOCHEL AND J. B. NICHOLS

Neoprene Type CG and Neoprene Type GN are polychloroprenes made in essentially identical emulsion systems at 10 and 40°, respectively. They are both sulfur-modified polymers plasticized with tetraethylthiuram disulfide, but they differ markedly in physical properties, particularly with respect to rate of crystallization.[2] The polymer made at 10°, Neoprene Type CG, on standing at 25° hardens by crystallization in a few hours compared to days required for comparable changes in Neoprene Type GN. Furthermore,[2] Neoprene Type CG has greater plasticity than Neoprene Type GN and its vulcanizates show higher tensile strengths at 25 and 70°. These differences in physical properties have become well known since the introduction of Neoprene Type CG in 1941. It was of particular interest therefore in this study of the structure of neoprene to compare these polymers to obtain information about the structural features responsible for the differences in their properties.

Among the first constants desired in the characterization of any high polymer are the average molecular weight and the molecular weight distribution. That information is available for Neoprene Type GN[3] and the corresponding values are now reported for Neoprene Type CG. The same experimental methods, involving fractional precipitation from dilute benzene solution under controlled temperature conditions, and viscometric and osmometric examination of each fraction, were employed.[3] It is recognized that the fractionation method has certain deficiencies[4] but no clearly satisfactory substitute for general use has appeared.

Experimental

Materials.—A sample (55 g.) of standard, commercial Neoprene Type CG, approximately two months old, was cut into small pieces and dissolved in 500 ml. of thiophene-free, dry benzene. The polychloroprene was precipitated completely with methanol, washed twice with methanol and redissolved immediately in 500 ml. of benzene. After the addition of 0.5 g. of phenyl-α-naphthylamine the solution was diluted to 5 l. and a sample removed for determination of the constants of the original polymer. From the concentration of polymer in this solution it was calculated that 48.8 g. of purified polymer, free from soap residues and other contaminants, had been recovered for the fractionation.

Fractionation.—The fractionation was carried out by fractional precipitation from the approximately 1% solution in benzene, using methanol as the precipitant. Each sample was precipitated at 25° as described previously.[3] The first three fractions were not isolated as dry polymers since it was found that they became cross-linked and insoluble on drying.

Measurements.—Number average molecular weights in benzene solution were measured by means of static type osometers. For each sample, duplicate determinations made at each of four different concentrations were plotted as π/c *vs.* c and extrapolated to zero concentration, assuming a straight line relationship. Representative curves are given in Fig. 1.

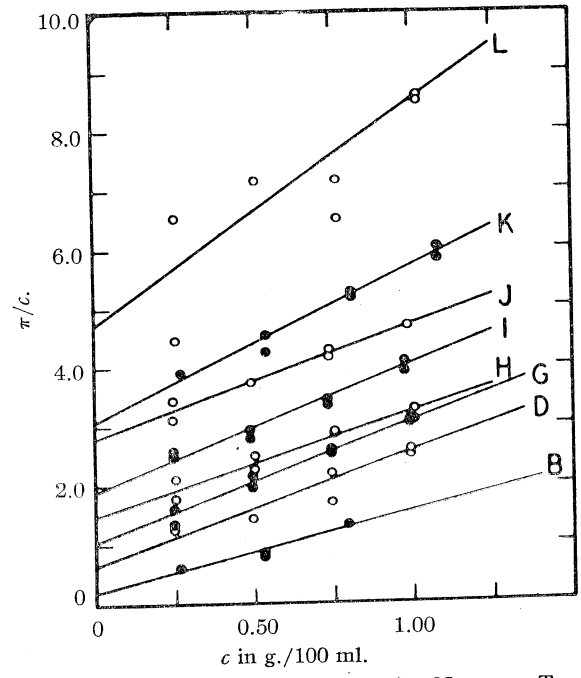

Fig. 1.—π/c *vs.* c curves for representative Neoprene Type CG fractions.

Viscosities were measured in benzene solution using an Ubbelohde suspended-level viscometer which had been modified by the substitution of a 50-ml. reservoir for the usual 5–10-ml. bulb. Dilutions were made directly in the viscometer and the viscosity measured at four different concentra-

(1) Part II, Mochel and Peterson, THIS JOURNAL, **71**, 1426 (1949).

(2) Walker and Mochel, *Proc. Inter. Rubber Tech. Conf.*, London, 1948, Preprint No. 11.

(3) Mochel, Nichols and Mighton, THIS JOURNAL, **70**, 2185 (1948).

(4) *Cf.* Bamford and Dewar, *Proc. Roy. Soc.* (*London*), **A192**, 329 (1948).

tions. The intrinsic viscosity and k' constants were then calculated by plotting reduced viscosity η_{sp}/c *vs.* c and applying the straight line equation, $\eta_{sp}/c = [\eta] + k'[\eta]^2 c$, developed by Huggins and others.[5] The experimental values are shown in Fig. 2. These procedures are described in greater detail in a previous publication.[3]

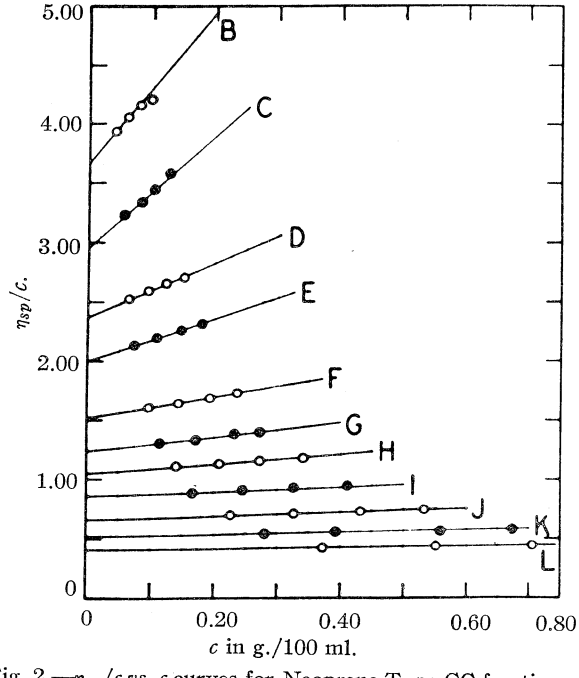

Fig. 2.—η_{sp}/c *vs.* c curves for Neoprene Type CG fractions.

Results and Discussions

The purified Neoprene Type CG was divided into 13 fractions having the properties given in Table I. The total weight of fractions isolated from the 48.8 g. of purified polymer used was 45.3 g. (93% recovery). It was assumed that the 7% loss that occurred had been uniformly distributed over all fractions and therefore the total weight of the isolated fractions was used in calculating that proportion of the whole each fraction constituted.

Fraction A, after precipitation, could not be redissolved in benzene even though the greatest care had been taken to avoid contact with air. Repetition of the experiment led to the same results, indicating that fraction A was probably inherently insoluble or very nearly so. The original whole polymer had been examined for gel content but was found to be completely soluble in benzene when tumbled with benzene and yielded only 0.6% gel when examined by a milder technique using the Baker cell.[6] However, a small amount of "microgel"[6] might well precipitate as a first fraction and carry down with it a small amount of soluble polymer in associated form, giving an insoluble product.

(5) Huggins, THIS JOURNAL, **64**, 2716 (1942); Schulz and Blaschke, *J. prakt. Chem.*, **158**, 130 (1941).

(6) Back, *Ind. Eng. Chem.*, **39**, 1339 (1947); Baker, *ibid.*, **41**, 511 (1949).

TABLE I

NEOPRENE TYPE CG FRACTIONS

Fraction	Weight, g.	%[a]	$\overline{M}_n$	B[b]	$[\eta]$	k'
Whole	(48.8)		168,000	2.02	1.56	0.60
A	3.00	6.6	gel	..	..	..
B	1.26	2.8	1,450,000 (?)	1.37	3.67	.47
C	1.86	4.1	579,000	1.67	2.96	.54
D	10.14	22.4	445,000	1.94	2.37	.41
E	2.04	4.5	362,000	1.86	2.00	.44
F	4.59	10.1	276,000	1.78	1.52	.37
G	4.60	10.2	276,000	2.07	1.23	.41
H	3.55	7.8	195,000	1.75	1.05	.38
I	4.16	9.2	153,000	2.10	0.86	.29
J	3.42	7.6	104,000	1.87	0.66	.35
K	2.60	5.7	93,400	2.62	.52	.31
L	2.10	4.6	61,400	3.75	.40	.33
Res.	2.0	4.4	.....	..	..	..
	45.32					

[a] Per cent. of total isolated in fractions. [b] Slope term of osmotic pressure equation.

Fraction B appeared to have a very high molecular weight but unfortunately the osmotic results for this fraction were scattered and a reliable molecular weight value was not obtained. Fraction D was larger than desirable for molecular weight distribution work; judging the amount of precipitant to add each time is one of the major problems of fractionation work. The molecular weight of fraction F or G is probably in error since it would not be expected that successive fractions would be identical. The number of fractions obtained was not as large as would be desired but it is believed that the general conclusions are valid. Reprecipitation of the fractions was not attempted since earlier work[3] had shown that the extra handling required for each fraction led to degradative changes which tended to nullify improvements in homogeneity.

The average molecular weight of whole Neoprene Type CG, 168,000, is considerably higher than that for Neoprene Type GN, 114,000, previously reported.[3] The calculated number average of the molecular weights of the individual fractions was 220,000, leaving out fraction A and the residue. This value is considerably higher than the measured value for the whole polymer due probably to the neglect of the residue. Assuming a reasonable molecular weight of 30,000 for the residue, the calculated number average would be 166,000. The molecular weight of fraction A would be high and would have little effect on the number average.

From the experimental values in Table I there is plotted the cumulative distribution curve of Fig. 3. From the smoothed curve there is calculated the differential molecular weight curve given in Fig. 4. Fifty per cent. of the Neoprene Type CG has a molecular weight above 250,000 compared to 165,000 for Neoprene Type GN. Also the maximum of the Type CG differential curve, *i. e.*, the

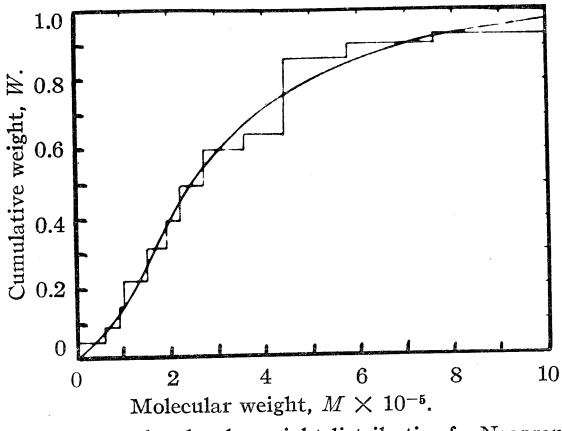

Fig. 3.—Integral molecular weight distribution for Neoprene Type CG.

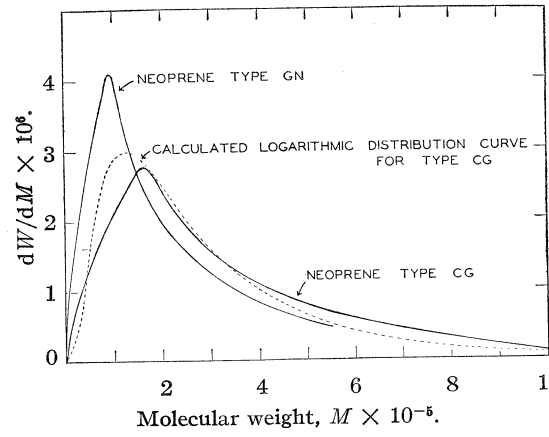

Fig. 4.—Differential molecular weight distribution curves for Neoprene Type CG and Neoprene Type GN. The logarithmic distribution curve (Type CG, calc.) was calculated by the method of Lansing and Kraemer.

most abundant species, is 160,000, compared to about 100,000 for Type GN. The molecular weight distribution curves for both polymers exhibit long extensions at the high molecular weight ends, believed to be due to the presence of soluble, branched and/or cross-linked material.[7] If the gelation of fraction A were due to cross-linking occurring after isolation, this extended tail on the molecular weight distribution curve should be decreased. However, it is believed, as stated before, that fraction A contained microgel and that the distribution curve as drawn is real.

A further difference between Neoprene Type CG and Type GN is that the maximum in the molecular weight distribution curve is not only at higher molecular weight for Type CG but the spread about this point is more uniform than in the case of Type GN. This uniformity is also shown by the lower value, $\beta = 1.12$, for the non-uniformity coefficient of Lansing and Kraemer[8] in contrast to the value, $\beta = 1.27$, reported for Neoprene Type GN[3] (Hevea rubber, $\beta = 0.70$). The logarithmic distribution curve calculated by the Lansing–Kraemer method is shown in Fig. 4 for comparison with the experimental curve. (For CG, $M_w/M_n = 316{,}000/168{,}000 = 1.88$, using the weight average molecular weight calculated from the fractions.)

From Table I it will be noted that the k' constants of the viscosity equations for the fractions of Neoprene Type CG are smaller than the value obtained for the whole polymer, in contrast to the results for Neoprene Type GN, where the fractions exhibited k' values as large or larger than that for the whole polymer.[3] It is believed that the reason for this difference in the case of Neoprene Type CG is that the whole polymer was not completely soluble but contained some microgel. Presumably, k' for fraction A would have been very high had it been possible to measure it. The k' constants for fractions B and C appeared to be slightly higher than average but the difference is not highly significant statistically because of the wide variations in k' constants for the other fractions. Assuming that this difference is real, it appears that fractions A, B and C, which constitute 13.5% of the total, are branched or cross-linked appreciably more than the rest of the polymer. Comparable fractions in Neoprene Type GN made up 25.2% of the total. These figures, however, should not be construed to be the actual percentages of branched or cross-linked material in either polymer. No evidence of micro gel was detected in GN, perhaps because of the lower molecular weight of the latter polymer. It will be noted that B, the osmotic slope term, is lower for fractions B and C than for the remainder. This can be due either to poorer solutions or to higher molecular weights and our evidence cannot distinguish between the two effects. B also shows a definite upward trend with decreasing molecular weight.[9] The k' values for fractions of Neoprene Type CG showed a significant correlation with the intrinsic viscosities (correlation coefficient = 0.787) even when the high values for fractions B and C were omitted. No such correlation was found for Neoprene Type GN.

A straight line relationship between number average molecular weights and intrinsic viscosities for fraction C to L, inclusive, is shown in Fig. 5. The equation for this line is $\log M = 5.2529 + 1.119 \log [\eta]$ or $M = 1.79 \times 10^5 [\eta]^{1.12}$. This may be rearranged into the more usual form $[\eta] = KM^a$ where K is 2.02×10^{-5} and a is 0.89. Agreement of most of the fractions with this relationship is seen to be very good; only B was in serious error and the osmotic value for B was dependent upon only four points in poor agreement. The significance of the high value for the exponent a is not fully understood. Note that the values of K and a for Neoprene Type GN are, respectively, 1.46×10^{-4} and 0.73 when calculated similarly.

(7) Valyi, Janssen and Mark, *J. Phys. Chem.*, **49**, 461 (1945).
(8) Lansing and Kraemer, THIS JOURNAL, **57**, 1369 (1935).
(9) *Cf.* Doty and Mark, *Ind. Eng. Chem.*, **38**, 682 (1946).

Statistical analysis has shown that there is less than one chance in a thousand that the exponents for Neoprene Type CG and Type GN are different because of experimental error alone.

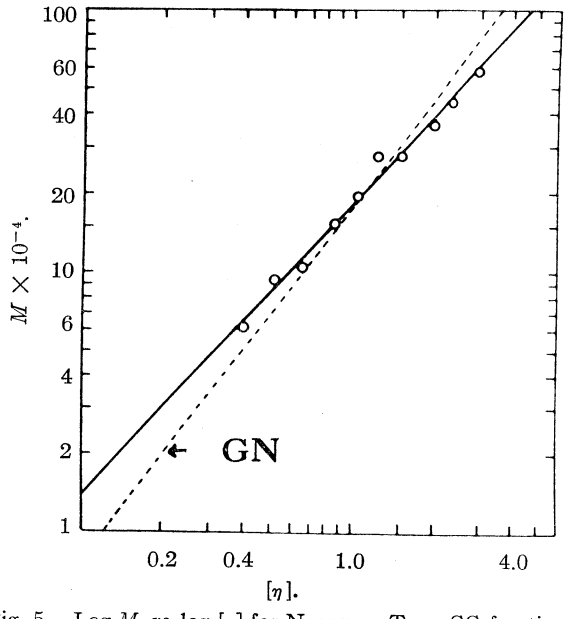

Fig. 5.—Log M_n *vs.* log $[\eta]$ for Neoprene Type CG fractions (GN, neoprene type GN).

The higher value of a for Neoprene Type CG than for Type GN would appear to indicate that the former polymer has less flexible molecules than has GN[10] or that the shielding effect is smaller,[11] due perhaps to greater intermolecular attraction. This exponent a was observed to *increase* with increasing polymerization temperature in the case of styrene,[12] a situation the opposite of that reported here for neoprene, and the results have been interpreted in terms of poorer symmetry, of a stereochemical type, in polystyrene made at high temperatures.[13] The change in a for neoprene may be reversed because of much greater interchain attractive forces, as evidenced by its tendency to crystallize. Certainly poorer symmetry would not be expected in Neoprene Type CG. An attempt to measure association of Neoprene Type CG in benzene solution by determination of intrinsic viscosities at 25 and 50° gave values whose ratio varied from 0.90 to 0.97. These are the same as observed for Type GN and as reported for polychloroprene of a different origin.[14] Whatever the explanation for the difference in values for a, it is evident that there must be a structural difference between Neoprene Type CG and Type GN, quite apart from the differences in molecular weight and molecular weight distribution.

Acknowledgments.—The authors gratefully acknowledge the aid and encouragement of Drs. B. C. Pratt, G. D. Patterson and D. M. McQueen and the assistance of Miss B. L. Price in the osmotic pressure measurements described in this research. Thanks for many helpful discussions go to Professor F. T. Wall, of the University of Illinois, and to Drs. H. W. Walker and M. A. Youker, of the Organic Chemicals Department of this Company.

Summary

The low temperature polychloroprene rubber, Neoprene Type CG, has been fractionated by partial precipitation from dilute solution and the fractions examined both osmotically and viscometrically in benzene solutions. The molecular weight distribution curve for Neoprene Type CG based on osmotic pressure measurements shows a pronounced maximum at 160,000 molecular weight compared to 100,000 for Neoprene Type GN and the curve has a more uniform distribution about the maximum value. Neoprene Type CG whole polymer has a higher number average molecular weight than GN, 168,000 *vs.* 114,000.

Calibration of the intrinsic viscosity–molecular weight relationship by osmotic pressure measurements gave good agreement with the equation $[\eta] = KM^a$ where $K = 2.02 \times 10^{-5}$ and $a = 0.89$. The exponent a, which is generally considered to be related to the flexibility of the molecules in solution, indicates that the molecules of Neoprene Type CG are less flexible or have greater intermolecular attraction than those of GN. It is clear therefore that there is a structural difference between these two polymers in addition to the observed differences in average molecular weight and molecular distribution.

WILMINGTON 98, DEL. RECEIVED FEBRUARY 11, 1949

(10) *Cf.* Huggins, *Ind. Eng. Chem.*, **35**, 980 (1943); Simha, *J. Chem. Phys.*, **13**, 188 (1945).

(11) Debye, *ibid.*, **14**, 636 (1946); Debye and Bueche, *ibid.*, **16**, 573 (1948).

(12) Alfrey, Bartovics and Mark, THIS JOURNAL, **65**, 2319 (1943). Values for k' of polystyrenes decreased as the polymerization temperature was raised; similarly k' of the neoprene made at 10° appears to be higher than that of the polymer made at 40°.

(13) Huggins, *ibid.*, **66**, 1991 (1944).

(14) Staudinger and Staudinger, *J. prakt. Chem.*, **162**, 148 (1943).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF POLAROID CORPORATION]

α,β,β-Trifluorostyrene and α-Chloro-β,β-difluorostyrene[1]

BY SAUL G. COHEN, HENRY T. WOLOSINSKI AND PAUL J. SCHEUER[1a]

Consideration of the useful properties of the polymers of tetrafluoroethylene, $CF_2=CF_2$,[1b] and chloro trifluoroethylene, $CF_2=CFCl$,[2] has indicated to us the desirability of preparing and studying the phenyl derivatives of these compounds. There are now in the literature several references to styrenes which contain fluorine or trifluoromethyl substituents in the benzene ring,[3] but apparently only one reference to a phenylperchlorofluoroethylene[4] and that to a monofluorodichlorostyrene with its exact structure unspecified. Recently an unsuccessful attempt to prepare β-fluorostyrene has been reported.[5] In this paper, we are reporting the preparation of α,β,β-trifluorostyrene, $C_6H_5CF=CF_2$ (I) and α-chloro-β,β-difluorostyrene, $C_6H_5CCl=CF_2$ (II).

In the course of this work, chlorodifluoroacetophenone, $C_6H_5COCClF_2$, trifluoroacetophenone, $C_6H_5COCF_3$, and difluoroacetophenone, $C_6H_5COCHF_2$ were prepared by the Friedel–Crafts reactions of the corresponding acid chlorides with benzene in the presence of aluminum chloride.

$$CX_3C(=O)-Cl + C_6H_6 \xrightarrow[CS_2]{AlCl_3} C_6H_5COCX_3 + HCl$$

Trifluoroacetyl chloride[6] and monofluoroacetyl chloride[5,7] have been used in this type of reaction, while treatment of benzene with chlorofluorocarbons and aluminum chloride has been unsuccessful.[8] Optimum conditions for carrying out this Friedel–Crafts reaction are described under the preparation of trifluoroacetophenone. Single attempts to prepare this compound by treatment of diphenylcadmium with trifluoroacetyl chloride[9] and by the Friedel–Crafts reaction of trifluoroacetic acid and benzene failed.

Each of the three ketones was converted to the corresponding dichloride by reaction with phosphorus pentachloride, leading to the compounds $C_6H_5CCl_2CClF_2$, (IV) $C_6H_5CCl_2CF_3$,[6] (V) and $C_6H_5CCl_2CHF_2$.

$$C_6H_5COCX_3 + PCl_5 \longrightarrow C_6H_5CCl_2CX_3 + POCl_3$$

Use of 50 mole per cent.[6] excess phosphorus pentachloride and long heating under reflux was found desirable. Removal of the excess phosphorus pentachloride, whether by filtration or washing,[6] was inconvenient and either was incomplete or led to diminished yields. Treatment of the reaction mixture with a quantity of acetone equivalent to the excess phosphorus pentachloride converted it to phosphorus oxychloride, from which the desired products were readily separated and isolated in 85–90% yield. This greatly facilitated our preparation of compounds IV and V.

The compounds IV and V, $C_6H_5CCl_2CClF_2$ and $C_6H_5CCl_2CF_3$, were each treated with one-third mole of antimony trifluoride and catalytic quantities of bromine at 140–170°.

$$C_6H_5CCl_2CX_3 + {}^1/_3SbF_3 \xrightarrow{Br_2} C_6H_5CClFCX_3 + {}^1/_3SbCl_3$$

The products were mixtures which appeared to contain both starting materials and the products of replacement of two chlorine atoms by fluorine as well as the desired products of replacements of one chlorine atom by fluorine, $C_6H_5CClFCClF_2$ (VI) and $C_6H_5CClFCF_3$[10] (VII). The latter compounds were isolated in about 35% yield.

The desired α,β,β-trifluorostyrene (I) and α-chloro-β,β-difluorostyrene (II) were prepared by the zinc dechlorination of the corresponding pentahaloethylbenzenes.

$$C_6H_5CClFCClF_2 + Zn \xrightarrow[\text{ethanol}]{\text{absolute}} C_6H_5CF=CF_2\ (I) + ZnCl_2$$

$$C_6H_5CCl_2CClF_2 + Zn \xrightarrow[\text{ether}]{\text{anhydrous}} C_6H_5CCl=CF_2\ (II) + ZnCl_2$$

α,β,β-Trifluorostyrene (I) was obtained in 48% yield, b. p. 68–69° (75 mm.), $n^{20}D$ 1.4741, m. p. −23.0 to −22°. Its formation in this way supplies evidence for the assigned structure of the intermediate, $C_6H_5CClFCClF_2$. α-Chloro-β,β-difluorostyrene (II) was obtained in 70% yield, b. p. 100° (100 mm.), $n^{20}D$ 1.5080.

Acknowledgment.—The authors wish to acknowledge helpful discussions with Dr. E. R. Blout.

Experimental

Sodium trifluoroacetate was obtained from the Hooker Electrochemical Company. **Sodium difluoromonochloroacetate** was obtained from Columbia Organic Chemicals, Inc.

Barium difluoroacetate and **sodium difluoroacetate** were prepared in 37% yield and 28% yield, respectively, by oxidation of 1,2-dichloro-3,3-difluoro-1-propene by a procedure similar to that described for the oxidation of the

(1) This work was sponsored by the Signal Corps, Department of the Army, and A. M. C., Electronics Subdivision, U. S. Air Force.

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(1b) Renfrew and Lewis, *Ind. Eng. Chem.*, **38**, 870 (1946).

(2) Anonymous, *Modern Plastics*, **26**, 168 (1948).

(3) Bachman and Lewis, THIS JOURNAL, **69**, 2022 (1947); Brooks, *ibid.*, **66**, 1295 (1944); Renoll, *ibid.*, **68**, 1159 (1946); Brooks and Nazzewski, U. S. Patent 2,406,319.

(4) Weinmayr, U. S. Pat. 2,398,483.

(5) Truce and Sack, THIS JOURNAL, **70**, 3959 (1948).

(6) Simons and Ramler, *ibid.*, **65**, 389 (1943).

(7) Gryszkiewicz-Trochimowski, Sporzynski and Wnuk, *Rec. trav. chem.*, **66**, 419 (1947).

(8) Henne and Newman, THIS JOURNAL, **60**, 1697 (1938).

(9) Jones, *ibid.*, **70**, 143 (1948).

(10) Simons and Herman, *ibid.*, **65**, 2064 (1943).

isomeric 1,1-dichloro-3,3-difluoro-1-propene.[11] 1,2-Dichloro-3,3-difluoro-1-propene was obtained from Halogen Chemicals, Inc.

Chlorodifluoroacetyl chloride was prepared by the interaction of sodium chlorodifluoroacetate (0.65 mole) and phosphorus trichloride (0.59 mole) for 2.5 hours at 100° under reflux. The product was distilled out, 77.5 g., (80% yield) boiling under 40°. A sample was converted to the amide, m. p. 76.5°. This chloride has been prepared by the chlorination of difluoroethanol,[12] b. p. 34°.

Trifluoroacetyl chloride[6] was prepared in 90% yield by the interaction of sodium trifluoroacetate (1.24 mole) and phosphorus oxychloride (1.83 moles) for twenty-one hours at 100° under reflux, the product condensing in a dry ice trap. A sample was converted to the amide, m. p. 74–75°.

Difluoroacetyl chloride was prepared by interaction of sodium difluoroacetate (0.312 mole) and phosphorus trichloride (0.69 mole) under reflux for twenty-one hours. The product boiled at 32–35°, 69% yield. The reported boiling point is 25°.[13]

α,α,α-Trifluoroacetophenone.[6]—Trifluoroacetyl chloride (180 g., 1.35 moles) was distilled over a period of four hours into a well stirred, cooled suspension of aluminum chloride (1.60 moles) in benzene (1.60 moles) and carbon disulfide (490 cc.). The reaction started at 10°, was run at 2–3°, and finally at room temperature for a short time. The complex was decomposed in 335 cc. of concentrated hydrochloric acid and 1900 g. of ice. The organic layer was separated, and the aqueous layer was extracted with ether. The extracts were combined, filtered free from a black precipitate which was then further extracted. The extracts were dried and distilled, leading to trifluoroacetophenone, 150.6 g., 64% yield, b. p. 66–67° (37 mm.), $n^{20}D$ 1.4576.

α,α,α-Difluorochloroacetophenone was prepared similarly, 68% yield, b. p. 95–97° (37 mm.), $n^{20}D$ 1.4954. *Anal.* Calcd. for $C_8H_5OClF_2$: Cl, 18.6. Found: Cl, 18.2. This compound has been obtained in 8% yield in the fluorination of trichloroacetophenone.[10]

α,α-Difluoroacetophenone was prepared, 58% yield, b. p. 84–87° (26–27 mm.), in a standard Friedel–Crafts procedure in carbon disulfide at 10°. This compound has been prepared by the fluorination of acetophenone and the fluorination of dibromoacetophenone.[10]

α,α-Dichloro-β,β,β-trifluoroethylbenzene, $C_6H_5CCl_2CF_3$.[6]—Trifluoroacetophenone (25 g., 0.14 mole) and phosphorus pentachloride (44 g., 0.21 mole) were heated under reflux for twenty-one hours, oil-bath temperature, 175°. Acetone (4.1 g., 0.07 mole) was added to the cooled reaction mixture, and, after the vigor of the ensuing reaction subsided, the product was fractionated and the desired material was obtained, 29 g., 90% yield, b. p. 88–90° (37 mm.), $n^{20}D$ 1.4767. *Anal.* Calcd. for $C_8H_5Cl_2F_3$: Cl, 31.0. Found: Cl, 31.5.

α,α,β-Trichloro-β,β-difluoroethylbenzene, $C_6H_5CCl_2CClF_2$, was prepared similarly from difluorochloroacetophenone, 78% yield, b. p. 98–99° (15 mm.), $n^{20}D$ 1.5106. *Anal.* Calcd. for $C_8H_5Cl_3F_2$: Cl, 43.5. Found: Cl, 42.4.

α,α-Dichloro-β,β-difluoroethylbenzene, $C_6H_5CCl_2CF_2H$, was prepared similarly except that excess phosphorus pentachloride was removed by repeated filtration. The product was obtained in about 70% yield, fuming liquid, b. p. 96–97° (26–27 mm.), $n^{30}D$ 1.5046.

α-Chloro-α,β,β,β-tetrafluoroethylbenzene, $C_6H_5CClFCF_3$.[10]—α,α-Dichloro-β,β,β-trifluoroethylbenzene was treated with one-third mole of antimony trifluoride and 10 mole per cent. of bromine at 150–170° for two hours with stirring. The product was cooled, washed, dried and distilled. Redistillation of the middle fraction, which boiled at 84–109° (100 mm.), led to the product, 35% yield, b. p. 85–86° (100 mm.), $n^{20}D$ 1.4463. *Anal.* Calcd. for $C_8H_5ClF_4$: Cl, 16.7. Found: Cl, 16.0.

α,β-Dichloro-α,β,β-trifluoroethylbenzene, $C_6H_5CFClCF_2Cl$.—α,α,β-Trichloro-β,β-difluoroethylbenzene, $C_6H_5CCl_2CClF_2$ (51 g. 0.21 mole), antimony trifluoride (12.5 g., 0.070 mole) and bromine (0.56 g., 0.0035 mole) were heated under reflux with stirring for one hour at 140°. The product was taken up in ether, washed dried and distilled. The desired product was obtained, 17.8 g., 37% yield, b. p. 92–94° (38 mm.), $n^{20}D$ 1.4766. *Anal.* Calcd. for $C_8H_5Cl_2F_3$: Cl, 30.8. Found: Cl, 30.3. Some starting material was recovered, 10.5 g., b. p. 101° (16–17 mm.), $n^{25.4}D$ 1.5075.

α-Chloro-β,β-difluorostyrene, $C_6H_5CCl{=}CF_2$.—α,α,β-Trichloro-β,β-difluoroethylbenzene (20 g., 0.081 mole) was treated with acid-washed zinc dust (5.55 g., 0.0854 mole) and one crystal of dried zinc chloride in 20 g. of anhydrous ether with stirring, under reflux. The solution was decanted from the residual zinc (0.014 g.), washed with dilute hydrochloric acid and water, dried and distilled through a 36″ wire spiral column at 10/1 reflux ratio. The product was obtained, 9.9 g., 70% yield, b. p. 100–100.5° (100 mm.), $n^{20}D$ 1.5080. *Anal.* Calcd. for $C_8H_5ClF_2$: C, 55.0; H, 2.9; Cl, 20.3; F, 21.7. Found: C, 54.8; H, 3.0; Cl, 20.1; F, 21.8, 22.3.

α,β,β-Trifluorostyrene, $C_2H_5CF{=}CF_2$.—α,β-Dichloro-α,β,β-trifluoroethylbenzene (12.9 g., 0.056 mole), acid washed zinc (3.8 g., 0.059 mole) and a few crystals of dried zinc chloride in 15 cc. of absolute ethanol were boiled under reflux for two hours with occasional shaking. The solution was decanted from residual solid (0.37 g.), washed with 10% hydrochloric acid and water, dried and distilled. The product was obtained, 4.3 g., 48% yield, b. p. 68–70° (75 mm.), m. p. −23 to −22°, $n^{20}D$ 1.4741. *Anal.* Calcd. for $C_8H_5F_3$: C, 60.8; H, 3.2; F, 36.0. Found: C, 60.7; H, 3.2; F, 35.7. This material appeared to contain about 0.4% Cl. Treatment with zinc at 120° for one hour and redistillation from the zinc led to a product which contained less than 0.2% Cl.

Summary

α,β,β-Trifluorostyrene, $C_6H_5CF_2{=}CF_2$, and α-chloro-β,β-difluorostyrene, $C_6H_5CCl{=}CF_2$ have been prepared by the dechlorination of α,β-dichloro-α,β,β-trifluoroethylbenzene, $C_6H_5CClFCClF_2$, and α,α,β-trichloro-β-β-difluoroethylbenzene, $C_6H_5CCl_2CClF_2$, respectively.

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(11) A. L. Henne, T. Alderson and M. S. Newman, *ibid.*, **67**, 918 (1945).

(12) Swarts, *Mém. couronnés acad. roy. Belg.*, 51 (1895).

(13) Swarts, *Chem. Centr.*, **7**, II, 710 (1903).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH AND FROM MELLON INSTITUTE]

The Infrared Spectra of a Number of Isomeric Normal Acetylenic Compounds

BY JOHN H. WOTIZ[1] AND FOIL A. MILLER[2]

This paper presents the infrared spectra of twenty-eight straight chain heptynes, heptynyl alcohols, halides, nitriles and *n*-octynoic methyl esters. Most of these compounds have recently been prepared for the first time.[3] Table I provides a list of the compounds and their numbering.

Measurement of the Spectra.—The spectrum of I is available in the A. P. I. catalog of infrared spectrograms,[7] and is not presented here. The spectra of all the other compounds were measured on a Beckman IR-2 infrared spectrometer in the Spectrographic Laboratory of the Department of Chemistry at The Ohio State University. The range 2–15 μ was covered with a sodium chloride prism. Samples were studied as liquids in cells 0.025, 0.10 or 0.40 mm. thick. The spectra are shown graphically in Figs. 1 and 2.

The Raman spectra of II,[8,9] III[10] and XXXIII[8] have been reported earlier. They provide values for the bands above 2000 cm.$^{-1}$ which are higher than ours by 20–40 cm.$^{-1}$. This is probably due to the poor dispersion of rocksalt in this region, and the Raman values are to be preferred.

TABLE I

A. NUMBERING OF THE COMPOUNDS DISCUSSED IN THIS PAPER; B. POSITION (IN CM.$^{-1}$) AND INTENSITY[a] OF THE C≡C BAND

vw = very weak, w = weak, m = medium, s = strong, vs = very strong.

Hydrocarbon skeleton	No.	—H Posn.	I	No.	—Cl Posn.	I	No.	—Br Posn.	I
$CH_3-(CH_2)_6-$	I	..	...	...	..	...	VIII	..	...
$H-C\equiv C-(CH_2)_5-$	II	2100	m	...	..	...	IX	2100	m
$CH_3-C\equiv C-(CH_2)_4-$	III	2210	vw	V	Missing[b]	...	X	2200	vw
$C_2H_5-C\equiv C-(CH_2)_3-$	IV	2190	vw	VI	2240	vw	..	..	...
n-$C_3H_7-C\equiv C-(CH_2)_2-$	IV	2190	vw	...	..	...	XI	2220	w
n-$C_4H_9-C\equiv C-CH_2-$	III	2210	vw	VII	2240	s	XII	2220	s
n-$C_5H_{11}-C\equiv C-$	II	2100	m	...	..	...	XIII	2110	w
		—OH			—CN			—$COOCH_3$	
$CH_3-(CH_2)_6-$	XIV	..	...	XX	..	..	XXVII	..	..
$H-C\equiv C-(CH_2)_5-$	XV	2140	m	XXI	2120	m	XXVIII	2120	m
$CH_3-C\equiv C(CH_2)_4-$	XVI	Missing[b]	...	XXII	Missing[b]	..	XXIX	Missing[b]	
$C_2H_5-C\equiv C-(CH_2)_3-$	XVII	2260	vw	XXIII	Missing		XXX	Missing[b]	
n-$C_3H_7-C\equiv C-(CH_2)_2-$	XVIII	2210	w	XXIV	Missing		XXXI	Missing	
n-$C_4H_9-C\equiv C-CH_2-$	XIX	2240	s	XXV	2220	s	XXXII	2240	w
n-$C_5H_{11}-C\equiv C-$	....	..	..	XXVI	2120	w	XXXIII	2210	vs

[a] In estimating intensities, an attempt was made to correct for the effect of the different cell thicknesses. [b] There is a weak or very weak band in the range 2070–2050 cm.$^{-1}$, but this is inordinately low for a C≡C band and probably belongs to a combination tone.

Experimental

Preparation of the Compounds.—The preparation and physical properties of most of these compounds are given in the paper by Newman and Wotiz.[3] The remaining compounds were prepared according to the references cited below. Some physical constants of the infrared-analyzed samples are compared with those in the references: **II**[4]: b. p. 100° (760 mm.), obs. 97° (745 mm.); $n^{20}D$ 1.4088, obs. 1.4038 (25°); **III**[5]: b. p. 107–111° (750 mm.), obs. 109° (721 mm.); $n^{25}D$ 1.4220, obs. 1.4199; **IV**[4]: b. p. 106–107° (?),[6] obs. 104° (748 mm.); $n^{25}D$ 1.415,[6] obs. 1.4165; **V**[3]: The original sample was found to contain the H—C≡ band at 3270 cm.$^{-1}$, indicating some isomerization during its preparation. The impurity was removed by making a mercury complex. **X**[3]: impure; contained $Br-(CH_2)_5-Br$. The curve is included because the spectrum of the impurity will add nothing new to the spectrum of X above 1000 cm.$^{-1}$; **XII**[3]: b. p. 84° (20 mm.), obs. 54° (4 mm.); $n^{25}D$ 1.4878, obs. 1.4844.

Anal. Calcd. for $C_7H_{11}Br$: C, 48.0; H, 6.3; Br, 45.6. Found: C, 48.5; H, 6.2; Br, 45.6.

Discussion of Results

A number of the observed bands can be attributed immediately to various structural groups in the molecule. These bands occur in their expected positions so that no discussion is needed.[11] We shall therefore confine our remarks to two topics: the intensity and position of the C≡C band,

(1) Department of Chemistry, University of Pittsburgh, Pittsburgh, Pa.

(2) Department of Research in Chemical Physics, Mellon Institute, Pittsburgh, Pa.

(3) Newman and Wotiz, THIS JOURNAL, **71**, 1292 (1949).

(4) Henne and Greenlee, *ibid.*, **67**, 484 (1945).

(5) Vaughn, Hennion, Vogt and Nieuwland, *J. Org. Chem.*, **3**, 1 (1937).

(6) "Handbook of Chemistry and Physics," 29th ed., 1945, p. 816.

(7) American Petroleum Institute Research Project 44, National Bureau of Standards, Washington, D. C.; curve 637.

(8) M. Bourgel and P. Daure, *Bull. soc. chim.*, **47**, 1349 (1930).

(9) M. J. Murray and F. F. Cleveland, THIS JOURNAL, **63**, 1718 (1941).

(10) B. Gredy, *Ann. chim.*, [XI] **4**, 5 (1935).

(11) See, for example, Barnes, Gore, Stafford and Williams, *Anal. Chem.*, **20**, 402 (1948).

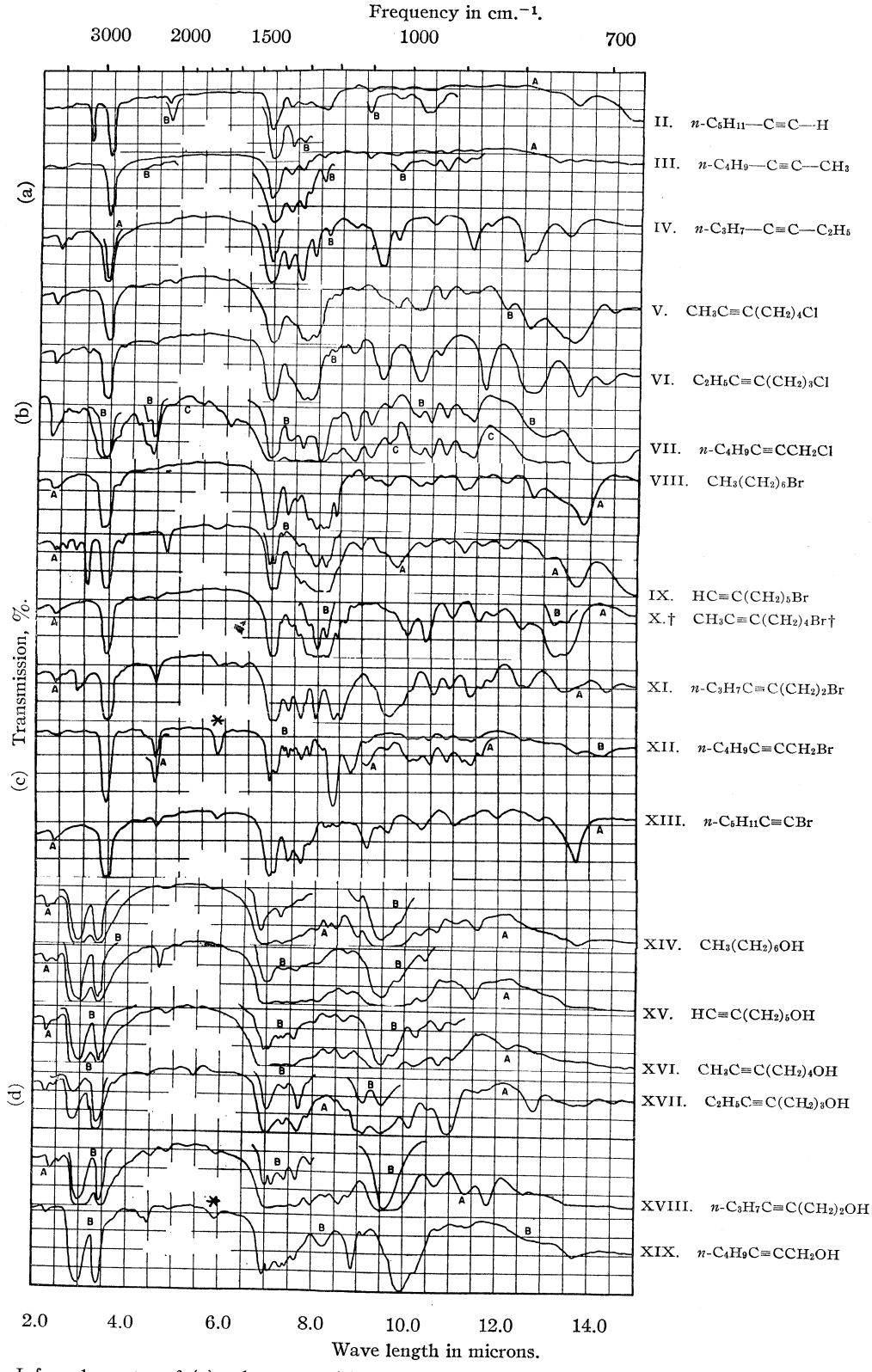

Fig. 1.—Infrared spectra of (a) *n*-heptynes, (b) *n*-heptynyl chlorides, (c) *n*-heptynyl bromides and (d) *n*-heptynyl alcohols: cell thicknesses, curves II–VII, A = 0.025 mm., B = 0.10 mm., C = 0.40 mm.; curves VIII–XIX, A = 0.10 mm., B = 0.025 mm. * See discussion of anomalous bands. † Sample impure. See "Experimental."

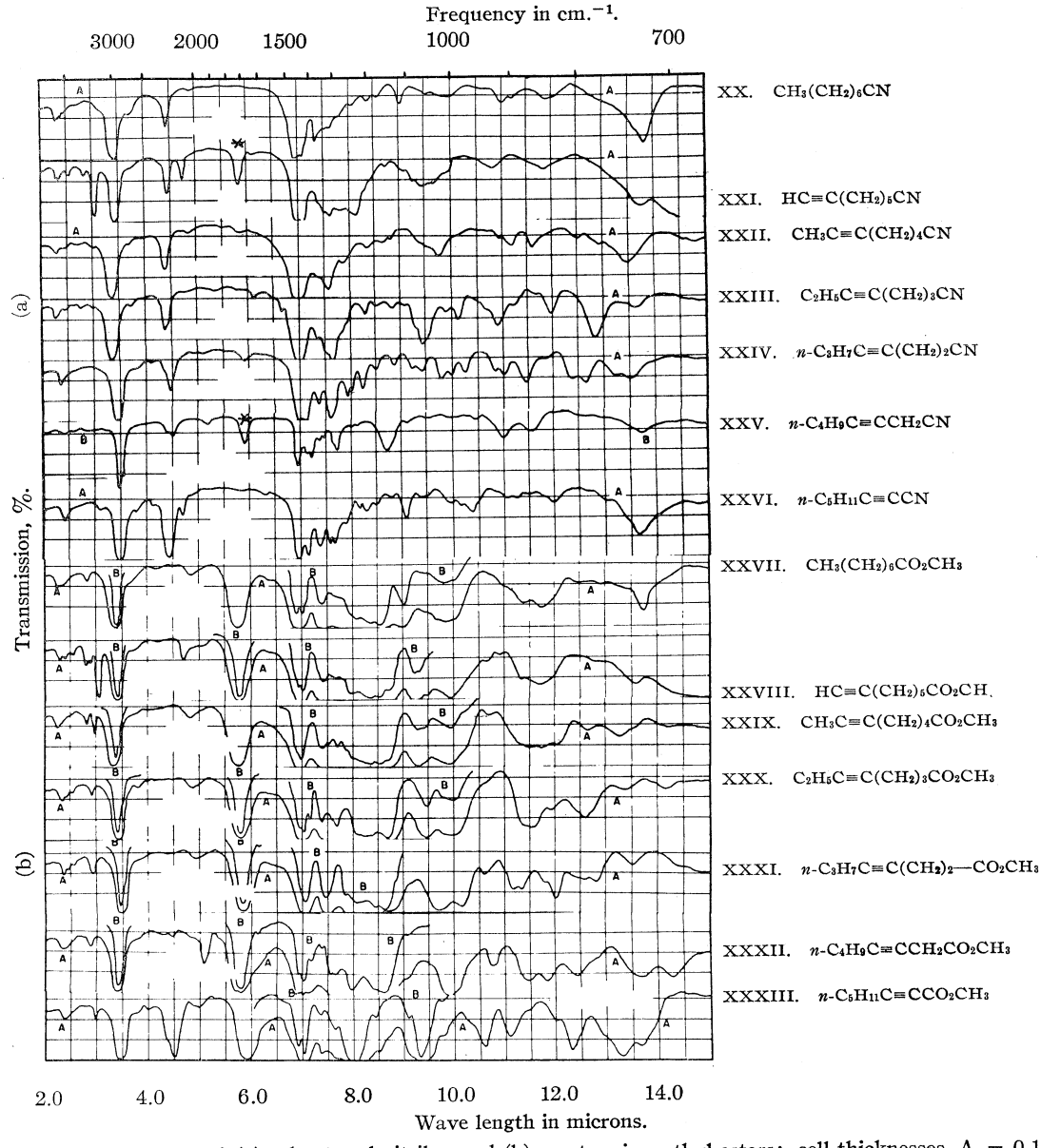

Fig. 2.—Infrared spectra of (a) *n*-heptynyl nitriles, and (b) *n*-octynoic methyl esters: cell thicknesses, A = 0.10 mm., B = 0.025 mm. * See discussion of anomalous bands.

and the presence of some anomalous bands in several of the spectra.

C≡C Band.—One of the interesting features of these spectra is the variable intensity of the C≡C band at 2100–2240 cm.$^{-1}$. In the infrared this intensity is appreciable only if the triple bond is near either end of the chain. As it is moved toward the center of the chain the corresponding band weakens and virtually disappears. This is shown in detail in Table I. The only exceptions occur in the bromide and nitrile series, where the band is more intense for *n*-C_4H_9—C≡C—CH_2— than for *n*-C_5H_{11}—C≡C—. The reason for these two exceptions is not apparent to us, but the explanation of the general behavior seems fairly simple. As the triple bond is moved toward the interior of the molecule, the change in the dipole moment during the valence vibration of the triple bond diminishes. Since (classically) the intensity of infrared absorption is proportional to the square of the rate of change of the dipole moment,[12] the intensity rapidly decreases. It is as though a pseudo center of symmetry were produced at the center of the triple bond. The stretching of the triple bond is symmetric toward this pseudo symmetry center, and so the vibration is inactive in the infrared. It is evident, then, that the infrared spectrum is not an infallible test for the absence

(12) Herzberg, "Infrared and Raman Spectra," D. Van Nostrand Co., Inc., New York, N. Y., 1945, p. 240.

of a triple bond even when the geometric symmetry is so low that there are no formal selection rules.[13]

A similar effect is known in the infrared spectra of olefinic compounds, where the C=C frequency is notorious for its variable intensity. For example, Kletz and Summer[14] have shown that the strength of this band in octenes decreases as the symmetry of substitution about the double bond increases. They explained these results in essentially the same way. It is not unexpected to find that Cl, Br, OH, CN and $COOCH_3$ are all much more effective than alkyl groups in enhancing the intensity of the C≡C band when substituted nearby.

The position of the C≡C band depends upon the number of substituents. For the series H—C≡C—R the band is at 2100–2140 cm.$^{-1}$; for R′—C≡C—R″ it is at 2190–2260 cm^{-1}.[15] This is known, through studies of the Raman spectra, to be a general result for acetylenic compounds.[16,17] It is interesting to note that this holds even when R equals Br (XIII). The Raman work has also shown that the compounds H—C≡C—R have a single line in the C≡C region, whereas in the series R′—C≡C—R″ there are two or more lines in this region, the "extra" ones being due to overtones or combination tones whose intensity has been enhanced by resonance with the fundamental. These same frequencies are observed in the infrared for those disubstituted acetylenes possessing a C≡C band of good intensity. In some cases these satellite bands appear only as weak inflections or shoulders on the C≡C band. Several of these spectra were redetermined on a Baird double-beam spectrometer, and the bands were then clearly resolved.

It is well known that the group ≡C—H has a stretching frequency of about 3270 cm.$^{-1}$. It is therefore simple to distinguish between a monosubstituted and a disubstituted acetylene from the position of either the C—H or the C≡C stretching frequency as follows[18]

	≡C—H	C≡C
H—C≡C—R	3270	2100–2140
R′—C≡C—R″	..	2190–2260 (plus nearby satellites)

Anomalous Bands.—Several of the spectra exhibit unexpected bands that warrant mention. For example, all the esters have some absorption at 3350–3500 cm.$^{-1}$, which may indicate a small amount of free acid. The strong band of XXXII at 1960 cm.$^{-1}$ is probably a combination tone; its intensity is partially illusory because the sample was much too thick.

Some of the nitriles seem to contain a carbonyl impurity. Compound XXI, for example, has a strong band at 1720 cm.$^{-1}$. Another sample was later prepared by an entirely different method—dehydration of the corresponding amide—and the carbonyl band was then much weakened.

The series n-C_4H_9—C≡CH_2— also contains evidence of a carbonyl group in the band at 1650–1710 cm.$^{-1}$, which ranges in intensity from very weak to strong. However, the existence of a carbonyl-containing impurity is open to question. The conversion of XII into XXV was done in the absence of an oxygen-containing reagent and solvent, and yet the "carbonyl" band has maintained its intensity in spite of an appreciable difference in physical properties of the two compounds and the resulting ease of separating them. Furthermore no evidence for an aldehyde or ketone could be found in the ultraviolet spectrum of bromide XII.[19] (This is admittedly not as sensitive a test as the infrared spectrum, however.) One must therefore consider the possibility that this band may be characteristic of compounds where the functional group is removed from the acetylenic linkage by one methylene group. A further investigation of such compounds is under way to determine whether this band is due to an impurity (perhaps an azeotropic mixture), or whether it is indeed characteristic of this type of molecule. If the latter proves to be true, it will be a surprising result.

Acknowledgment.—One of us (J. H. W.) wishes to express his gratitude to Dr. M. S. Newman of The Ohio State University for his aid in the synthesis of the compounds, and for his permission to publish this work in the present form. We are indebted to Mrs. Shirley Forgerson and Dr. Edward Pickett of the Department of Chemistry, The Ohio State University, for determining the infrared spectra.

Summary

The infrared spectra of twenty-eight normal acetylenic compounds and four substituted normal heptanes are presented. The intensity of the C≡C band is observed to vary greatly. The band is most intense when the triple bond is near the end of the chain. If the triple bond is three or more positions from the end, the band is scarcely detectable.

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(13) By contrast, the C≡C frequency appears with good intensity in the Raman spectra of all acetylenic compounds regardless of where the triple bond is located. References 16 and 17 provide many such examples.

(14) T. A. Kletz and A. Summer, *J. Chem. Soc.*, 1456 (1948).

(15) Compound XXVI is an exception to this, since for it the C≡C band is at 2120 cm.$^{-1}$. However, the C≡C is conjugated with C≡N in this case. Since the "normal" frequencies of these groups are close together, it is probable that Fermi resonance has lowered the C≡C band below its "normal" position.

(16) J. H. Hibben, "The Raman Effect and its Chemical Application," Reinhold Publishing Corp., New York, N. Y., 1939, p. 200 ff.

(17) Reference 9 and earlier papers cited therein.

(18) Hibben states (ref. 16, p. 208) that a Raman line at 1380 cm.$^{-1}$ is quite generally present in the disubstituted acetylenes. This is not a useful criterion in the infrared because this frequency is characteristic of a methyl group.

(19) An isoöctane solution of XII was studied with a Cary spectrophotometer. The only band observed had $\lambda_{max.}$ at 216 mμ, with a molecular extinction coefficient ϵ = 3300.

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF WASHINGTON]

The Viscosities of Perchloric Acid Solutions

BY L. H. CLARK AND G. L. PUTNAM

Introduction

There is reason to believe that the efficiency of electrolytic cells for the production of ozone[1] may be improved by the study of the anode film temperature in relation to current density and viscosity of the electrolyte. In order to correlate the effect of the viscosity of the electrolyte (aqueous perchloric acid) on anode film temperature, it is necessary to have available the viscosities of the electrolyte at various concentrations for temperatures well below 0°. Since this data could not be found in the literature, experiments were conducted for the purpose of measuring the viscosity of aqueous perchloric acid solutions as a function of temperature and concentration.

In electrolytic cells, such as the one using perchloric acid for the production of ozone, it is believed that the electrode temperature—not the temperature of the electrolyte—is the temperature which controls the primary formation of electrode products. Since the efficiency of the electrolytic cell can be markedly affected by controlling the temperature difference between the anode and electrolyte, it is of great importance to study the variables affecting this temperature.

To correlate the effect of viscosity on the anode film temperature, we have measured the viscosity of 20, 40 and 60% perchloric acid solutions. The temperature range, being limited by the freezing point of the solutions, varies from +50 to −58°. This paper presents the results of these viscosity measurements. A later paper will correlate viscosity to anode film temperature and current efficiency.

Not much work has been done on the viscosity of perchloric acid solutions. Van Wyk[2] and Reyher[3] give values for various concentrations of perchloric acid at 20, 25 and 50° only. As far as could be ascertained from the literature, no authors have previously measured the viscosity of aqueous perchloric acid solutions below 0°.

Experimental

Apparatus.—The viscosity measurements were made using an Ostwald viscometer suspended in a Dewar flask containing the temperature controlled bath. The Dewar flask had a strip of unsilvered glass on the side to permit visual observations of the indices on the viscometer. Uniformity in the temperature of the bath was obtained by an electric stirrer placed in the flask.

The volume of efflux of the viscometer was approximately 1.45 ml. The working volume was 10 ml., this quantity of the desired solution always being pipetted into the viscometer in order to maintain a constant head of solution. The time of efflux was observed by visual observation of the meniscus and was measured to 0.1 of a second using a Waltham type A-8 stopwatch, which on checking against an electric timer showed a negligible difference in one hour. The time of efflux varied from 26 to 1788 seconds for the calibrating liquids and from 24.2 to 710 seconds for the perchloric acid solutions. No kinetic energy corrections were applied as they were less than the experimental error of the work.

In order to measure as accurately as possible the temperature of the solution in the viscometer, a calibrated glass-enclosed copper–constantan thermocouple was inserted directly in the solution in the reservoir of the Ostwald viscometer. Temperatures were read to the nearest 0.1°. The temperature of each run represents an average of several temperatures recorded during the run. The bulb of the viscometer was always kept below the level of the cooling liquid to aid in equalizing temperatures before the liquid passed through the capillary tube.

The viscometer was calibrated by measuring the time of efflux of liquids of known viscosity and density; and subsequently, plotting the computed ratios of kinematic viscosity to time of discharge *versus* the reciprocal of the discharge time squared. This method of calibrating the viscometer is the one described by the Bureau of Standards.[4] The calibrating liquids included distilled water,[5,6] pure ethyl alcohol[5,6] and a 38.6 weight per cent. sulfuric acid solution.[4] The time of efflux for the liquids was measured at temperatures ranging from +45 to −50°, four determinations being made at each temperature.

Since a straight line was obtained for the calibration curve over the range of kinematic viscosities and temperatures measured, the following equation will hold for any unknown over the same range of kinematic viscosities

$$\left(\frac{\eta}{\rho}\right)_T = At - \frac{B}{t}$$

where η/ρ = kinematic viscosity; t = time of flow in seconds; A, B = constants of the instrument, T = temperature of the liquid.

Materials.—Twenty per cent., 40 and 60% weight solutions of C. P. perchloric acid in water were measured at temperatures between −58 and +50°.

The composition of these solutions, expressed as per cent. perchloric acid, was determined by titrating two weighed portions of each solution. The percentages obtained were 20.0, 40.0 and 60.0. As a check on these determinations the specific gravity at 23°/23° of each solution was determined on a Westphal balance. The densities at 23° were then calculated and converted to percentages.[7] The average difference between the measurements by titration and specific gravity was less than 0.1 weight per cent.

In order to calculate the viscosity of these solutions from the kinematic viscosity, it is necessary

(1) Putnam, Moulton, Fillmore and Clark, *J. Electrochem. Soc.*, **93**, 211–221 (1948).

(2) Van Wyk, *Z. anorg. Chem.*, **48**, 1 (1906).

(3) Reyher, *Z. physik. Chem.*, **2**, 744 (1888).

(4) Vinal and Craig, *J. Research Natl. Bur. Standards*, **10**, 781–793 (1933).

(5) "International Critical Tables," Vol. V, pp. 10–11 (1929).

(6) *Ibid.*, Vol. III, pp. 25, 27 (1928).

(7) Perry, "Chemical Engineers' Handbook," 2nd ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 421.

TABLE I

GRAMS PER ML. DENSITIES OF PERCHLORIC ACID SOLUTIONS

Temp., °C.	Weight per cent. perchloric acid 10	20	30	40	50	60
50	1.041	1.107	1.181	1.267	1.375	1.494
40	1.046	1.113	1.188	1.276	1.385	1.507
30	1.051	1.119	1.195	1.285	1.395	1.520
20	1.056	1.125	1.203	1.294	1.405	1.534
10	1.061	1.131	1.210	1.303	1.415	1.547
0	1.066	1.137	1.217	1.312	1.425	1.560
−10		1.144	1.225	1.321	1.435	1.573
−20			1.232	1.330	1.445	1.586
−30				1.339	1.455	1.599
−40				1.348	1.465	
−50				1.357		
−58				1.364		

to know the density of each solution at each temperature. Data from Perry,[7] from Markham,[8] and our own experimental results at temperatures below 0° have been used as a basis for computing densities needed at the various concentrations and temperatures. By experimentally determining the densities of perchloric acid solutions at several temperatures below 0°, it was found that a linear interpolation of the densities is valid, straight lines being obtained when temperature was plotted *vs.* the combined data of Perry,[7] Markham[8] and our own. Table I gives the densities of perchloric acid interpolated from the combined data of Perry, Markham and the authors.

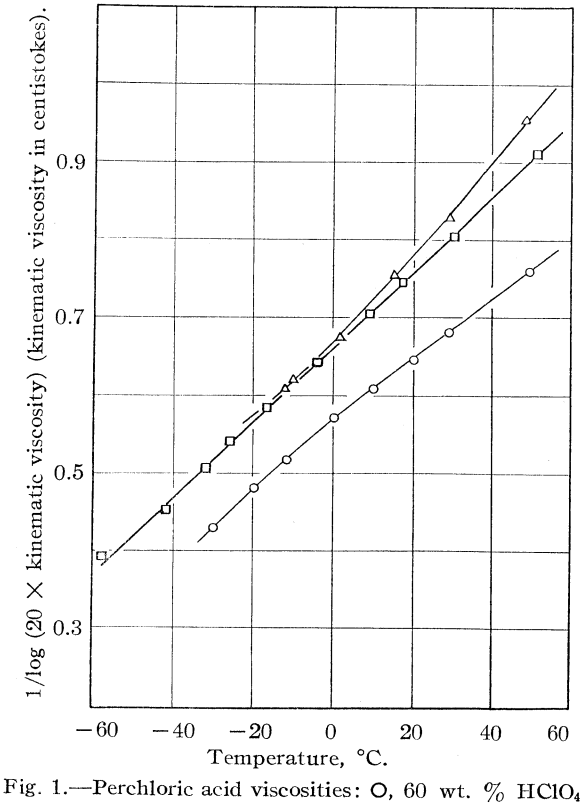


Fig. 1.—Perchloric acid viscosities: O, 60 wt. % $HClO_4$; □, 40 wt. % $HClO_4$; △, 20 wt. % $HClO_4$.

Results

The experimental results of viscosity measurements are shown in Fig. 1. In plotting these curves, the reciprocal of the log (20 × kinematic viscosity in centistokes) was plotted against temperature as recommended by Vinal.[4] This was done in order to obtain an approximately linear relationship which permits a more accurate interpolation of the curves. The values of the function 1/[log (20 × kinematic viscosity)] were read from Fig. 1 at each 10° of temperature and these values replotted as isothermal lines having per cent. composition of solution as the abscissas. These new working curves facilitated the reading of the kinematic viscosities of perchloric acid at the desired temperatures and compositions.

Table II gives a summary of the numerical values for the absolute viscosity of aqueous perchloric acid solutions at various temperatures. The values for the 10% perchloric acid solution have been obtained by interpolation of the working curves from 20% perchloric to pure water.[9]

TABLE II

ABSOLUTE VISCOSITIES OF PERCHLORIC ACID SOLUTIONS IN CENTIPOISES

Temp., °C.	Weight per cent. perchloric acid 10	20	30	40	50	60
50	0.560	0.610	0.700	0.820	1.051	1.552
40	0.666	0.721	0.815	0.960	1.260	1.855
30	0.812	0.867	0.959	1.142	1.492	2.190
20	1.006	1.040	1.144	1.338	1.782	2.73
10	1.318	1.357	1.451	1.681	2.265	3.38
0	1.66	1.779	1.921	2.165	2.77	4.29
−10		2.355	2.555	2.88	3.86	6.50
−20			3.48	4.01	5.50	9.75
−30				5.90	8.56	17.1
−40				9.10	14.0	
−50				16.3		
−58				23.3		

Discussion

Accuracy.—Considering sources of error as discussed by Vinal,[4] it is believed that the viscosity values determined in this paper are in error by not more than 1 to 3%. These statements, however, are based on the assumption that the viscosities and densities of the liquids used in calibrating the viscometer, as given in the literature, are sufficiently accurate for the purpose.

Comparison with Accepted Values.—The only values for the viscosity of perchloric acid solutions were taken from the early literature.[2,3,10] Data are available only for 20, 25 and 50° and a comparison of these with our data at 20 and 50° has been made in Table III. Since the 25° values were for very dilute solutions only, they are not shown in the comparison. It is seen that excellent agreement has been obtained for nearly all the

(8) Markham, THIS JOURNAL, **63**, 874–875 (1941).

(9) "International Critical Tables," **5**, 10 (1929).

(10) *Ibid.*, Vol. V, p. 12 (1929).

TABLE III

VISCOSITIES[a] OF PERCHLORC ACID SOLUTIONS—COMPARISON OF EXPERIMENTAL RESULTS WITH LITERATURE[2,3,9]

$HClO_4$, % by wt.	η, 20°C. (Lit.)	η, 20°C. (Exp.)	η, 50°C. (Lit.)	η, 50°C. (Exp.)
10	1.01	1.006	0.572	0.562
20	1.035	1.040	0.610	0.610
30	1.135	1.144	0.682	0.700
40	1.338	1.338	0.808	0.820
50	1.783	1.782	1.068	1.051
60	2.73	2.73	1.60	1.552

[a] η = Absolute viscosity in centipoises.

given values. The value at 50° for 60% concentration shows the greatest deviation (about 3%).

Summary

Measurements of the viscosity of perchloric acid solutions containing 20 to 60% acid have been made over a temperature range from +50 to −58°, except as the measurements were limited by the freezing points. The viscosity of these solutions at 0° is about three times as great as at +50°, but at −50° the viscosity is about thirty times as great.

SEATTLE, WASHINGTON RECEIVED FEBRUARY 21, 1949

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF BRITISH COLUMBIA]

The Density and Transition Points of Solid Hexamethylethane

BY WM. F. SEYER,* R. B. BENNETT AND F. C. WILLIAMS

Numerous studies have been made of the various solid phases of *n*-paraffin hydrocarbons. As a result a considerable amount of knowledge has accumulated concerning their crystal structure, transition points and latent heats. In contrast a corresponding knowledge of the branched hydrocarbons is exceedingly small. The reason for this is undoubtedly the great difficulty encountered in preparing these compounds in the pure state. Calingaert, Soroos, Hnizda and Shapiro prepared recently hexamethylethane in a high state of purity.[1] In a series of measurements dealing with the physical chemical properties of this hydrocarbon, they detected the existence of an unstable solid phase just below the melting point. To establish the nature of these solid phases, the above investigators sent two samples of this material to our laboratory, requesting us to measure its densities and coefficient of expansion by the dilatometer method used previously for some of the *n*-paraffin hydrocarbons.[2]

We were informed that the m. p. of both of the samples was 100.63° and that they had a purity of 99.96 ± 0.04%. One of the characteristics of this hydrocarbon is its small liquid range (5.61°) at normal pressures and another is its high sublimation pressure. It was therefore necessary to develop a special technique for transferring this compound from the glass stoppered ampoule in which it was received to the dilatometer.

Experimental Procedure

Preliminary measurements soon verified the observations of the workers from the chemical research laboratories of the Ethyl Corporation. After several unsuccessful methods were tried for filling the bulb, the following was adopted. The bulb, a funnel with a long drawn out stem and the ampoule containing the hydrocarbon were sealed in a glass tube as shown in Fig. 1. To avoid sublimation during the sealing operation, Dry Ice was placed about the lower end of the containing vessel. The sealing process having been completed, the vessel was then exhausted and refilled with hydrogen several times to remove the air. At the last filling, the hydrogen pressure was brought up to about 2.5 atmospheres. The tube was now inverted and heat applied at the upper end while dry ice was placed about the lower end which contained the bulb. In this manner any amount of hydrocarbon could be melted and run into the bulb. The glass tube was then broken in the center, the bulb removed, stoppered and weighed. The procedure from here on was then the same as with the other hydrocarbons.

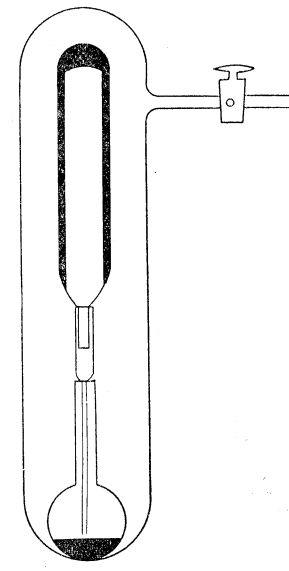


Fig. 1.—Filling the bulb.

A series of density measurements was then made over a temperature range of from 20.69 to 103.50° on the two different lots of materials. Both samples within the limits of accuracy of the measurements gave the same density values. Measurements were first made over intervals of about 2° with both ascending and descending temperatures. In regions near the transition points and rapid density changes the temperature intervals were in the neighborhood of 0.10 to 0.20°, which required an extraordinary amount of bath temperature control. This was found possible with the use of a sensitive thermoregulator and a calibrated Leeds and Northrup platinum resistance thermometer. The absolute density values are considered to be correct to only the third place of decimals while the differential values are within three units of the fourth place. Two phases were found to exist between 20° and the m. p., 100.63°. The density values are given in Table I. The values up to 90° were taken from a large scale plot constructed from the density values obtained in numerous runs. Above 90° to the m. p. actual values of a typical run for phase (1) are given in order to illustrate the manner of approaching a suspected transition or melting point. A similar set of values is given for phase 2.

* Department of Engineering, University of California, Los Angeles.

(1) Calingaert, Soroos, Hnizda and Shapiro, THIS JOURNAL, **66**, 1389 (1944).

(2) Seyer, Keays and Patterson, *ibid.*, **66**, 179 (1944).

The phase stable above 20° up to 74.25° is referred to as phase 1 and that stable between 74.25 and 99.65°, as phase 2.

It was found that at the low temperatures equilibrium could be reached in about fifteen minutes, above 80° in over thirty minutes; but near the transition temperatures it required as much as seventy-two hours before the mercury level in the capillary tube became constant.

TABLE I

PHASE 1

Temp., °C.	Density, g./cc.	Temp., °C.	Density, g./cc.	
20.0	0.8242	90.0	0.7780	
30.0	.8188	95.89	77.25	
40.0	.8128	98.35	.7690	
50.0	.8065	99.45	.7683	
60.0	.8000	99.96	.7652	
70.0	.7955	100.10	.7641	
73.0	.7913	100.34	.7610	rising
74.4	.7900	100.52	.7538	temp.
80.0	.7858	100.56	.7519	only,
85.0	.7823	100.63 m. p.	.6569	calcd.

LIQUID PHASE

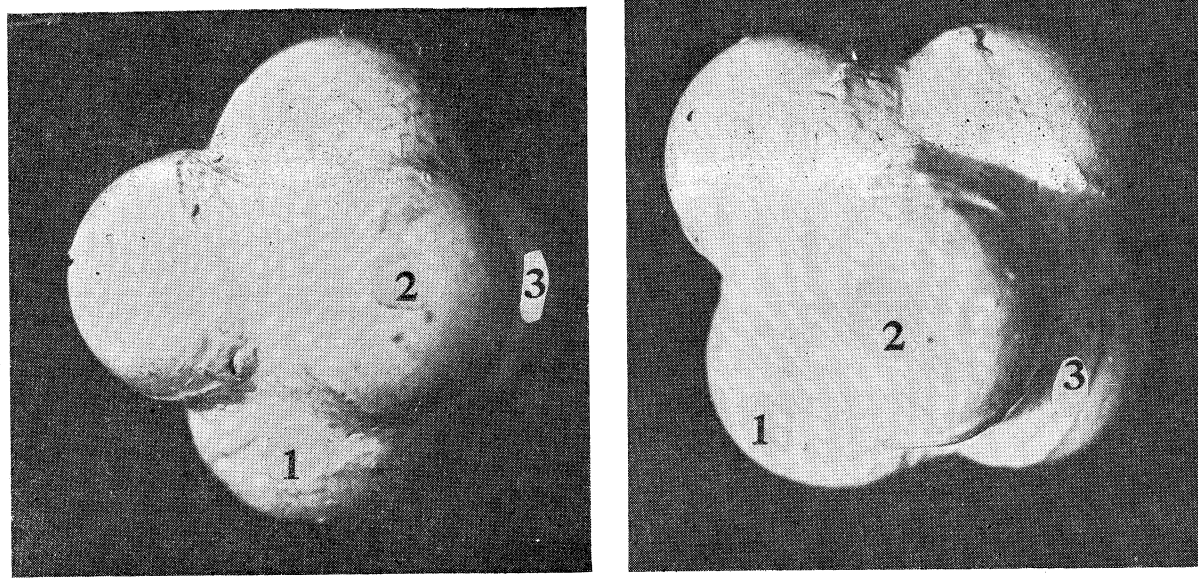
Temp. rising	Density, g./cc.	Temp. falling	Density, g./cc.
100.71	0.6568	100.84	0.6566
101.92	.6557	101.18	.6563
102.28	.6553	102.81	.6549

PHASE 2

Temp. rising	Density, g./cc.	Temp. falling	Density, g/cc.
74.85	0.7554	99.65	0.7334
75.02	.7552	97.75	.7353
81.75	.7480	93.52	.7385
84.09	.7456	88.37	.7421
89.67	.7412	86.35	.7435
90.73	.7406	85.71	.7439
91.57	.7398	83.31	.7465
92.95	.7391	79.63	.7502
94.61	.7379	75.96	.7541
95.43	.7372	74.85	.7554
96.55	.7361	74.30	.7558
97.12	.7358	74.25	.7902
98.70	.7343		
99.65	.7334		

Discussion.—The unusual behavior of this hydrocarbon is shown very clearly when densities are plotted against temperatures (Fig. 2). There is an over-all resemblance to the behavior of the even numbered, C_{18}, C_{20}, C_{22}, hydrocarbons of the normal paraffin series, but there is this difference, that the enclosed region for hexamethylethane does not represent a region in which the possible cooling paths with different cooling rates may lie.[2] Here only two definite paths have been found even though the cooling rates in some cases were as low as 0.5° per day. With ascending temperatures, the path was always along ABCD through the melting point to the liquid. Along ABC the path could be retraced at will to the left of C upon either heating or cooling. In general, once beyond C, along CD such was not the case, for increase of temperature led to D, the m. p. The point C was never actually measured. It was established by drawing a line parallel to the density axis through the point F, which was the first equilibrium point that could be obtained upon cooling the hydrocarbon from the liquid state. As mentioned before, measurements in the neighborhood of C and D were made with temperature intervals of less than a tenth of a degree, with heating and cooling rates from 0.1 to 0.5° per day. Yet no transition point could be detected at 74.25° or at 99.65° with an ascending temperature for phase 1, although Calingaert, Soroos, Hnizda and Shapiro, in their communications with us stated that they had twice observed a break in the density–temperature curve, once at 99.59° and once at 99.63° when proceeding toward the melting point on cooling. In our experience both hydrocarbons samples always behaved in the same way. Reproducible points on a large scale curve could readily be obtained for phase 1 with either ascending or descending temperature runs providing the temperature did not exceed 99.96°. Points beyond this were only obtained when proceeding toward the m. p. Whenever the temperature of 99.96° was exceeded it was not found possible to reverse the path toward B because the mercury level in the dilatometer tube never became steady within a time limit of twenty-four hours. At times the mercury column even began to vibrate and it was necessary to cool it below 70° to again obtain a steady state. Why this was so we are unable to explain except to suggest that the time limit of twenty-four hours was too short.

Starting with the liquid and cooling, the hydrocarbon invariably followed the path EDCFGBA instead of the expected one, EDFGBA. There was at no time mistaking this peculiar behavior of the hydrocarbon of first contracting and then when all the liquid had more or less completely solidified suddenly expanding. Before it was understood what was occurring, the rapidity of the expansion was so great as to force some of the mercury out of the dilatometer. In fact, to make measurements at all over this range, it was necessary to construct a special dilatometer with such tube and bulb dimensions that mercury did not overflow into the reservoir upon re-expansion. The action of the hexamethylethane in detail was somewhat as follows: Upon cooling the liquid to 100.5° solidification began and continued for about a period of from one to two hours. After this time as far as one could observe, all the material had solidified, yet the mercury level in the manometer would still keep falling slowly even after seventy-two hours. Lowering the temperatures by decrements of about 0.1° caused further contraction but no steady state. At 99.65° a sudden expansion occurred, causing a change in the mercury level of from 3 to 5 cm., depending upon the dimensions of the particular dilatomer in use. Simultaneously, the solid changed from being opaque to translucent. Furthermore, the above temperature was the first at which equilibrium



(a) Rotation at right angles to 001 plane possible. (b) No rotation with three methyl groups in 001 plane.

Fig. 2.

could be obtained upon cooling from the liquid phase. The decrease in density between the points C and F was approximately 0.033 or about 4.5%. Further cooling brought about contraction of what is called phase 2 along the line FG until a temperature of 74.25° was reached when transformation into phase 1 took place and the density rose to a value corresponding to point B on the original ABC path.

Once equilibrium had been established just a little to the left of B and the sample then heated, phase 1 did not revert back to phase 2, but persisted in the metastable state along the line BC. Of course it is quite conceivable that had phase been seeded with crystals from phase 2 at the first transformation point (74.25) the latter phase would have formed. However, this was impractical with our present type of apparatus. Furthermore, with all the other hydrocarbons so far investigated this was not necessary to bring about transformation.

Heating phase 2 moved the densities along the line FG. Beyond F to the m. p. no equilibrium states whatever could be obtained. Nor were there any pronounced indications of a contraction equivalent to FC taking place. Thus, as far as could be ascertained with the dilatometer, the path on warming phase 2 was along the path GFD, and not GFCD. In other words, the fusion and solidification processes were not mechanically reversible. A similar situation was recently found when measuring the dielectric constants of *cis* and *trans* decahydronaphthalene, through the melting and freezing regions.[3]

(3) Seyer and Barrow, *ibid.*, **70**, 802 (1948).

Some sort of transformation, about one degree below the melting point, was observed in the case of several long chain normal paraffins by Piper, *et al.*[4] They inferred the existence of a transition point because of a change in optical properties. The dilatometer method used in this Laboratory for measuring the density of these hydrocarbons in the solid phase failed to show any change in volume at this so-called second transition point.

As a result of the X-ray work of Mueller[5a,b] we have a good knowledge of the crystal structure of the *n*-paraffin hydrocarbons in the various solid phases. There appear to be three forms, one of which is stable in a region 5 to 6° below the m. p. In this form the molecules stand upright on a rectangular base, the 001 plane. Another form common to the even numbered *n*-paraffins has the molecules tilted to the base at an angle of about 60°. There is still another form intermediate between the two mentioned in which the angle of tilt is somewhat less than 60° and the base may be more or less of a rectangle. West, from X-ray data, deduced that hexamethylethane at room temperatures has a cubic body centered dodecahedron crystal structure, which is almost spherical.[6]

Any explanation of the unusual behavior of this compound must of necessity be of a tentative nature until X-ray and specific heat measurements have been made. Hence the following attempted explanations must be considered in this light. While the structural formula would indicate that

(4) Piper, *et al.*, *Biochem. J.*, **25**, 2073 (1931).

(5) (a) Mueller, *Proc. Roy. Soc.* (*London*), **A127**, 417 (1930); (b) **A138**, 514 (1932).

(6) *Z. Krist.*, **88**, 195 (1934).

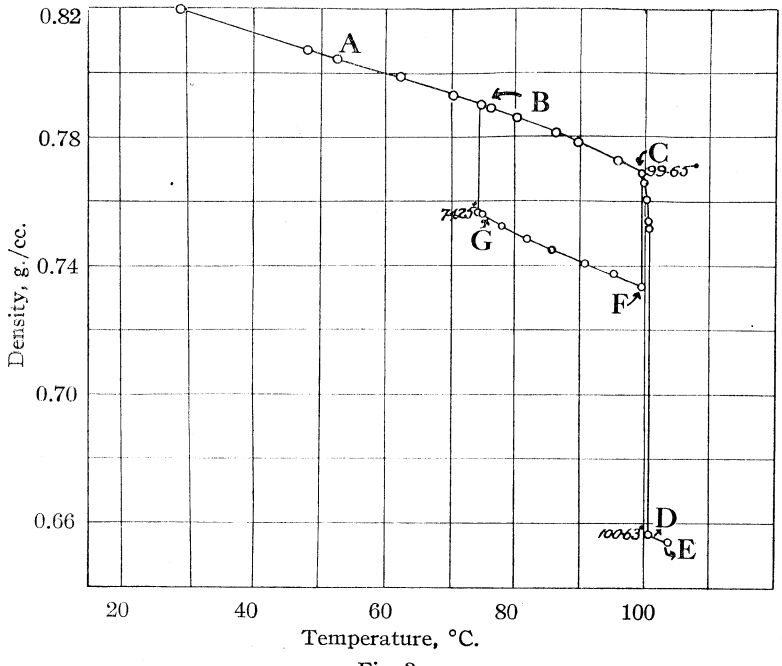


Fig. 3.

hexamethylethane is completely symmetrical, spatial considerations prove that this is not quite so. A geometrical model of the molecule prepared for us by Dr. Robert Delavault with the help of Pauling's data illustrates this clearly in the accompanying photographs. The rounded protuberances represent approximately the volumes swept out by the rotations of the methyl groups attached to the ethane skeleton which is itself buried in the inside of the figure.

West has discussed the crystal modification of C_2X_6 molecules.[6] He reasoned that these derivatives of ethane had not more than one principal axis of rotation. He assumed further that in the cubic modification, there is a large degree of thermal vibration approaching a rotation of the molecules as units, which permits them to simulate a higher degree of symmetry than they actually possess. Consequently, the hexamethylethane molecule might under certain conditions be regarded as a sphere, particularly if it rotated on an axis at right angles to the 001 plane as in Fig. (a) where only one carbon atom of the methyl group lies in this plane.

Unlike the *n*-paraffin hydrocarbons above C_{16} the conditions for the formation of the two solid phases appear to be reversed in the case of this symmetrical octane. Here immediately below the m. p. the stable phase is probably the monoclinic or "tilted form," while at room temperatures the stable one is the cubic form with the long axis at right angles to the 001 plane Fig. 3(a). The former phase could be formed from the latter by merely twisting the molecule through a solid angle of about 30°, so that three of the carbon atoms would lie in the 001 plane (Fig. 3(b)). It is further assumed that in this form no rotation occurs, also that such a form would be anisotropic since that of the cubic form according to West[6] is isotropic.

Hexamethylethane like hexachloroethane appears to be trimorphous. Parks, Huffman and Thomas measured the specific heat of this hydrocarbon from −184.3 to 22.4° and obtained a transition point at −125°.[7] The crystal form below this transition is unknown but from the evidence available, the cubic form is the stable one from this temperature to 74.25°. Let us now assume that the hexamethylethane is heated, that it exists in the form stable above −125.0° which according to West is the cubic form and that rotation of the molecule takes place such as is shown in Fig. 3(a). It is generally considered that the extraordinary stability of solids composed of symmetrical molecules is connected with molecular rotation. Returning again to our Fig. 2, we find that heating causes thermal expansion, only, along the line ABC even beyond the second t. p. 74.25°. Such a belated conversion is not uncommon among the hydrocarbons. At about 99.63° signs of melting appear, the solid becoming soft and more or less plastic in character indicating a loosening up of the polycrystalline mass. This behavior suggests that the melting process is of the type postulated by Mott and Gurney in their discussion on the theory of liquids.[8]

A noteworthy fact was that within the limits of experimental error the amount of expansion at 99.65°, 4.5%, was equal to that found for contraction at 74.25°.

Briefly, the anomalous behavior of hexamethylethane between the temperatures of 101.63 and 99.65° might be regarded as part of the freezing or solid forming process. Were the type of packing in the liquid analogous to that of the GF phase of the solid, this abrupt contraction and re-expansion would probably not take place.

The density of the stable phase at 20° is 0.824. West gave a value of 0.83.[5] The density equation for the liquid phase on the basis of six measurements was established as

$$D_t = 0.6568 - 0.00089\ (t - 100.63)$$

where D_t is density at any temperature t. The extrapolated liquid density at 20° is 0.728 g./cc. Calingaert obtained 0.7219 from solutions of hexamethylethane in *n*-octane.[9]

Their average coefficient $d(D_t)/dt$ for several

(7) Parks, Huffman and Thomas, THIS JOURNAL, **52**, 1032 (1930).
(8) Mott and Gurney, *Trans. Faraday Soc.*, **35**, 364 (1939).
(9) Calingaert, Beatty, Kuder and Thomson, *Ind. Eng. Chem.*, **33**, 103 (1941).

branched hydrocarbons is 0.000850, a little lower than that of the symmetrical isomer which is 0.00089.

In conclusion, we wish to acknowledge the helpful suggestions offered by G. Calingaert and his co-workers of the Ethyl Corporation, and also that of R. Delavault, who, as mentioned before, took great pains to prepare a model for us.

Summary

1. The density of hexamethylethane has been measured over a temperature range of from 20° to 103.5°.

2. Two transition points were obtained upon cooling from the liquid, one at 99.65° and the other at 74.25°.

3. The contraction and re-expansion of the hydrocarbon between 100.63 and 99.65° might be considered as part of the freezing process.

4. The existence of the two forms can be explained in a similar manner as that of normal paraffins except that in this case the stable form has a cubic structure with the molecule standing upright in the 001 plane instead of being tilted as are the long hydrocarbon chains.

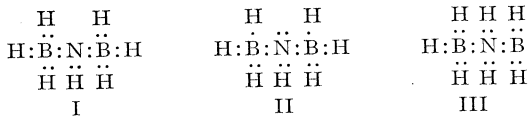
VANCOUVER, B. C. RECEIVED MARCH 17, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SOUTHERN CALIFORNIA]

The N-Methyl Derivatives of B_2H_7N[1]

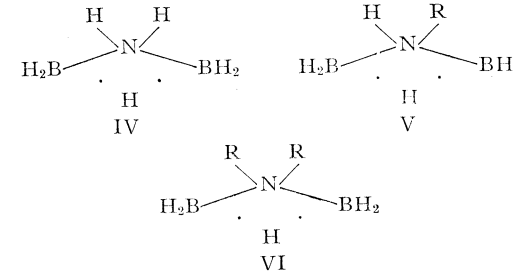
BY ANTON B. BURG AND CARL L. RANDOLPH, JR.

The structure of the aminoboron compound B_2H_7N has not been intelligible in terms of the known chemical facts,[1a] and the application of current theories of electron-deficient bonding has awaited knowledge of the positions of the hydrogen atoms on the B–N–B skeleton. The early electron-diffraction studies[2] suggest an arrangement in which the boron atoms are equivalent, like carbon atoms in dimethylamine. A resonance-structure composed of models such as I and II was suggested but the less symmetrical model III accounts far better for the 1:1 addition compounds formed by B_2H_7N with bases such as ammonia or trimethylamine. On the other hand, the electron-deficiency of the right-hand boron atom in III would demand an irreversible dimerization like that of CH_3BH_2,[3] $(CH_3)_2BH$[4] or $(C_2H_5)_2BH$.[5] Actually B_2H_7N does not dimerize in the least degree.



I II III

The present paper describes the N-methyl derivatives of B_2H_7N, prepared from diborane and methylamine or dimethylamine. Both are more stable and more volatile than B_2H_7N itself, but present the same structural problem. The existence of the N-dimethyl derivative, $(CH_3)_2NB_2H_5$, narrows the problem by eliminating models I and II, but III remains unsatisfactory unless a way can be found to shift electrons toward the tercovalent boron atom. Earlier concepts of the electronic structure of diborane threw no light on this problem, but the recent proposal that each of the two hydrogen atoms of Dilthey's bridge structure[6] is "half-bonded" to two boron atoms without resonance-relation to the other,[7] justifies the replacement of one bridge-hydrogen atom by nitrogen, thus:



IV V VI

These models are like III, except that one hydride unit has moved into a position suitable for sharing electrons equally with the two boron atoms, improving the symmetry and orbital-filling, and achieving a lower energy state by the resonance principle. Base-addition still can occur in terms of structure III, by suppressing one side of the B–H–B bridge linkage in structure IV. Thus structure IV is not only in agreement with the chemical behavior of B_2H_7N, but is also compatible with the suggestion of equivalent boron atoms advanced by Bauer.

The bridge-model for B_2H_7N and its derivatives was suggested by Professor Arthur J. Stosick of this Department in October, 1947.[8] With the as-

(1) Presented in part in the Symposium on Organometallic Compounds at the Chicago Meeting of the American Chemical Society, April, 1948.

(1a) H. I. Schlesinger, D. M. Ritter and A. B. Burg, THIS JOURNAL, **60**, 2297 (1938).

(2) S. H. Bauer, *ibid.*, **60**, 524 (1938).

(3) H. I. Schlesinger, N. W. Flodin and A. B. Burg, *ibid.*, **61**, 1078 (1939).

(4) H. I. Schlesinger and A. O. Walker, *ibid.*, **57**, 621 (1935).

(5) H. I. Schlesinger, L. Horwitz and A. B. Burg, *ibid.*, **58**, 407 (1936).

(6) W. Dilthey, *Z. angew. Chem.*, **34**, 596 (1921).

(7) R. E. Rundle, THIS JOURNAL, **69**, 1329 (1947).

(8) Essentially the same suggestion has been made independently by E. Wiberg, A. Bolz and P. Buchheit, *Z. anorg. Chem.*, **256**, 286 (1948).

sistance of Dr. Kenneth W. Hedberg and Mr. George B. Guthrie at the California Institute of Technology, he has obtained electron-diffraction photographs over a wide range of intensities for B_2H_7N and $(CH_3)_2NB_2H_5$. The results agree with models having BNB angles of 96 and 89°, respectively. Without the postulated hydrogen-bridging the angles should have been nearly tetrahedral. Structures such as IV, V, and VI thus are fully supported by physical and chemical facts.

Aside from the structural problem, the compounds B_2H_7N, $CH_3NHB_2H_5$ and $(CH_3)_2NB_2H_5$ offer interesting series comparisons of both physical and chemical properties. They also imply the existence of many other new compounds based upon the same bonding principle.

The nomenclature of such compounds is difficult, but it seems most satisfactory to follow the convention established by the mono-halogen derivatives of diborane. It seems highly probable that bromodiborane is bridged through bromine and that chlorodiborane is similarly B–Cl–B bonded. Hence $(CH_3)_2NB_2H_5$ may be called dimethylaminodiborane without creating new language.

Dimethylaminodiborane, $(CH_3)_2NB_2H_5$

The preparation of the compound $(CH_3)_2NB_2H_5$ was accomplished by two methods, both dependent upon dimethylaminoborine, $(CH_3)_2NBH_2$, a substance discovered by Wiberg and his co-workers.[9,10] We describe first a procedure for making $(CH_3)_2NBH_2$, a method more adaptable to large-scale operation than the original, and involving less secondary aminolysis.

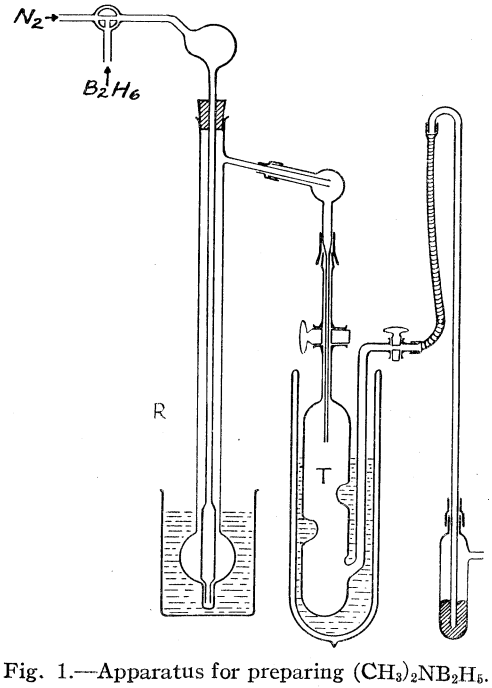


Fig. 1.—Apparatus for preparing $(CH_3)_2NB_2H_5$.

(9) E. Wiberg and A. Bolz, *Ber.*, **73B**, 209 (1940).

(10) E. Wiberg, A. Bolz and P. Buchheit, *Z. anorg. Chem.*, **256**, 285 (1948).

Preparation of $(CH_3)_2NBH_2$.—Diborane is passed into dry liquid dimethylamine at −42°, in the bottom of a 25 × 650 mm. test-tube. This container then is attached through a sealed-on ground joint to the high vacuum system, and the excess amine is pumped off, at room temperature, leaving the liquid compound $B_2H_6 \cdot 2(CH_3)_2NH$ (structure uncertain). Dry nitrogen now is admitted to bring the pressure to 400 mm., and the lower part of the tube is heated to 130° by a tubular electric furnace. Hydrogen is evolved and $(CH_3)_2NBH_2$ sublimes into the cool upper part of the tube, escaping further aminolysis. The yield thus is nearly quantitative. The crude product, containing little of the more volatile bis-dimethylaminoborine[9] and a trace of less volatile liquid, is purified by means of a fractionating column, operating at 98° and 400 mm. pressure (dry nitrogen) and delivering into the vacuum system. The elevated pressure and temperature are necessary to avoid solidification during the process.

A sample produced by this method was purified still further by recrystallization from low-boiling petroleum ether. Its purity was checked by hydrolysis in aqueous hydrochloric acid at 110°: 18.7 mg. yielded 14.78 cc. of hydrogen (gas at S. C.)—theoretical, 14.72. The melting range was determined as 74.5–75° (previous value, 73.5°)[10] and the vapor tension as 9.1 mm. at 23°. Precise measurements of the variation of the vapor density with temperature are in course.

Preparation of $(CH_3)_2NB_2H_5$.—Of two methods of preparing $(CH_3)_2NB_2H_5$ the more direct is the addition-reaction of diborane with dimethylaminoborine, a reaction which can be completed slowly in a sealed bulb at 80°, or very rapidly at 135° in a flow system. By either process, the reaction

$$2(CH_3)_2NBH_2 + B_2H_6 \longrightarrow 2(CH_3)_2NB_2H_5$$

is essentially quantitative, occurring in preference to the thermal decomposition of the diborane. If a large-scale preparation is desired, one proceeds without isolating the $(CH_3)_2NBH_2$, for the small loss of yield (due to secondary reactions) is more than offset by the speed and convenience of this procedure. Diborane is passed into dimethylamine at −42°, in the bottom of the tube R, Fig. 1; then the excess amine is distilled off and the bath temperature slowly raised to 135°. As the resulting $(CH_3)_2NBH_2$ begins to reflux in the upper part of tube R, diborane is bubbled in at the rate of 100–200 cc. per minute. The product is caught at −196° in the trap T, from which it later is distilled into the vacuum system and separated from unused diborane and $(CH_3)_2NBH_2$. About 75–85% of the diborane undergoes reaction and the remainder is recovered. By this process, it is convenient to prepare 25 g. of $(CH_3)_2NB_2H_5$ in the course of two hours, but there is no doubt that a much higher rate would be feasible with larger apparatus.

Small samples of $(CH_3)_2NB_2H_5$ are best purified by a slow high-vacuum distillation from a tube at −78.5° into a trap at −112°, with a second trap at −196° to catch more volatile impurities. The portion condensed at −112° should have a constant vapor tension of 101 mm. (uncor.) at 0°. If a large sample is to be purified by a fractionating column, the reflux temperature should be near −55°. Total elimination of $(CH_3)_2NBH_2$ is difficult.

The second method of preparing $(CH_3)_2NB_2H_5$ was discovered during an attempt to form a boron fluoride addition compound of $(CH_3)_2NBH_2$. The reaction was found to require a temperature of 90°; it was then tried in a sealed bulb (16 hours, 90°), with 142.5 cc. of $(CH_3)_2NBH_2$ (gas at S. C., determined by weight) and 176 cc. of boron trifluoride. Separation of the $(CH_3)_2NB_2H_5$ from diborane and the solid products of low volatility was readily accomplished by fractional condensation in traps at −42, −112 and −196°. The desired product was trapped at −112°. The material balance could be interpreted by the following equations, in which R designates methyl and the coefficients represent cc. of gas at standard conditions (equivalent to molar relationships):

$$19.6R_2NBH_2 + 9.8BF_3 \longrightarrow 9.8(R_2N)_2BH \cdot BF_3 + 4.9B_2H_6$$

TABLE I

VAPOR TENSIONS OF $(CH_3)_2NB_2H_5$

t, °C.	−35.6	−21.0	−17.7	−12.7	−5.5	−1.7	0.0	2.9
$p_{mm.}$ obsd.	12.5	32.7	39.7	52.5	77.2	93.3	101.4	116.1
$p_{mm.}$ calcd.	13.0	32.7	39.6	52.3	76.6	92.8	101.0	116.1
t, °C.	9.5	13.0	22.4	28.2	33.3	38.9	45.7	50.3
$p_{mm.}$ obsd.	158.1	184.3	274.0	345.2	419.2	515.0	652.1	760.2
$p_{mm.}$ calcd.	157.8	184.2	274.5	346.6	419.8	515.0	652.1	760.4

$$61.8R_2NBH_2 + 41.2BF_3 \longrightarrow 30.9(R_2N)_2BF\cdot BF_3 + 20.6B_2H_6$$

$$13.9R_2NBH_2 + 4.6BF_3 \longrightarrow 4.6(R_2N)_3B\cdot BF_3 + 4.6B_2H_6$$

$$47.2R_2NBH_2 + 23.6B_2H_6 \longrightarrow 47.2\ R_2NB_2H_5 \text{ (obsd. yield)}$$

The reaction actually used 57.5 cc. of boron trifluoride (calcd., 55.6). The resultant diborane was 6.0 cc. (calcd., 6.5). The white solid was treated with trimethylamine to remove boron trifluoride and the resulting inseparable mixture, assumed to be $(R_2N)_2BH$ and $(R_2N)_2BF$, was distilled off and weighed as 201.8 mg. (calcd. 206.4). The mixture, having a vapor tension of 11 mm. at 0°, was hydrolyzed to yield 9.1 cc. of hydrogen (calcd., 9.8). The original white solid was closely similar to $(R_2N)_2BH\cdot BF_3$, which was especially prepared for comparison. The postulated compound $(R_2N)_3B$, which may have resulted from the amine treatment of the solid, was not isolated.

Proof of Formula.—The molecular weight of the new compound was determined from vapor density measurements as 71.8 (calcd., 70.6). Boron-linked hydrogen was determined by acid hydrolysis: an 11.08-cc. sample yielded 56.30 cc. of hydrogen (calcd., 55.40 cc.). Aminoid nitrogen was determined as 11.09 cc. gas (calcd., 11.08), by a modified Kjeldahl-type distillation and titration. Boron was determined on a separate 9.16-cc. sample by hydrolysis, neutralization to the methyl red end-point, and titration of the mannitol spirane to the phenolphthalein end-point. The result was equivalent to 18.28 cc. of gaseous B (calcd., 18.32).

Carbon was converted to carbon dioxide by fuming nitric acid at 200° during forty-eight hours. Gases volatile at −80° were passed over copper at 300°, after which the carbon dioxide was trapped out of the gas stream. A 6.72-cc. sample, treated in this way, gave 13.88 cc. of carbon dioxide (calcd., 13.54 cc.).

That the $(CH_3)_2N$ group is conserved as such in the formation of $(CH_3)_2NB_2H_5$, was confirmed by the recovery of 14.40 cc. of $(CH_3)_2NH$ after hydrolysis of 17.65 cc. of the compound. The non-condensable gas from this hydrolysis was proved to be hydrogen (88.70 cc.) by reaction with hot copper oxide to form only water. These results leave no doubt of the formula $(CH_3)_2NB_2H_5$.

Volatility.—The vapor tensions of a highly purified sample of dimethylaminodiborane, measured over the temperature range −36 to 50° are given in Table I. They determine the equation $\log_{10} P_{mm} = -1727.64/T + 1.75 \log T - 0.004661\ T + 5.3370$, which implies a boiling point of 50.3°. The heat of vaporization at the boiling point is estimated as 6670 cal./mole, and the Trouton constant is 20.6 cal./deg. mole.

Melting Point.—The melting range, determined visually, using the ammonia vapor tension thermometer[11] was −54.7 to −54.4° and −54.8 to −54.4° in two separate determinations.

Liquid Density.—A small capillary-dilatometric pycnometer was used to determine the density equation $d = 0.6456 - 0.001066t$ in the range 0–25°. For comparison, the densities of B_2H_7N were measured in the same range, determining the equation $d = 0.6486 - 0.0075t$.

Thermal Stability.—A relatively high degree of thermal stability sharply differentiates dimethylaminodiborane from the parent compound B_2H_7N: while the latter is appreciably decomposed in the vapor state at 45° during several hours heating, samples of $(CH_3)_2NB_2H_5$ are unaffected over much longer periods of time at temperatures as high as 90°. Vapor or liquid samples standing at room temperature for five months showed no signs of decomposition, whereas B_2H_7N is almost wholly decomposed under similar conditions.

Reaction with Trimethylamine.—Dimethylaminodiborane adds trimethylamine at low temperatures to give the stable product $(CH_3)_2NB_2H_5\cdot N(CH_3)_3$, paralleling the behavior of aminodiborane (B_2H_7N) toward nitrogen bases. Thus when a purified sample of $(CH_3)_2NB_2H_5$ amounting to 7.53 cc. was treated with 17.83 cc. of $(CH_3)_3N$ at −80° and warmed slowly to −42° during two hours, only 9.98 cc. of amine could be regained from the reaction, implying the absorption of 7.8 cc. of $(CH_3)_3N$, and the formation of the compound $(CH_3)_2NB_2H_5\cdot(CH_3)_3N$. This equimolar addition constitutes strong chemical evidence of the structural similarity of $(CH_3)_2NB_2H_5$ and B_2H_7N.[1a]

On warming to room temperature, the addition-product appeared as a white solid, exhibiting a saturation pressure of 4 mm. at room temperature—much more volatile than $B_2H_7N\cdot N(CH_3)_3$. There is no indication that further amine addition occurs, since the $(CH_3)_2NB_2H_5\cdot(CH_3)_3N$ absorbed no more trimethylamine during a two-hour treatment at −42°. Although the material appears to be stable indefinitely at room temperature, heating to 85° causes almost complete decomposition according to the equation

$$(CH_3)_2NB_2H_5\cdot N(CH_3)_3 \longrightarrow (CH_3)_2NBH_2 + (CH_3)_3N\cdot BH_3$$

Thus a homogeneous sample of $(CH_3)_2NB_2H_5\cdot(CH_3)_3N$, amounting to 0.846 mmole, gave 0.724 mmole $(CH_3)_3N\cdot BH_3$ and 0.756 mmole of $(CH_3)_2NBH_2$. These products were effectively separated by repeated fractional condensation through a U-tube at −18°. The $(CH_3)_2NBH_2$ passing this trap was identified by its vapor tension of 9.5 mm. at 18°, while the $(CH_3)_3N\cdot BH_3$, retained at 18°, was recognized by its orthobaric melting point of 92–92.5°.

Reaction with Ammonia and with Sodium in Liquid Ammonia.—Like trimethylamine, ammonia adds in a 1:1 ratio to dimethylaminodiborane, but it is also possible to form a diammoniate. This may be the salt $NH_4^+(CH_3)_2NB_2H_5NH_2^-$, for a 9.86-cc. sample of $(CH_3)_2NB_2H_5$, dissolved in liquid ammonia and allowed to react with 27.9 mg. of sodium at −70°, yielded 4.63 cc. of hydrogen during twenty minutes, increasing to 4.89 cc. (1.01 equiv.) during two hours. In a typical addition experiment, 5.58 cc. of $(CH_3)_2NB_2H_5$, treated with three volumes of ammonia, absorbed 10.4 cc. of ammonia during two and one-half hours at −80°. At −40°, evacuation brought the ratio of ammonia to $(CH_3)_2NB_2H_5$ to 1.47, but no lower. At 0° the compound decomposed, yielding $(CH_3)_2NBH_2$ and a non-volatile solid.

Behavior toward Boron Fluoride.—Dimethylaminodiborane (24.3 cc.) and boron fluoride (22.5 cc.) were heated together in a sealed tube for one hundred and forty hours at 100°, to yield 1.6 cc. of diborane at the expense of 4.0 cc. of boron trifluoride and 3.5 cc. of $(CH_3)_2NB_2H_5$. These results seemed most simply explained by assuming the equilibrium $(CH_3)_2NB_2H_5 + BF_3 \rightleftarrows {}^1/_2B_2H_6 + (CH_3)_2NBH_2\cdot BF_3$—a displacement of a borine group by boron fluoride. On the other hand, there is a possibility that disproportionation reactions, like those observed in the reaction of boron fluoride with $(CH_3)_2NBH_2$, occur.

A Chloro Derivative of Dimethylaminodiborane.—In view of the probable applicability of the structural prin-

(11) A. Stock, *Z. Elektrochem.*, **29**, 354 (1921).

ciple of the aminodiboranes to bromodiborane and chlorodiborane (halogen-bridge instead of N-bridge), it seemed both feasible and theoretically of interest to synthesize a halogenated aminodiborane, involving parallel B–Cl–B and B–N–B linkages in the same molecule. Accordingly, the thermally unstable compound $(CH_3)_2NB_2H_4Cl$ was prepared by the reaction of dimethylaminodiborane with chlorodiborane at 25°.

In a typical experiment, 193 cc. of diborane and 63 cc. of boron trichloride were allowed to react to form the equilibrium amount of B_2H_5Cl during two hours at room temperature. A sample of dimethylaminodiborane amounting to 187 cc., was then condensed into the reaction flask by means of liquid nitrogen. After standing fourteen hours at 25°, the crude product was separated from the more volatile components of the mixture by rapid distillation through a trap cooled to −42°.

Final purification of the product was effected by the use of a micro fractionating column[12] operating at a reflux temperature of −42°. After removal of impurities volatile at this temperature, the reflux temperature was raised to −25° and the chloro compound distilled out. The pure material was kept at −196° except during brief periods of experimentation.

The composition of the material was found by analysis of weighed samples for hydrogen, boron and nitrogen as previously described, and for chlorine by an adsorption-indicator titration of the hydrolysis residue. The resulting empirical formula $[(CH_3)_2N]_{0.97}B_{1.9}H_{4.0}Cl_{1.1}$ indicated the ideal formula to be $(CH_3)_2NB_2H_4Cl$.

This compound, formally named B-chloro-N-dimethylaminodiborane, spontaneously inflames in air. Its vapor tension at 0° is 6.5 mm.; at 20°, 18 mm. Good measurements at higher temperatures proved unfeasible on account of the increased rate of decomposition.

This decomposition was studied by allowing a pure sample of $(CH_3)_2NB_2H_4Cl$ (35.0 cc.) to stand at room temperature for six days, during which the original liquid phase disappeared, leaving a white, semicrystalline solid. The mixture then yielded 7.12 cc. of B_2H_6, 7.21 cc. of $(CH_3)_2NB_2H_5$ and 12.9 cc. of $(CH_3)_2NB_2H_4Cl$, implying the equation

$$3(CH_3)_2NB_2H_4Cl \longrightarrow B_2H_6 + (CH_3)_2NB_2H_5 + (CH_3)_4N_2B_2Cl_3H$$

The solid product was unaffected by a hot solution of hydrochloric acid or sodium hydroxide, and was removed from the apparatus only by boiling nitric acid.

Methylaminodiborane, $CH_3NHB_2H_5$

The high stability and volatility of dimethylaminodiborane, relative to aminodiborane, appears to result from the influence of the two methyl groups bonded to the central nitrogen atom. Hence it was reasonable to expect that methylaminodiborane, possessing a single methyl group, would represent a situation intermediate between that of the parent compound and its N-dimethyl derivative.

The synthesis of this compound has been accomplished by the reaction of methylamine with diborane, and, as expected, the chemical and physical properties of the new material fall between the previously studied extremes.

Preparation.—The formation of methylaminodiborane in good yields required a flow method like that used for aminodiborane,[1a] for closed-bulb heating methods involving diborane with the liquid $B_2H_6{\cdot}2CH_3NH_2$ complex or with its decomposition product $(CH_3NHBH_2)_x$ gave only negligible yields. Evidently $CH_3NHB_2H_5$ is more stable than B_2H_7N, for it forms in better yields under less critical conditions, as indicated in Table II. These yields are based upon the diborane used up in single passages over a larger quantity of methylaminated diborane.

TABLE II

Temp., °C.	Flow rate, cc./min.	Total B_2H_6, cc.	Used B_2H_6, cc.	Product, cc.	Yield, %
92–97	30	337	48	66	69
90–95	40	340	42	75	90

The product was readily purified by passage through a trap at −42° and fractional condensation at −90°; it then showed a constant and reproducible vapor tension of 47.5 mm. at 0°.

Proof of Formula.—The empirical formula of this methyl derivative was established by analysis for hydrolyzable hydrogen, nitrogen, boron and carbon. The methods were as given for $(CH_3)_2NB_2H_5$. A 6.43-cc. sample gave 31.1 cc. of hydrogen, 6.51 cc. of ammonia and 13.3 "cc." of B, while 11.5 cc. of the vapor yielded 11.8 cc. of carbon dioxide. These data are represented by the literal formula $(CH_3)_{1.03}(NH)_{1.01}B_{2.06}H_{4.84}$, or essentially $CH_3NHB_2H_5$.

The molecular weight, calculated from the vapor density, was 56.9 (calcd. 56.73), clearly confirming the formula.

Vapor Tensions.—Intermediate in volatility between B_2H_7N and $(CH_3)_2NB_2H_5$, methylaminodiborane has an extrapolated boiling point of 66.8°, as determined from the vapor pressure equation derived from the data of Table III, namely

$$\log P_{mm} = -2158.56/T + 1.75 \log T - 0.00806T + 7.51883$$

The heat of vaporization thus is estimated to be 6,666 cal./mole, while the Trouton constant is 19.6, a value consistent with this type of equation.

TABLE III

VAPOR TENSIONS OF $CH_3NHB_2H_5$

t °C.	−33.0	−26.3	−19.6	−14.1	0.0	11.4	29.6	39.4
$P_{obs.}$, mm.	5.9	9.4	14.6	20.7	47.6	84.9	195.7	290.6
$P_{calcd.}$, mm.	5.8	9.4	14.7	21.0	47.6	86.2	195.8	288.2

Behavior toward Trimethylamine.—The structural similarity of methylaminodiborane to aminodiborane and dimethylaminodiborane is indicated by the formation of a 1:1 addition compound with trimethylamine. This fact is interpreted, as before, in terms of a B–N–B skeletal pattern. Thus 7.88 cc. of methylaminodiborane absorbed 8.16 cc. of a 17.25-cc. portion of trimethylamine during two hours at −42°. The amine in excess of the 1:1 ratio was removed only with difficulty on warming to room temperature. The white solid product of composition corresponding to the formula $CH_3NHB_2H_5{\cdot}N(CH_3)_3$, showed no detectable vapor tension at room temperature, nor did any increase in volatility occur on standing. It is concluded that the decomposition typical of such compounds, yielding $(CH_3)_3N{\cdot}BH_3$, does not take place at room temperature.

Thermal Stability.—A slow and highly reversible dissociation of methylaminodiborane into diborane and polymeric methylaminoborine places it as expected, between aminodiborane and dimethylaminodiborane in order of increasing thermal stability. Although no deviation from ideal behavior could be detected on heating a gas sample at constant volume to 90° over a five-hour period, a 17.50-cc. sample, held as a liquid at 45° for thirteen days, yielded 2.7 cc. of hydrogen, 3.17 cc. of diborane and solid methylaminoborine polymer. The original sample was 39% decomposed. The mixture appeared to be approaching equilibrium according to the equation

$$2xCH_3NHB_2H_5 \rightleftharpoons (CH_3NHBH_2)_x + xB_2H_6$$

The reversible nature of the reaction was shown by the fact that when solid CH_3NHBH_2[13] was treated with a

(12) A. B. Burg, THIS JOURNAL, **56**, 500 (1934).

(13) Prepared by heating diborane and methylamine at 100° for two hours, and pumping off the volatile products.

17.28-cc. sample of diborane during three days at 40°, 0.8 cc. of diborane was absorbed, producing 1.03 cc. of $CH_3NHB_2H_5$ and 0.7 cc. of hydrogen. Shorter reaction periods, typified by an experiment in which diborane under 100 mm. pressure was passed over polymeric CH_3NHBH_2 at 100°, produced no detectable amount of methylaminodiborane.

Discussion

The observed regular trend toward increased thermal stability as methyl groups are successively substituted for N-bonded hydrogen atoms in the aminodiborane series appears to be inversely related to the stability of the polymeric forms of the aminoborines from which these compounds are formally derived.

Thus it is noteworthy that NH_2BH_2, CH_3NHBH_2 and $(CH_3)_2NBH_2$ show volatility characteristics indicative of a progressively lower degree of polymerization, while the corresponding aminodiboranes exhibit a complementary increase in thermal stability. Formation of a stable polymer withdraws aminoborine units from equilibria such as $B_2H_6 + 2BH_2NH_2 \rightleftarrows 2B_2H_7N$, accounting for the relative instability of B_2H_7N. This effect is lessened in the case of methylaminodiborane, and becomes immeasurable in dimethylaminodiborane, due to the low free energy change in the association of $(CH_3)_2NBH_2$—approximately 1.8 kcal./mole at 100°, according to preliminary experiments in this Laboratory.

The decrease of polymerization energy with N-methylation of the aminoborines might be related to the electron-releasing (+I) effect of the methyl groups, permitting resonance-contribution by structures in which boron has a complete octet. However, steric effects may well be more important.

The regular increase in volatility from B_2H_7N to dimethylaminodiborane is most convincingly attributed to steric factors; thus the reverse trend of boiling points (76.2, 66.8 and 50.3°) with increasing molecular weights, is in harmony with the suggestion that more methyl groups force the molecular dipoles farther apart, sharply lowering the intermolecular attraction.

Acknowledgment.—The generous support of this work by the Office of Naval Research is gratefully acknowledged.

Summary

The new compounds $CH_3NHB_2H_5$ and $(CH_3)_2NB_2H_5$ have been prepared from diborane and methylamine or dimethylamine. These and the parent compound, B_2H_7N, are regarded as derivatives of diborane in which a bridging hydrogen atom is replaced by N. A second hydrogen atom can be replaced by chlorine, yielding the volatile, unstable and self-inflaming $(CH_3)_2NB_2H_4Cl$. Volatility, stability and ease of preparation increase in the order $NH_2B_2H_5$, $CH_3NHB_2H_5$, $(CH_3)_2NB_2H_5$; the last can be stored permanently at ordinary temperatures.

LOS ANGELES 7, CALIF. RECEIVED JANUARY 17, 1949

[CONTRIBUTION FROM THE GEORGE M. MOFFETT RESEARCH LABORATORIES, CORN PRODUCTS REFINING COMPANY]

The Molecular Weight of the β-Amylase Limit Dextrin from Corn Starch

BY RALPH W. KERR AND FRANK C. CLEVELAND

Difficulty is experienced in the determination of the molecular weight of starch molecules by physical measurements on dispersions in appropriate solvents owing to the reluctance of these molecules or their derivatives to dissociate, or to become disentangled from each other. It is presumed that this difficulty arises because of the linear or long, thread-like structure of the amyloses, or because of the many linear branches on the large amylopectin molecules. On occasion, some branched starch derivatives are found to be so highly associated that they swell but do not dissolve to any very great extent in any neutral solvent. Accordingly, although molecular weight determinations on the amyloses have been reported frequently,[1-5] examinations of the amylopectins have either been approached with considerable caution, or the results have been given with the qualification that the error may be very large.[1,2,6] However, it appeared that if the linear terminal branches were removed, such as, by hydrolysis with β-amylase, association effects would be minimized when observations were made on the residual portion of the amylopectin molecules. Furthermore, inasmuch as branched starch molecules are thought to be of considerable size and measurements such as osmotic pressure determinations are of a very low order, it is obvious that by removing the end branches which constitute, on the average, nearly half the weight of amylopectin molecules, material would be provided the molecular weight of which could be estimated with very much greater accuracy. Lastly, since it has now generally been concluded that the action of β-amylase on amylopectin stops at a definite end-point, leaving the molecule intact behind points of branching, then it fol-

(1) K. H. Meyer, P. Bernfeld and W. Hohenemser, *Helv. Chim. Acta*, **23**, 885 (1940).

(2) F. E. Horan, Dissertation, Columbia University, New York, 1944.

(3) J. F. Foster and R. M. Hixon, THIS JOURNAL, **66**, 557 (1944).

(4) G. V. Caesar, N. S. Gruenhut and M. L. Cushing, *ibid.*, **69**, 617 (1947).

(5) F. C. Cleveland and R. W. Kerr, *ibid.*, **71**, 16 (1949).

(6) A. L. Potter and W. Z. Hassid, *ibid.*, **70**, 3774 (1948).

lows that a determination of the molecular weight of this limit dextrin, divided by the fractional yield of this material from the hydrolysis, should provide a fairly accurate calculation for the molecular weight of the parent molecules.

The principal deterrent to this enzymic approach has been doubt concerning the reliability of β-amylase preparations. The isolation of crystalline β-amylase by Balls, Thompson and Walden[7] which may be highly purified by repeated crystallizations, has served to remove this limitation.

Experimental

Preparation of Corn Limit Dextrin.—Fifty grams, dry basis of corn B-fraction, prepared by the use of Pentasol precipitation on autoclaved, defatted corn starch according to the method of Schoch[8] was dissolved in 1500 ml. of hot water by stirring and bringing to a boil. The solution was cooled to 45° with stirring. The *p*H was 6.0. Then 3 drops of a saturated ammonium sulfate suspension of four times recrystallized β-amylase[9] was added and the hydrolysis mixture held at 45°. The reaction was followed by removal of 5-ml. aliquots (40 ml. in all) from time to time and oxidation with alkaline potassium ferricyanide according to the method of Gore and Steele.[10] Hydrolysis was apparently at an end after three hundred and twenty minutes, at which time 54.4% of the B-fraction had been hydrolyzed to maltose.

It would appear from the method used by Balls and co-workers[7] to prepare the enzyme, wherein the crude β-amylase was pretreated with hydrochloric acid at *p*H 3.25 to 3.30 and wherein the enzyme was exposed for long periods of time to *p*H levels of about 3.5, that freedom from α-amylase activity in the final product was assured. This fact was confirmed by Balls and co-workers. It seems reasonable to assume also that after 4 recrystallizations of the β-amylase, a high degree of chemical purity was attained as well as biochemical purity. However, to test the possibility that this crystalline enzyme sample was not free from traces of α-amylase activity, the limit dextrin which remained in the reaction mixture after three hundred and twenty minutes was treated with another drop of enzyme suspension and the reaction was allowed to proceed for an additional nineteen hours, under toluene. No further increase in reducing value, whatsoever, was observed, the final value being equal to 54.3% conversion to maltose. The solution was brought to a boil, evaporated under reduced pressure to 625 ml. and two volumes of methanol were added with stirring to precipitate the limit dextrin. It was obvious that the dextrin consisted of two fractions of about equal parts by weight. The first precipitated when the concentration of methanol reached about 50% by volume and the second in the region of 60–67%. The entire yield of dextrin was combined and further purified by dissolving in water, adding methanol with stirring until the alcohol content reached 67% and collecting the precipitate. The purification procedure was repeated until the supernatant liquor was substantially free from soluble reducing material. Then the dextrin in a concentrated water solution was poured into absolute methanol, filtered and washed 4 times over a period of four days with 200 ml. of methanol. The methanol was removed *in vacuo* at room temperature. The yield of dextrin was 19.98 g., dry basis, or 41.1%, when allowance is made for the samples removed for analysis during the hydrolysis. This value is 90% of the calculated yield. The ferricyanide reducing value[11] of the limit dextrin is 0.79. For comparison, other ferricyanide reducing values are corn starch, 1.00; corn A-fraction, 1.43; corn B-fraction, 0.46.

Acetylation of Corn Limit Dextrin.—Three grams of the dextrin, dry basis, was ground to a powder and dispersed in 60 ml. of formamide.[12] The mixture was heated with stirring to 85° in about fifteen minutes, cooled to room temperature and diluted with 100 ml. of pyridine. To the clear, limpid solution, 80 ml. of acetic anhydride was added dropwise with stirring and the reaction mixture was allowed to stand at room temperature overnight. The clear solution was added slowly to 1500 ml. of water which was stirred with a circular motion. Unexpectedly, the product showed a very pronounced tendency to precipitate in fibrous form. The acetate was washed three times, each with one liter of water, separated by filtration and dried in the air. The dry material was mixed with 75 ml. of pyridine until dispersed and then heated over a period of about fifteen minutes to 85°. The solution was cooled to room temperature, 60 ml. of acetic anhydride added and the balance of the acetylation procedure completed as in the first phase. The final product, which also was fibrous, was washed with 5 one-liter portions of water and the washing period extended over a period of five days. The yield of acetate was 4.84 g., dry basis, or approximately 90%; acetyl = 44.7%. Polarimeter readings on a 2% solution of the acetate in chloroform gave a value $[\alpha]^{25}D$ 166.5°.

Determination of Osmotic Pressures.—Osmotic pressures were determined at several concentrations in chloroform solution according to general procedures given previously.[11] Solution of the acetate in chloroform appeared to be rapid and complete at room temperature. However, the solutions were held at the boiling point for fifteen minutes and cooled to 30° before use. Static measurements were made at all concentrations, since the experimental error inherent in the dynamic method was considered to be too large in relation to the small actual pressures which were developed in this series of experiments. Moreover, although the actual temperature of the osmotic pressure cell is of some importance in all measurements, it was readily apparent that in the determination of very small pressures, variation in temperature during the period of observation, such as the normal variation, or periodic fluctuation of a well-regulated, thermostatically controlled bath, may set up disturbances which cause very large errors. Accordingly, in addition to using a large metal cell of high heat capacity, the cell was brought to 30° and then heavily insulated in addition to being placed in a cabinet thermostatically held at 30 ± 0.05°. Under these conditions, a thermometer fitted into a metal well on the cell showed a variation of only a few thousandths of a degree during periods of observations.

Permeability of the membrane in the osmometer to small fragments of carbohydrate molecules which might possibly be present in the limit dextrin sample was determined as follows: When the highest concentration of solute used was in the osmometer (2.0349 g. per 100 ml.), it was allowed to stand seventy-two hours, the osmotic pressure was determined as shown and then the liquid in the solvent side was drawn into a weighed evaporating dish. The volume was 12 ml., and the residual weight after evaporation was 0.0003 g. The volume in the solution side was 15 ml. and contained therefore 0.3052 g. Accordingly, less than one part per thousand of the acetate diffused through the membrane.

Several tests at lower concentrations gave residues within the experimental error of weighing.

Discussion

The results of osmotic pressure measurements for the triacetate of the β-amylase limit dextrin from corn B-fraction are shown in Fig. 1 and Table

(7) A. K Balls, R. R. Thompson and M. K. Walden, *J. Biol. Chem.*, **173**, 9 (1948).

(8) T. J. Schoch, *Advances in Carbohydrate Chemistry*, **1**, 247 (1945).

(9) This preparation was kindly supplied by Dr. A. K. Balls.

(10) H. C. Gore and H. K. Steele, *Ind. Eng. Chem., Anal. Ed.*, **7**, 324 (1935).

(11) F. C. Cleveland and R. W. Kerr, *Cereal Chem.*, **25**, 133 (1948).

(12) J. F. Carson and W. D. Maclay, THIS JOURNAL, **68**, 1015 (1946).

TABLE I

OSMOTIC PRESSURES OF THE ACETATE OF β-AMYLASE LIMIT DEXTRIN FROM CORN B-FRACTION IN CHLOROFORM

C, concn., g. per 100 ml.	π, g. per square cm.	π/C
0.1021	0.100	0.979
.1924	.147	.765
.3036	.228	.751
.4504	.280	.622
.6075	.426	.701
.8008	.648	.809
1.0130	.825	.815
1.4530	1.604	1.104
2.0349	3.003	1.480

I. It will be observed that the slope of the curve plotting π/C against C is negative at very low concentrations, then changes in slope and at relatively high concentrations assumes a positive slope. A similar shape has been observed by Steurer[13] for high molecular weight ethyl cellulose in toluene. This shape has also been observed by us previously in unreported studies on derivatives of hydrolyzed branched starch molecules although we were unable to observe a similar effect with the acetates of linear starch molecules,[5] at least using concentrations as low as 0.3 g. per 100 ml., which appeared to be the limit for reliable measurements using techniques which were available at that time. In studies on hydrolyzed, branched starch molecules, and using concentrations in the range of 0.2 to 0.8 g. per 100 ml., it was at first assumed that the osmotic pressure curves had very nearly zero slope. More extended observations by improved techniques on branched fractions from acid hydrolyzed starch of the order of DP_n 500–1000 (which will be the subject of a future report) have shown in this case also, that the slope of the curve becomes negative as infinite dilution is approached. This is presumed to be due to residual association between solute molecules; the effect vanishes at low orders of DP_n. At relatively high concentrations, the curve for branched starch molecules shows the usual anomalous osmotic pressure effects given generally by high polymers which has been discussed recently by Bawn.[14]

Extrapolation of curves of the shape shown is difficult and constitutes the principal element of uncertainty of the results reported. It is believed, however, that the extrapolation shown in Fig. 1 indicates at least the correct order of magnitude for the osmotic pressure of the limit dextrin acetate at infinite dilution. The corresponding DP_n value is 810.

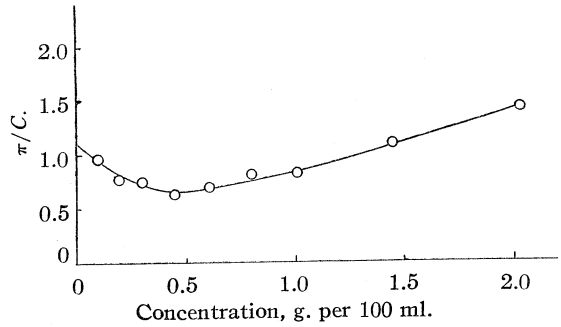


Fig. 1.—Osmotic pressure–concentration relationship for corn limit dextrin acetate in chloroform solution at 30°. The ordinate gives values for π/C as explained in Table I. The abscissa gives values for concentration in grams per 100 ml.

From this value and from the calculated yield of 46% limit dextrin, the indicated DP_n value for the parent amylopectin fraction is of the order of 1800.

In making this computation the assumption is made that each molecular weight group of corn B-fraction is made up of a variety of molecules which give the same average limit of hydrolysis as the total parent fraction. This may not be strictly true since a limited subfractionation of the butanol, non-precipitable fraction of corn starch by Kerr[15] showed that the subfraction of highest apparent molecular weight had a limit of conversion about 10% greater than the subfraction of lowest molecular weight. However, if the difference between various molecular weight groups is not substantially greater than 10%, then the calculation employed would be expected to give the correct order of magnitude for the DP_n of corn amylopectin.

Summary

A limit dextrin has been prepared in 90% of the calculated yield from corn B-fraction using crystalline β-amylase, and its ferricyanide reducing value determined.

The triacetate of the dextrin was found to be readily dispersible in chloroform, have a specific rotation of $[\alpha]^{25}D$ of 166.5° and an osmotic pressure at 30° equivalent to a DP_n of 800.

It was observed that the dextrin acetate tended to precipitate in fibrous form.

ARGO, ILL. RECEIVED MAY 11, 1949

(13) E. Steurer, *Z. physik. Chem.*, **A190**, 1 (1941).

(14) C. E. H. Bawn, "Chemistry of High Polymers," Interscience Publishers, New York, N. Y., 1948, p. 156.

(15) R. W. Kerr, *Arch. Biochem.*, **7**, 377 (1945).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

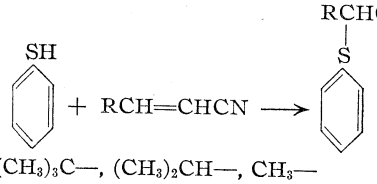
Cyanoalkylation: The Addition of Thiophenol to β-Alkylacrylonitriles

BY ROBERT M. ROSS[1]

Although cyanoethylation has been the subject[2] of considerable work within recent years, no systematic study has been reported anent the relationship of acceptor structure to the reactivity of the conjugate system in alkylated acrylonitriles. Consequently, it became the purpose of this research to investigate the cyanoalkylations of an active hydrogen component by substituted acrylonitriles, wherein alkyl groups were located in the β-position.

The addition of compounds which contain labile hydrogen atoms to acrylonitrile[2] proceeds readily with the formation of excellent yields of adducts. However, substituted acrylonitriles almost invariably react less readily than acrylonitrile with nearly all active hydrogen components. Among the nitriles which have been described in reactions of this type are α-methylacrylonitrile,[2] crotonitrile,[3] cinnamonitrile[4] and 1-cyano-1,3-butadiene.[5] Although the behavior of various addenda with such alkylacrylonitriles has been investigated, thiophenol has seen little or no use in this capacity. Furthermore, since thiophenol has shown especial reactivity[6] in cyanoethylation, it was decided to determine whether β-alkylacrylonitriles would again present difficulties of decreased reactivity even with thiophenol.

Thiophenol was added in the conjugate manner to the following unsaturated nitriles: β-*t*-butylacrylonitrile, β-isopropylacrylonitrile and β-methylacrylonitrile. Triton B[7] was employed as a catalyst, and the reactions were carried out under constant conditions in each of the cyanoalkylations. The poorest yield of adduct was obtained from β-*t*-butylacrylonitrile and thiophenol (21%), whereas crotononitrile afforded the best yield (54%) of the β-phenylmercapto addition compound. It should be noted that these yields are not nearly as satisfactory as those reported[6] for the reaction between thiophenol and acrylonitrile. Apparently, even with the extraordinarily active thiophenol, β-alkylacrylonitriles do not possess the high order of reactivity which is characteristic of acrylonitrile in the presence of a Triton B catalyst.



R = $(CH_3)_3C$—, $(CH_3)_2CH$—, CH_3—

A further study of the thiophenol reaction, however, has brought to light a catalyst which affords high yields even with the alkylated acrylonitriles. It has been found that a mixture of Triton B and piperidine produced β-alkyl-β-phenylmercaptopropionitriles in yields which varied from 87 to 93% of the theoretical value. No significant difference in yields was apparent whether the acceptor molecule was β-*t*-butylacrylonitrile, β-isopropylacrylonitrile or crotononitrile. Reaction conditions for this series of experiments were identical to those employed previously with the Triton B catalyst. Possibly, the mixture of piperidine and Triton B counteracted any adverse equilibrium conditions present when Triton B was the sole catalyst.

A series of similar cyanoalkylations were carried out using piperidine alone as a catalyst. The yields of adducts thus prepared corresponded closely to those obtained with a mixture of piperidine and Triton B; in every instance, however, the yields were slightly less than in the case of the mixed catalyst. Whether or not the diminution of yield was significant is debatable.

All of the adducts were characterized by micro and infrared analyses of the substituted phenylmercaptopropionitriles, hydrogen peroxide oxidation of the adducts to the corresponding sulfonyl derivatives, and microanalyses of the sulfones thus obtained. On the basis of precedent, the addition was assumed to take place in the normal 1,4-manner, since the reactions were not carried out under the influence of peroxides.

It is believed that the true catalyst responsible for the increased yields in those cyanoalkylations carried out with the piperidine and Triton B or piperidine catalysts is a salt or complex of thiophenol and piperidine. This phase of the work is to be investigated further.

Experimental[8]

β-Alkylacrylonitriles.—New methods for the preparation of β-*t*-butylacrylonitrile and β-isopropylacrylonitrile have been described elsewhere.[9] Crotononitrile was prepared by a modification of the method described by Dollfus,[10] which involved acetic anhydride dehydration of crotonaldoxime.[11]

(1) A portion of this investigation was carried out during the period in which the author was the du Pont Postdoctoral Fellow at the University of Illinois; the author is indebted to the du Pont Company for the opportunities made available during this time.

(2) Bruson, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. V (in press).

(3) Bruylants, *Bull. soc. chim. Belg.*, **31**, 225 (1922).

(4) Borsche, *Ber.*, **42**, 4496 (1909).

(5) Charlish, Davies and Rose, *J. Chem. Soc.*, 227 (1948).

(6) Hurd and Gershbein, THIS JOURNAL, **69**, 2328 (1947).

(7) Triton B is a 35% aqueous solution of trimethylbenzylammonium hydroxide which may be procured from Rohm and Haas.

(8) The author is indebted to Emily Davis, Ruth Kopel and Jane Wood for all microanalyses reported, and to Elizabeth M. Petersen for the infrared data.

(9) Ross and Burnett, THIS JOURNAL, **71**, 3562 (1949).

(10) Dollfus, *Ber.*, **25**, 1920 (1892).

(11) The author is indebted to Mary Louise Burnett for preparing the crotononitrile used in this work.

TABLE I

β-ALKYL-β-PHENYLMERCAPTOPROPIONITRILES AND β-ALKYL-β-PHENYLSULFONYLPROPIONITRILES

β-Alkyl substituent, g.	β-Alkyl-β-phenylmercaptopropionitriles, RCH(SC$_6$H$_5$)CH$_2$CN: Method and % yield	B. p., °C.[a] adduct	n^{20}D[e]	Analyses, % Calcd. C	Calcd. H	Found C	Found H	β-Alkyl-β-phenylsulfonylpropionitriles, RCH(SO$_2$C$_6$H$_5$)CH$_2$CN: M. p., °C.[a] oxidation product	Yield, %	Analyses, % Calcd. C	Calcd. H	Found C	Found H
t-Butyl 2.20	A 93 B 77 C 21[f]	108 (0.5 mm.)[d]	1.5546	71.18	7.81	71.06	7.72	97.3–98	52[b]	62.12	6.82	62.34	6.86
Isopropyl 1.90	A 87 B 85 C 32	110 (0.38 mm.)[d]	1.5535	70.20	7.37	70.15	7.38	79.7–80.5	75[c]	60.73	6.37	60.90	6.35
Methyl 1.34	A 89 B 85 C 54	114 (0.9 mm.)	1.5581	67.75	6.26	68.01	6.45	92.5–93.5	73	57.39	5.33	57.56	5.42

[a] All boiling points and melting points are uncorrected. [b] β-*t*-Butyl-β-phenylsulfonylpropionamide was obtained as a white solid (10% yield) from the fractional crystallization, m. p. 182.2–183.2°. *Anal.* Calcd. for $C_{13}H_{19}NO_3S$: C, 57.96; H, 7.11. Found: C, 57.86; H, 7.30. [c] A small amount (19%) of crude β-isopropyl-β-phenylsulfonylpropionamide was isolated from the hydrogen peroxide oxidation by fractional crystallization, m. p. 145–154°. Further recrystallizations from hot ethyl acetate did not alter its purity sufficiently so that the product could be analyzed. [d] The infrared absorption spectra for these adducts were in complete agreement with the proposed structure. [e] Constants listed are those observed from a middle cut of constant refractive index. [f] A considerable amount (1.6 g.) of unchanged β-*t*-butylacrylonitrile was recovered during the distillation.

Addition of Thiophenol to β-Alkylacrylonitriles

Method A (Triton B and Piperidine Catalyst).—A mixture of 0.02 mole of β-alkylacrylonitrile and 2.20 g. (0.02 mole) of thiophenol[12] was placed in a 10-ml. flask equipped with a reflux condenser. To the contents of the flask was added 5 drops of dry, freshly distilled piperidine. A white precipitate, believed to be the salt of thiophenol and piperidine, formed immediately. After the reaction mixture was allowed to stand for forty-five minutes, 5 drops of Triton B and 2.5 ml. of peroxide-free dioxane[13] were added. The homogeneous contents of the flask were refluxed for twenty-four hours at an oil-bath temperature of 112°. At the end of this time, the source of heat was removed and the amber-colored solution was allowed to stand overnight at room temperature.

The dioxane was removed by distillation under atmospheric pressure, and the residue was extracted with 10 ml. of benzene. The benzene solution was scrubbed successively with 10-ml. portions of water, 5% aqueous sodium hydroxide solution, and finally with water. This procedure was found to be effective in removing any unreacted thiophenol. The benzene extract was dried over anhydrous magnesium sulfate, and the excess benzene removed by distillation. A distillation done under reduced pressure yielded the adduct as a slightly yellow, viscous oil. Redistillation of several combined runs was effected in order to obtain an analytical sample. A middle fraction of colorless β-alkyl-β-phenylmercaptopropionitrile of constant refractive index was obtained.

Method B (Piperidine Catalyst).—Other than the omission of Triton B as a catalyst component, the amounts of reactants and the procedure utilized remained the same as that described under Method A.

Method C (Triton B Catalyst).—The conditions for this method were the same as for Method A with the exception that Triton B alone was employed as the catalyst.

(12) "Organic Syntheses," Coll. Vol. I, second edition, 1946, p. 504.

(13) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., second edition, 1941, p. 368.

β-Alkyl-β-phenylsulfonylpropionitriles.—A mixture of 1.0 g. of the β-alkyl-β-phenylmercaptopropionitrile and 1.8 ml. of glacial acetic acid was placed in a test-tube and 2.0 g. of 30% hydrogen peroxide was added. The resulting mixture was stoppered, shaken occasionally, and allowed to stand for eight days at room temperature. At the end of two days, shaking was no longer necessary since solution had been effected.

A total of 6 ml. of water was added to the contents of the tube which usually contained some white crystals of oxidation product. These crystals had separated during the eight-day period of standing. Complete crystallization was effected after the tube and contents were chilled at 0° for several hours. The white, crystalline material was removed by filtration, washed with water, and dried in air. The product thus obtained was found to be a mixture of a β-alkyl-β-phenylsulfonylpropionitrile and a β-alkyl-β-phenylsulfonylpropionamide. Six fractional crystallizations using the mixed solvent pair, ethyl acetate and *n*-hexane, were effective in separating the nitrile from the amide. All the amides were found to be less soluble in this solvent pair; thus, the nitrile was isolated in a satisfactory state for elementary analysis by concentrating to dryness the mother liquors from each recrystallization and subjecting the residue to further crystallizations.

Summary

The addition of thiophenol to some *beta*-alkylated acrylonitriles has been studied. It has been found that a catalyst which consists of piperidine and Triton B causes the reaction to proceed with the formation of excellent yields of β-alkyl-β-phenylmercaptoacrylonitriles. Piperidine was also effective in affording high yields, but the use of Triton B as the sole catalyst gave significantly smaller amounts of adduct.

URBANA, ILLINOIS RECEIVED JUNE 11, 1949

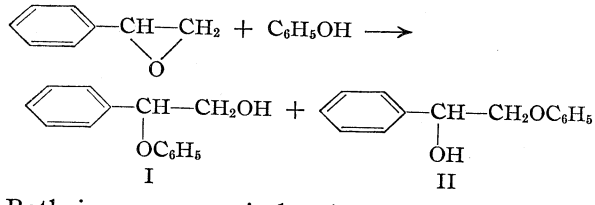
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

The Reaction of Styrene Oxide with Phenol

BY CYRUS O. GUSS

From the results of previous studies of the alkali-catalyzed reaction of olefin oxides with phenol it was concluded that the products were ether-alcohols. In the case of propylene oxide, an unsymmetrical olefin oxide, the early work[1] indicated that an isomeric mixture of the two possible ether-alcohols was obtained. Recent work[2,3] has shown, however, that the alkali-catalyzed reaction of propylene oxide with phenols produced predominantly or entirely the isomer having a secondary alcohol group. Alcohols were reported[3,4,5] to react with propylene oxide in a similar manner.

In the present investigation it was found that the alkali-catalyzed reaction of styrene oxide with phenol proceeded as shown



Both isomers were isolated and their structures proved by independent synthesis. In most cases the primary alcohol (I) was formed in greater amount, a result in contrast to the analogous reaction of propylene oxide with phenol under similar conditions.

In Table I are summarized some data obtained in this study. The alkali-catalyzed reactions were run in water, or dioxane, and excess phenol. In the presence of water the isomeric mixture was found to consist of approximately three parts of the primary alcohol (I) to one part of the secondary alcohol (II). In dioxane the relatively slower reaction produced the two isomers in more nearly equal amounts. Thus, there was an apparent effect of the reaction medium on the course of the ring-opening reaction. It was also noted, as shown in Table I, that as the concentration of sodium phenoxide was increased, the relative amount of the secondary alcohol (II) formed also increased. This effect of sodium phenoxide concentration was most pronounced in dioxane.

The separation of the two isomers from each other was most easily accomplished by taking advantage of the differences in their rate of reaction with phthalic anhydride.[6] However, since the separation by this method was not attained quantitatively, it was necessary to resort to other means to ascertain the composition of the isomeric mixture more precisely. The use of a phase diagram made it possible to obtain the composition data in Table I.

TABLE I

REACTION OF 0.1 MOLE OF STYRENE OXIDE WITH 0.3 MOLE OF PHENOL[a]

Solvent used	Catalyst	Time, hr.	Yield of mixture, I + II, %	I in mixture, %
15 cc. of water	0.005 mole NaOH	2.5	65.9	78
15 cc. of water	.1 mole NaOH	1.0	85.0	76
15 cc. of water	.3 mole NaOH	1.0	74.8	70
20 cc. of water	.2 mole NaOH	1.0	76.6	75[b]
25 cc. of dioxane	.004 mole Na	3.5	74.8	68
25 cc. of dioxane	.1 mole Na	3.5	89.7	49
25 cc. of dioxane	.25 mole Na	3.0	66.8	39
25 cc. of dioxane	.15 mole Na	3.0	74.7	53[b]
None	None	4.0	32.2[c]	88
15 cc. of water	0.0016 mole HOTs[d]	1.0	14.0[e]	67
None	0.0026 mole HOTs	0.5	..[f]	

[a] All runs in dioxane were at reflux temperature, the uncatalyzed run and those in water at 100°-bath. The last run in the table was at 200°-bath. [b] Styrene bromohydrin (0.1 mole, b. p. 114–115° (3 mm.), $n^{20}D$ 1.5780) was used instead of styrene oxide. [c] A large amount of higher boiling material was also formed. [d] *p*-Toluenesulfonic acid monohydrate. [e] Other products were phenyl glycol (11.6%) and higher boiling material, part of which was alkali soluble. [f] A solid product formed which softened at 80–100° and was alkali soluble. Only 0.1 mole of phenol was used in this run.

Styrene bromohydrin gave the same relative amounts of primary alcohol (I) and secondary alcohol (II) in the isomeric mixture as styrene oxide when it was used instead of styrene oxide in the alkali-catalyzed reaction, showing that the oxide was undoubtedly the species reacting with the phenol. This result excluded the use of the bromohydrin in the reaction as a means for structure proof, and it also seriously jeopardized the validity of the structure proof employed by Emerson[7] in his study of the reaction of styrene oxide with alcohols.

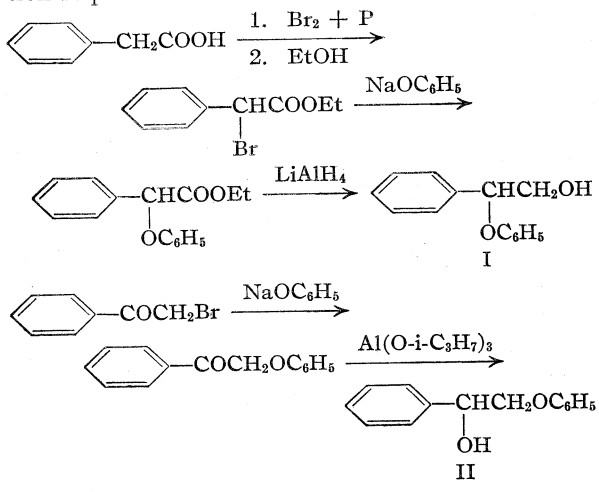
The uncatalyzed reaction of styrene oxide with phenol gave a relatively low yield of the isomeric mixture in which the primary alcohol (I) was present in a ratio of nearly nine to one.

The use of *p*-toluenesulfonic acid to catalyze the reaction of styrene oxide with phenol gave a product that was alkali soluble. When water was present also, as indicated in Table I, a low yield of the isomeric mixture of I and II was formed together with phenyl glycol and higher-boiling materials, part of which was alkali soluble. The alkali-soluble material must have resulted from a reaction of the oxide with the nucleus of the phenol. A study of this latter type of reaction is nearly completed and will be reported upon soon.

The structures of I and II were assigned on the

(1) Boyd and Marle, *J. Chem. Soc.*, **105**, 2117 (1914).
(2) Hurd and Perletz, THIS JOURNAL, **68**, 38 (1946).
(3) Sexton and Britton, *ibid.*, **70**, 3606 (1948).
(4) Chitwood and Freure, *ibid.*, **68**, 680 (1946).
(5) Swern, Billen and Knight, *ibid.*, **71**, 1152 (1949).
(6) Cox, Nelson and Cretcher, *ibid.*, **49**, 1080 (1927).
(7) Emerson, *ibid.*, **67**, 516 (1945).

basis of identity with the products from the reaction sequences



The results from the present study supplement the knowledge of the effect of groups and media on the direction of the ring opening of substituted ethylene oxides. Since propylene oxide is found to give the secondary alcohol in the alkali-catalyzed reaction with alcohols[4,5] or with phenols,[2,3] the course of the reaction is said to be guided by the electron-releasing action of the methyl group.[4,5] In 3,4-epoxy-1-butene, in which the vinyl group is present instead of the methyl group as in propylene oxide, one interpretation that is suggested[5] to account for an observed formation of a primary alcohol exclusively in the reaction of the oxide with sodium alloxide in allyl alcohol is also based on an electron release by the vinyl group. Alternatively, Bartlett and Ross,[8] who find that 3,4-epoxy-1-butene reacts with sodium methoxide in methanol to give the secondary alcohol predominantly but also some primary alcohol, suggest that allylic resonance in a transition state might account for the formation of the primary alcohol. If this concept of resonance in a transition state is applied to the alkali-catalyzed reaction of styrene oxide with alcohols and with phenols, the expected result would be to find the formation of the primary alcohol predominant or exclusive, since the lowering of the energy of the transition state leading to the primary alcohol ought to be greater in the case of styrene oxide than in the case of 3,4-epoxy-1-butene. The present results can be cited in support of this interpretation, as can also the finding by Swern, Billen and Knight[5] that styrene oxide reacts with allyl alcohol and sodium alloxide to give the primary alcohol predominantly. The latter authors explain their results on the basis of an electron-attracting action by the phenyl group. On the other hand, Russell and VanderWerf[9] present the point of view that the phenyl group in styrene oxide is electron releasing in the reaction with sodium diethyl malonate. Perhaps a study of the effect of temperature and other factors of the reaction environment might help to resolve some of the present difficulties in the interpretation of the ring-opening reactions of olefin oxides.

(8) Bartlett and Ross, THIS JOURNAL, **70**, 926 (1948).

(9) Russell and VanderWerf, *ibid.*, **69**, 11 (1947).

Experimental[10]

Reaction of Styrene Oxide with Phenol.—The runs reported in Table I were all made in a similar manner. The phenol, water or dioxane, and the sodium hydroxide, or sodium, or *p*-toluenesulfonic acid were brought together in a three-necked flask equipped with stirrer, condenser and a dropping funnel. As soon as but one phase existed at the temperature used, the styrene oxide[11] (n^{20}D 1.5352) was added dropwise over a period of five to ten minutes. Heating and stirring were continued for the indicated time. These reactions, except for the first run in Table I, were one-phase. The amber or red reaction mixture was then poured into 200 g. of an ice-water mixture containing sufficient sodium hydroxide to react with the excess free phenol. The insoluble material was then taken up in two 75-cc. portions of ether, and the ether solution was dried over anhydrous potassium carbonate or anhydrous sodium sulfate. After distillation of the ether, the residue was distilled in a 50-cc. modified Claisen flask packed with 3″ of 1/8″ glass helices. A small amount of material boiling in the range 50–60° (0.5 mm.) was usually obtained, after which the temperature rose immediately to 150–160° (0.5 mm.) over which interval the mixture of I and II distilled. A higher-boiling residue that remained was usually not distilled, but it was noted on one occasion to have a boiling point above 200° (0.5 mm.). The fraction boiling at 150–160° (0.5 mm.) rapidly solidified. It was this material whose melting point was now measured to determine the relative amounts of I and II present by the use of the phase diagram.

Determination of Composition of Mixture of Isomers I and II.—The apparatus used was similar to the Beckmann freezing-point depression arrangement, employing a thermometer calibrated in 0.5°. A system of crossed polaroid glasses was used to observe the disappearance of the last crystal. Table II gives the melting points thus obtained for the mixtures of known composition.

TABLE II

MELTING POINTS OF KNOWN MIXTURES OF I AND II

I, %	M. p., °C.	I, %	M. p., °C.
4.88	60.25	40.20	46.00
9.33	58.50	47.68	53.50
16.99	55.50	68.88	65.75
28.97	50.50	86.97	74.50
35.00	47.00		

The graph made from these data was used in the usual manner to determine the composition of the mixture of isomers resulting from the interaction of styrene oxide and phenol.

Separation of I and II.—It was found that isomer I was much more easily esterified than II, and it was this observation that led to the use of the following procedure to separate the two isomers.

A solution of the mixture of isomers (5 g., 0.0234 mole, 76% I), phthalic anhydride (7.4 g., 0.05 mole), and pyridine (4.9 g., 0.062 mole) in dioxane (25 cc.) was allowed to stand at room temperature for five hours. This solution was then dissolved in 100 cc. of ether. The ether solution was shaken with 100 cc. of water containing 10 cc. of concd. hydrochloric acid to remove the pyridine. The half-ester of I and any phthalic acid were removed by shaking the ether solution with 150 cc. of 7.5% sodium carbonate.

(10) Microanalyses reported in this paper were performed by the analyst at the California Institute of Technology, Pasadena, California. All melting points are uncorrected.

(11) Alquist and Guss, U. S. Patent 2,237,284 (April 8, 1941).

The remaining ether solution was then washed with 100 cc. of water, dried over anhydrous potassium carbonate, and the removal of the ether then left a white solid. Two or three recrystallizations from heptane left 0.5 g., m. p. 62–64°, identified as **1-phenyl-2-phenoxyethanol** (II) by mixed melting with an authentic sample.

To the aqueous solution of the half-ester of I was added 4 g. of sodium hydroxide and the solution refluxed for one hour. The insoluble material that separated was taken up in 75 cc. of ether and the ether solution dried over anhydrous potassium carbonate. After removal of the ether and two recrystallizations of the resulting solid from heptane, 3.0 g., m. p. 80–81° was obtained and identified as **2-phenyl-2-phenoxyethanol** (I) by mixed melting point.

The above procedure thus gave a 70% yield of the two pure isomers. The separation was not found to be clean-cut, and the remaining 30% consisted of mechanical loss and a mixture of approximately equal parts of the two isomers. An initial mixture containing 49% I gave a 60% yield of pure I and pure II when carried through the above procedure. The reprocessing of the unseparated portion would undoubtedly lead to a higher over-all yield of the two separated isomers.

Preparation of 2-Phenyl-2-phenoxyethanol (I).—Ethyl α-bromophenylacetate (b. p. 102–104° (0.4 mm.), $n^{20}D$ 1.5380) was prepared in 70.7% yield by the procedure of Anschütz[12] from phenylacetic acid, bromine, phosphorus and absolute ethanol. This ester (36.5 g., 0.15 mole) was added dropwise in fifteen minutes to sodium phenoxide (0.15 mole) and phenol (0.15 mole) in dry dioxane (23 cc.) at 100°. After forty-five minutes the reaction mixture was cooled and added to 300 cc. of water. The organic layer was extracted with 200 cc. of ether, dried over anhydrous sodium sulfate, and distilled to give 26.1 g. (68%), b. p. 155–156° (0.8 mm.), $n^{20}D$ 1.5452. That this material was ethyl α-phenoxyphenylacetate was shown by its hydrolysis in refluxing 4% sodium hydroxide to α-phenoxyphenylacetic acid, m. p. 108–109.5°. Meyer and Boner[13] have reported m. p. 108°.

Ethyl α-phenoxyphenylacetate was reduced to 2-phenyl-2-phenoxyethanol (I), needles, m. p. 80–81°, in 84% yield by the use of lithium aluminum hydride according to the usual procedure.[14] Heptane was used for recrystallization. This product mixed with I from the styrene oxide and phenol reaction melted without depression.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.50; H, 6.60.

The *p*-nitrobenzoate of this alcohol was prepared in the usual manner[15] with the exception that the reaction mixture was not heated externally but allowed to stand for one hour before working up. The ester was recrystallized from ethanol as platelets, m. p. 86–87°.

Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72. Found: C, 69.63; H, 4.88.

Preparation of 1-Phenyl-2-phenoxyethanol (II).—Phenacyl bromide was converted into ω-phenoxyacetophenone, m. p. 71–72°, by the procedure of Mohlau[16] in 61% yield; oxime, m. p. 113–114°, as reported by Fritz.[17] The 2,4-dinitrophenylhydrazone was made by the ordinary method,[18] m. p. 183–184°. It was recrystallized from an ethanol–ethyl acetate mixture.

Anal. Calcd. for $C_{20}H_{16}N_4O_5$: C, 61.22; H, 4.11. Found: C, 61.11; H, 4.14.

The ω-phenoxyacetophenone was reduced with aluminum isopropoxide to the corresponding alcohol, 1-phenyl-2-phenoxyethanol (II), needles, m. p. 63–64° in 86.5% yield. The recrystallization solvent was heptane. This product was shown to be identical with II resulting from the reaction of styrene oxide with phenol by the absence of a mixed melting point depression.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.75; H, 6.58.

The *p*-nitrobenzoate, prepared in the manner employed for the isomer above, crystallized from ethanol as fine needles, m. p. 83–84°.

Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72. Found: C, 69.72; H, 4.96.

Summary

1. Styrene oxide was found to undergo an alkali-catalyzed reaction with phenol to give 66–90% yields of an isomeric mixture of 2-phenyl-2-phenoxyethanol (I) and 1-phenyl-2-phenoxyethanol (II) in which the content of I varied from 39 to 78% depending on the conditions used. Resonance stabilization of a transition state is mentioned to explain this difference in the direction of ring opening relative to propylene oxide.

2. The uncatalyzed reaction produced low yields of the isomeric mixture in which I constituted 88% of the total.

3. Acid catalysis of the reaction gave large amounts of an alkali-soluble material presumed to result from the reaction of the oxide with the nucleus of the phenol.

4. Styrene bromohydrin gave the same relative amounts of I and II as styrene oxide in the alkali-catalyzed reaction, indicating intermediate formation of the oxide.

LOS ANGELES 7, CALIFORNIA RECEIVED MAY 20, 1949

(12) Anschütz, *Ann.*, **354**, 127 (1907).

(13) Meyer and Boner, *ibid.*, **220**, 51 (1883).

(14) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

(15) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1948, p. 164.

(16) Mohlau, *Ber.*, **15**, 2497 (1882).

(17) Fritz, *ibid.*, **28**, 3028 (1895).

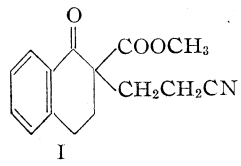
(18) Reference 15, p. 171.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

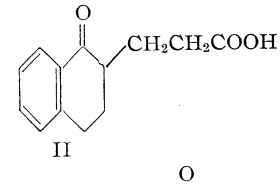
3-Ketohydrophenanthrenes and 2′-Ketohydro-1,2-cyclopentenonaphthalenes

BY W. E. BACHMANN AND G. DANA JOHNSON[1]

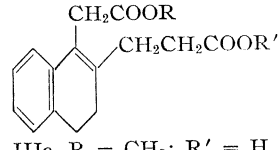
1-Tetralone-2-β-propionic acid (II) was prepared from 2-carbomethoxy-1-tetralone by reaction of its sodio derivative with methyl β-bromopropionate and by cyanoethylation to I followed by hydrolysis and decarboxylation. Reaction of the methyl ester of the acid with zinc and methyl bromoacetate gave the unsaturated acid ester IIIa and not the normal hydroxy ester. The acid ester may have resulted through the intermediate formation of the δ-lactone IV followed by hydrolysis in the isolation process. That the



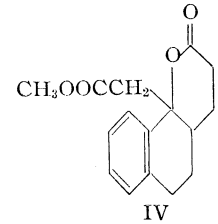
I



II



IIIa, R = CH_3; R′ = H
IIIb, R = R′ = CH_3
IIIc, R = R′ = H



IV

product which was isolated was not the lactone was indicated by its acidic nature and its high absorption maximum (log ε = 4.12) at 264 mμ in the absorption spectrum (Fig. 1). This is to be compared with the spectrum of the γ-lactone VIII (which is similar in structure but more resistant to hydrolysis than the δ-lactone) which absorbs much less strongly (log ε = 2.72) in this region. The double bond appears to be in the ring and not in the exocyclic position in the acetic acid side chain judging from the failure of the corresponding diacid IIIc (which shows the same absorption as the acid ester) to be reduced by sodium amalgam and water. This conclusion is supported by the correspondence of the absorption maximum with the peak of 1,2-dihydronaphthalene at 262 mμ (log ε = 4.01) in hexane.[2]

A Dieckmann cyclization of the dimethyl ester (IIIb) of the unsaturated acid followed by acid hydrolysis and decarboxylation of the resulting β-keto ester yielded 3-keto-1,2,3,9,10,10a-hexahydrophenanthrene (V), which had the same melting point as the ketone prepared from 2-dimethylaminomethyl-1-tetralone and acetoacetic ester in the presence of sodium methoxide.[3] The position of a maximum with log ε = 4.28 at 298 mμ in the absorption spectrum indicated conjugation of the double bond with the aromatic ring and with the carbonyl group.[4] Apparently a shift of the double bond occurs at some stage of the cyclization process.

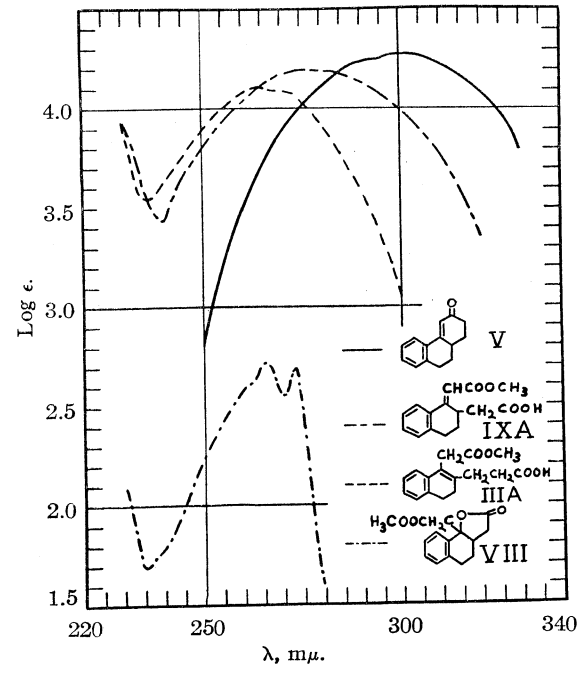
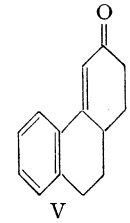
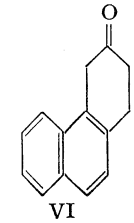


Fig. 1.—Ultraviolet absorption spectra.

The dimethyl ester IIIb was dehydrogenated smoothly by sulfur to the dimethyl ester of 1-car-



V



VI

boxymethylnaphthalene-2-β-propionic acid, which was cyclized to 3-keto-1,2,3,4-tetrahydrophenanthrene (VI), a rather unstable ketone. The position of the keto group was proved by conversion of the ketone into 3-methylphenanthrene by reaction with methylmagnesium iodide, followed by dehydration and dehydrogenation of the carbinol.

The saturated diester prepared by hydrogenation of IIIb in the presence of Adams catalyst was cyclized to 3-keto-1,2,3,4,4a,9,10,10a-octahydro-

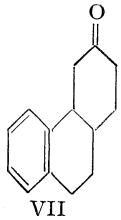
(1) From the Ph.D. dissertation of G. Dana Johnson, 1946. Present address: Department of Chemistry, Indiana University.

(2) Morton and de Gouveia, *J. Chem. Soc.*, 916 (1934).

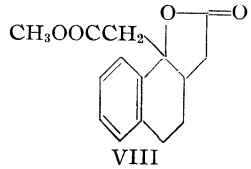
(3) Mannich, Koch and Borkowsky, *Ber.*, **70**, 355 (1937).

(4) Compare (a) Wilds, *et al.*, THIS JOURNAL, **69**, 1985 (1947); (b) Bachmann and Dreiding, *J. Org. Chem.*, **13**, 317 (1948).

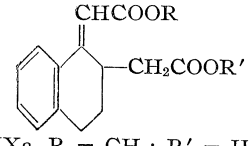
phenanthrene (VII). Only one of the two possible forms (*cis* and *trans*) was obtained; its configuration has not been established. All three 3-ketohydrophenanthrenes, the tetrahydro-, hexahydro- and the octahydro-compound, were converted into phenanthrene by a Wolff–Kishner reduction followed by dehydrogenation of the product.



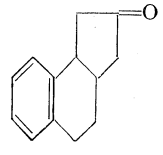
VII



VIII



IXa, R = CH_3; R′ = H
IXb, R = R′ = CH_3
IXc, R = R′ = H



X

A similar series of ketones in which the carbonyl group was part of a five-membered ring was prepared in a similar manner from diesters which contained one less methylene group in the side chain in the 2-position of the naphthalene ring. The starting material was 1-tetralone-2-acetic acid which was prepared from 2-carbomethoxy-1-tetralone and methyl bromoacetate and also from 2-bromo-1-tetralone and malonic ester in the manner of Bergs.[5] The methyl ester of 1-tetralone-2-acetic acid in a Reformatsky reaction with methyl bromoacetate gave the lactone VIII. Hydrolysis of the lactone with one equivalent of alkali yielded the isomeric acid ester IXa. The position of the double bond in the diacid IXc appears to be different from that in the homolog IIIc, since reduction of IXc by sodium amalgam proceeded readily. This indicated the existence of the triple conjugation shown in the formula. Moreover, the maximum in the ultraviolet absorption spectrum of IXa and of IXc is located about 11 mμ higher than in IIIc as would be expected of a completely conjugated system.

The dimethyl ester IXb was cyclized to $\Delta^{1-1'}$-2′-keto-3,4-dihydro-1,2-cyclopentenonaphthalene (like X but with a double bond). The intense absorption (log ϵ = 4.38) at 287 mμ indicated that the double bond was conjugated with the carbonyl group and the benzene ring; the peak is located at a lower wave length than the corresponding maximum in the homologous hexahydrophenanthrene ketone V. As this work was being completed, Wilds and Johnson[6] reported the synthesis of this ketone by a different method. The absorption curve for our compound is identical with that obtained by them.[4a]

(5) Bergs, *Ber.*, **63**, 1285 (1930).

(6) Wilds and Johnson, THIS JOURNAL, **68**, 86 (1946).

Although it was possible to cyclize the dimethyl ester of naphthalene-1,2-diacetic acid (prepared by sulfur dehydrogenation of IXb) to a crystalline cyclic β-keto ester, satisfactory hydrolysis and decarboxylation of the β-keto ester to 2′-keto-1,2-cyclopentenonaphthalene has not yet been accomplished.

Sodium amalgam reduction of the unsaturated acid IXc gave a mixture of the *cis* and *trans* forms of 1,2,3,4-tetrahydronaphthlane-1,2-diacetic acid in about equal amounts, from which the *cis* and *trans* forms of 2′-keto-1,2,3,4-tetrahydro-1,2-cyclopentenonaphthalene (X) were synthesized. Both forms of the cyclic ketone yielded the known 1,2-cyclopentenonaphthalene when subjected to a Wolff–Kishner reduction followed by dehydrogenation of the resulting hydrocarbons.

Experimental[7]

1-Tetralone-2-β-propionic Acid (II). (a) By Cyanoethylation of 2-Carbomethoxy-1-tetralone.—To a stirred solution of 100 g. of 2-carbomethoxy-1-tetralone[8] in 800 ml. of dry, peroxide-free dioxane 4 ml. of Triton B (38% aqueous trimethylbenzylammonium hydroxide) was added in five minutes, followed by a solution of 36 ml. of acrylonitrile[9] in 50 ml. of dioxane in the course of twenty minutes. The reaction failed completely with dioxane which contained peroxide. The temperature rose from room temperature to about 40°. Stirring was continued for an additional two hours; sufficient 10% hydrochloric acid was added to the dark solution to give a clear brownish-yellow solution; and the dioxane was removed in a current of air. Addition of methanol induced crystallization of the product, which was collected by filtration and washed thoroughly with a saturated, ice-cold solution of 60–70° petroleum ether in methanol; yield, 110 g. of nearly colorless needles; m. p. 75–76°. From the filtrates an additional 6 g. of the product was obtained; total yield, 92%. In this manner 293 g. of 2-carbomethoxy-1-tetralone was converted to 338 g. of **2-carbomethoxy-2-(β-cyanoethyl)-1-tetralone** (I). The compound crystallized from a mixture of methanol and 60–70° petroleum ether in colorless needles; yield 331 g. (90%); m. p. 76–77°. Two more recrystallizations of a sample from methanol resulted in no change in the melting point.

Anal. Calcd. for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.98; H, 5.62; N, 5.46.

A solution of 51.5 g. of the nitrile in 150 ml. of glacial acetic acid, 300 ml. of concentrated hydrochloric acid, and 20 ml. of water was heated on a steam-bath for four hours, cooled somewhat, and poured with stirring on a mixture of 1000 g. each of ice and water; yield, 42.3 g. (97%); m. p. 105–107°. In this manner 327 g. of the cyanoethyl product gave 270 g. of **1-tetralone-2-β-propionic acid** (II). Recrystallization from acetone gave 264 g. (95%) of colorless rhombs; m. p. 108–110°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.54; H, 6.52.

(b) From 2-Carbomethoxy-1-tetralone and Methyl β-Bromopropionate.—To the solution of sodium methoxide from 1.6 g. of sodium and 80 ml. of absolute methanol was added a solution of 7.1 g. of 2-carbomethoxy-1-tetralone in 80 ml. of dry benzene. The mixture was refluxed on a steam-bath for one hour, cooled, and treated with 11.7 g. of methyl β-bromopropionate. The reaction mixture was allowed to stand for one and one-half hours with oc-

(7) Most of the analyses were performed by the Micro-Tech Laboratories, Skokie, Illinois, and the rest by Mrs. Lea Gafney of the Chemistry Department, Indiana University, Bloomington, Indiana.

(8) Bachmann and Thomas, THIS JOURNAL, **63**, 598 (1941).

(9) Bruson, *ibid.*, **64**, 2457 (1942).

casional shaking; during this time nearly all solid material disappeared. The mixture was then refluxed for one-half hour in a water-bath, cooled, treated with ice-water and extracted with benzene. The product, which was obtained as a liquid by evaporation of the benzene, was heated with 50 ml. of concentrated hydrochloric acid, 50 ml. of glacial acetic acid, and 5 ml. of water for two hours on a steam-bath. The cooled mixture was diluted with 300 ml. of water and extracted with benzene. The benzene solution was extracted with 5% sodium hydroxide and the solution of the sodium salt was treated with Norit, filtered, and acidified; yield 5.4 g. (71%) of crude 1-tetralone-2-β-propionic acid (II); m. p. 99–103°. Upon crystallization of a sample from a mixture of acetone and water, fine colorless needles were obtained exactly as in (a); m. p. 108–110°.

1-Carboxymethyl-3,4-dihydronaphthalene-2-β-propionic Acid (IIIc).—To a solution of 100 g. of 1-tetralone-2-β-propionic acid in 320 ml. of absolute methanol was slowly added with swirling 32 ml. of concentrated sulfuric acid. The solution was refluxed on a steam-bath for one hour, about one-half of the solvent was removed by distillation under reduced pressure on a steam-bath, the residue was diluted with 800 ml. of water, and the mixture was extracted with ether. The ether extracts were washed with saturated sodium bicarbonate solution, dried, and treated with Norit. The liquid dimethyl ester isolated by evaporation of the solution was dried thoroughly in a vacuum desiccator.

To a solution of 20 g. of the methyl ester in 200 ml. of dry benzene was added 20 g. of clean, dry 20-mesh zinc, 14 ml. of methyl bromoacetate, and a small crystal of iodine. The mixture was refluxed on a steam-bath with frequent shaking until the reaction started. At forty-five-minute intervals thereafter 10 g. of zinc was added until a total of three hours reaction time had elapsed. After one hour an additional 6 ml. of methyl bromoacetate was added. After three hours the cooled mixture was treated with 150 ml. of cold 10% hydrochloric acid and shaken vigorously. The solutions were decanted into a separatory funnel and the zinc was washed thoroughly with ether by decantation. The combined extracts were separated and the aqueous layer was extracted with ether. The combined ether–benzene extracts were washed with water and extracted with concentrated aqueous ammonia which had been diluted with an equal volume of water. The ammoniacal extracts were acidified with hydrochloric acid, extracted with ether, and the dried ether solution was treated with Norit. Removal of the ether left **1-carbomethoxymethyl-3,4-dihydronaphthalene-2-β-propionic acid (IIIa)**; yield, 16.8 g.; m. p. 84–88°. A sample after three recrystallizations from methanol formed fine colorless needles; m. p. 94–95°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.22; H, 6.59.

The ultraviolet absorption spectrum (Fig. 1) was obtained on a 0.0011% solution of the acid ester IIIa in methanol by means of a Beckman quartz spectrophotometer.

A solution of 20 g. of the acid ester in 100 ml. of methanol and 300 ml. of 0.5 *N* sodium hydroxide was refluxed for one hour on a steam-bath. After removal of one-half of the solvent in a current of air, the residual solution was acidified with concentrated hydrochloric acid and chilled; yield, 18.2 g. (96%); m. p. 145–148°. A sample of **1-carboxymethyl-3,4-dihydronaphthalene-2-β-propionic acid** after three recrystallizations from benzene formed fine colorless needles; m. p. 147–149°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.33; H, 6.31.

The acid reacted immediately with a solution of bromine in carbon tetrachloride and with potassium permanganate solution.

3-Keto-1,2,3,9,10,10a-hexahydrophenanthrene (V).—The dimethyl ester of 3,4-dihydronaphthalene-1-acetic acid-2-β-propionic acid was obtained readily by esterification of the diacid IIIc and the acid ester IIIa by means of anhydrous methanol and concentrated sulfuric acid. A Dieckmann cyclization was run as for the production of VI with sodium methoxide from 0.5 g. of sodium and 0.93 g. of the dimethyl ester in 10 ml. of dry benzene; yield, 0.65 g.; m. p. 110–121°. After three recrystallizations from methanol–water, a sample of **2(or 4-)-carbomethoxy-3-ketohexahydrophenanthrene** formed fine colorless needles; m. p. 126–128°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.96; H, 6.24.

The compound gave no color with ferric chloride, even on heating. It reacted immediately with bromine in carbon tetrachloride, and with potassium permanganate solution.

Hydrolysis and decarboxylation of 0.95 g. of the β-keto ester was accomplished as for the production of VI; yield, 0.7 g.; m. p. 68–75°. After three recrystallizations from methanol–water the cyclic ketone formed needles with a very pale yellow color; m. p. 79–80° (reported,[2] 80°).

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.40; H, 7.24.

The ketone instantly decolorized bromine–carbon tetrachloride solution. The ultraviolet absorption was measured on a 0.0005% solution of the ketone in methanol; a maximum ($\log \epsilon = 4.28$) appears at 298 mμ (Fig. 1).

The 2,4-dinitrophenylhydrazone crystallized from methanol in clusters of crimson prisms; m. p. 204–206° dec.

Anal. Calcd. for $C_{20}H_{18}O_4N_4$: N, 14.81. Found: N, 14.75.

The semicarbazone crystallized from acetic acid in fine colorless needles; m. p. 244–245° dec. It turned yellow in a few hours even when kept in an evacuated desiccator in the dark. This phenomenon has been noted with the semicarbazones of other β-aryl-substituted α,β-unsaturated ketones. A satisfactory analysis was not obtained. A suspension of 0.25 g. of the semicarbazone in ethanolic sodium ethoxide, prepared from 0.5 g. of sodium and 15 ml. of absolute ethanol, was heated in a bomb tube at 170° for twenty hours. Dehydrogenation of the product gave phenanthrene.

3-Keto-1,2,3,4-tetrahydrophenanthrene (VI).—A test-tube containing a mixture of 2 g. of the crude diester IIIb and 0.225 g. of sulfur and fitted with a one-hole stopper bearing a short length of capillary tubing was lowered to the level of the mixture in a metal-bath at 220°. The temperature of the bath was raised to 280° in the course of ten minutes. The cooled mixture was refluxed with 50 ml. of methanol and 20 ml. of 0.5 *N* sodium hydroxide for one hour on a steam-bath. After the solvent had been removed, a solution of the product in 50 ml. of water was heated with Norit; acidification gave 1.56 g. (87%) of the acid; m. p. 178–181°. A sample of **1-carboxymethyl-naphthalene-2-β-propionic acid** after three recrystallizations from a mixture of acetone and water formed fine colorless needles; m. p. 183–184°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.56; H, 5.62.

Dehydrogenation with 10% palladium-on-charcoal gave a poor yield of the acid.

The crude dimethyl ester formed by esterification of the acid with methanol and sulfuric acid was dried thoroughly. A solution of 2 g. of the diester in 25 ml. of dry thiophene-free benzene was added to dry sodium methoxide (made by the reaction of 0.32 g. of sodium with 5 ml. of absolute methanol followed by evaporation under reduced pressure on a steam-bath). The mixture was refluxed in an atmosphere of nitrogen in a water-bath for two hours, the cooled mixture was treated with cold 5% hydrochloric acid and extracted with ether, and the combined ether–benzene extracts were washed with water, dried and treated with Norit. Removal of the solvent under reduced pressure yielded 1.54 g. of **2(or 4-)-carbomethoxy-3-keto-1,2,3,4-tetrahydrophenanthrene**; m. p. 113–120°. A sample crystallized three times from methanol formed colorless leaflets; m. p. 124–125°. It gave a light blue-green color with alcoholic ferric chloride upon heating.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.38; H, 5.66.

A solution of 0.25 g. of the β-keto ester in 20 ml. of glacial acetic acid, 10 ml. of concentrated hydrochloric acid, and 1.8 ml. of water was heated on a steam-bath for four hours in an atmosphere of nitrogen, cooled, diluted with 100 ml. of cold water, and extracted with ether. The ether extracts were washed with water and with cold 2% aqueous sodium hydroxide, dried, treated with Norit, and filtered. The solvent was removed under reduced pressure in an atmosphere of carbon dioxide; yield, 0.12 g. (62%); m. p. 54–58°. After evaporative distillation at 0.01 mm., and three recrystallizations from 60–70° petroleum ether, the **3-keto-1,2,3,4-tetrahydrophenanthrene** formed fine colorless needles; m. p. 64–65°. The ketone was unstable in air, being converted to a dark gummy mass in the course of a few hours. A satisfactory analysis was not obtained. The **2,4-dinitrophenylhydrazone**, which was stable, crystallized from a mixture of benzene and methanol in extremely fine red needles; m. p. 246–248° dec.

Anal. Calcd. for $C_{20}H_{16}O_4N_4$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.66; H, 4.58; N, 14.74.

The oxime crystallized from a mixture of acetic acid and water in clusters of fine colorless needles; m. p. 139–141°.

Anal. Calcd. for $C_{14}H_{13}ON$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.00; H, 5.84; N, 6.96.

The semicarbazone crystallized in very fine colorless needles upon diluting an acetic acid solution of the substance with water; m. p. 205–207°.

Anal. Calcd. for $C_{15}H_{15}ON_3$: C, 71.12; H, 5.97. Found: C, 71.38; H, 5.95.

A suspension of 0.3 g. of the semicarbazone in ethanolic sodium ethoxide from 0.5 g. of sodium in 15 ml. of absolute ethanol was heated in a bomb tube at 170° for twenty hours, and the product was dehydrogenated with 0.1 g. of 10% palladium–charcoal catalyst at 310–320° for forty-five minutes. The phenanthrene (m. p. 99–100°) and its picrate (m. p. 141–142.5°) were identified through their melting points and by mixed melting points with authentic specimens.

The carbinol formed from 0.5 g. of the ketone and methylmagnesium iodide was heated with 1.7 g. of potassium acid sulfate for one and one-half hours in a bath maintained at 160–165°. The product was heated with 0.2 g. of 10% palladium–charcoal catalyst for forty-five minutes in a bath maintained at 300–320°. The resulting 3-methylphenanthrene after distillation at 0.02 mm. crystallized from alcohol in colorless needles; m. p. 61.5–63° (reported, 61–62°,[10] 62–63°[11]); m. p. picrate, 136–138° (reported,[11] 137–138°).

3-Keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VII).—Numerous attempts to effect a sodium amalgam reduction of 3,4-dihydronaphthalene-1-acetic acid-2-β-propionic acid (IIIc) failed. Catalytic hydrogenation of the diester IIIb was successful. A solution of 5 g. of the diester in 50 ml. of absolute methanol in the presence of 0.2 g. of platinum oxide catalyst was hydrogenated at 30 pounds pressure in four hours. The end of the reaction was indicated by the failure of the solution to decolorize bromine in carbon tetrachloride. Hydrolysis of 2 g. of the crude dimethyl ester in 20 ml. of methanol with 30 ml. of 0.5 *N* sodium hydroxide by one hour of refluxing on a steam-bath gave 1.8 g. (99%) of **1-carboxymethyl-1,2,3,4-tetrahydronaphthalene-2-β-propionic acid**; m. p. 125–129°. A sample after two recrystallizations from acetone–water formed fine colorless needles; m. p. 130–131°. The acid does not decolorize dilute solutions of bromine in carbon tetrachloride or aqueous potassium permanganate.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; neut. equiv., 131. Found: C, 68.34; H, 6.95; neut. equiv., 132.

A Dieckmann cyclization of 2 g. of the crude dimethyl ester of 1,2,3,4-tetrahydronaphthalene-1-acetic acid-2-β-propionic acid carried out as described for VI gave 1.58 g. of **2(or 4-)-carbomethoxy-3-keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene**; m. p. 76–83°. The compound crystallized from methanol in colorless, broad, flat needles; m. p. 93–95°. No crystalline isomer was found; only a small amount of dark-colored oil which resisted crystallization was found in the filtrate.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.37; H, 7.14.

The β-keto ester gave a purple-gray color with alcoholic ferric chloride. It rapidly decolorized bromine in carbon tetrachloride and aqueous potassium permanganate.

Hydrolysis and decarboxylation of 0.3 g. of the β-keto ester by the procedure used for VI gave 0.21 g. of crude **3-keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VII)**; m. p. 53–56°. Three recrystallizations of the material from 60–70° petroleum ether formed colorless prisms; m. p. 73–74°.

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.64; H, 8.11.

The 2,4-dinitrophenylhydrazone crystallized from a mixture of chloroform and methanol in globular clusters of fine orange needles; m. p. 175–177°.

Anal. Calcd. for $C_{20}H_{20}O_4N_4$: N, 14.73. Found: N, 15.00.

The semicarbazone crystallized from aqueous acetic acid in clusters of fine colorless needles; m. p. 229–231° dec.

Anal. Calcd. for $C_{15}H_{19}ON_3$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.49; H, 7.21; N, 16.05.

A Wolff–Kishner reduction of 0.35 g. of the semicarbazone gave 0.15 g. of hydrocarbon which was dehydrogenated with palladium-on-charcoal to phenanthrene.

1-Tetralone-2-acetic Acid. (a) **From 2-Bromo-1-tetralone.**—A solution of the 2-bromo-1-tetralone[5] from 10 g. of 1-tetralone[12] in 50 ml. of benzene was added to a cooled suspension of sodiomalonic ester which had been prepared by refluxing on a steam-bath 21 ml. of diethyl malonate, 2.4 g. of sodium powder and 100 ml. of dry benzene for four to five hours. The mixture was heated on a steam-bath for one and one-half hours. The crude substituted malonic ester was heated with a solution of 17 g. of potassium hydroxide, 50 ml. of ester and 20 ml. of 95% alcohol on a steam-bath for four hours. The cooled solution was extracted with benzene to remove non-acidic materials, treated with Norit, filtered, cooled, and acidified with 50 ml. of cold concentrated hydrochloric acid; yield, 10.4 g. of tan-colored 1-tetralone-2-malonic acid; m. p. 164° with evolution of gas. Extraction of the aqueous filtrates with ether afforded an additional 3.5 g. of somewhat oily material (presumably partially decarboxylated) which on decarboxylation gave the required acid; total yield, 81%. Bergs[5] employed dry ether in the malonic ester condensation and was unable to obtain a satisfactory yield of the malonic acid (m. p. 168° after recrystallization from alcohol). The dried acid was decarboxylated at 160–180° and the solution of the sodium salt was treated with Norit; yield of 1-tetralone-2-acetic acid, 10.9 g. (95%); m. p. 98–102°. A sample recrystallized from a mixture of ether and petroleum ether melted at 105–108° (reported,[5] 109–110°).

(b) **From 2-Carbomethoxy-1-tetralone.**—By the same procedure used to prepare 1-tetralone-2-β-propionic acid (II), the sodio derivative of 6 g. of 2-carbomethoxy-1-tetralone was condensed with 5.9 g. of methyl bromoacetate. The resulting **methyl ester of 2-carbomethoxy-1-tetralone-2-acetic acid** crystallized from methanol in fine colorless needles; m. p. 81.8–82.1°.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.20; H, 5.84. Found: C, 65.06; H, 5.84.

Hydrolysis and decarboxylation of the product gave 5 g. (83%) of 1-tetralone-2-acetic acid; m. p. 100–105°. After two recrystallizations from a mixture of ether and

(10) Bachmann and Cortes, THIS JOURNAL, **65**, 1329 (1943).

(11) Haworth, *J. Chem. Soc.*, 1125 (1932).

(12) Thompson, *Organic Syntheses*, **20**, 94 (1940).

petroleum ether, a sample had a m. p. 106–108°, alone and when mixed with the product in (a).

Preparation of the Lactone VIII.—The **methyl ester of 1-tetralone-2-acetic acid,** prepared with diazomethane, crystallized in small colorless plates from methanol containing a little water; m. p. 55–56.5°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.35; H, 6.36.

A Reformatsky reaction was carried out with 2.18 g. of the methyl ester, 10 ml. of dry ether, 10 ml. of dry benzene, 10 g. of 20-mesh zinc, 1.5 ml. of methyl bromoacetate and a small crystal of iodine. The mixture was stirred with a wire Hershberg stirrer[13] while it refluxed on a water-bath. The reaction began after fifteen to thirty minutes; it was continued in the manner described for IIIa. The cooled mixture was treated with cold, dilute acetic acid, and extracted with benzene. The benzene extracts were washed with water, dried, treated with Norit, filtered, and the benzene removed under reduced pressure. When the residual oil was treated with a little methanol, the **lactone of 1-hydroxy-1-carbomethoxymethyl-1,2,3,4-tetrahydronaphthalene-2-acetic acid** (VIII) crystallized in colorless prisms; yield, 1.53 g. (59%); m. p. 97–98°. A sample recrystallized from methanol melted at 100–100.5°. The lactone is insoluble in aqueous ammonia and only slowly soluble in aqueous sodium hydroxide.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.46; H, 6.49.

The ultraviolet absorption (Fig. 1) was measured on a 0.01% solution of the lactone in methanol.

Hydrolysis of the Lactone to the Unsaturated Acid Ester (IXa).—In one experiment in which 7.5 g. of the lactone (VIII) was refluxed for one hour with only one equivalent of sodium hydroxide (60 ml. of 0.5 *N*) and 100 ml. of methanol, 5.5 g. (74%) of the **methyl ester of 2-carboxymethyl-1-tetrahydronaphthylideneacetic acid** (IXa) was obtained; m. p. 113–116°. A sample crystallized from benzene in fine colorless needles; m. p. 116–117°. A mixture of this compound and the lactone (VIII) melted at 85–88°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.35; H, 6.48.

The ultraviolet absorption spectrum was measured on a 0.001% solution of the acid ester in methanol; log ϵ = 4.19 at 275 mμ (Fig. 1).

Hydrolysis of the Lactone to the Unsaturated Diacid (IXc).—A solution of 1.53 g. of the lactone (VIII) and 8.03 ml. of 0.977 *N* sodium hydroxide in 20 ml. of methanol was refluxed on a steam-bath for one hour. From this solution 1.33 g. (91%) of the unsaturated acid was isolated; m. p. 197–198°. A sample of **1-tetrahydronaphthylidene-1,2-diacetic acid** (IXc) crystallized from a mixture of benzene and acetone in fine, colorless needles; m. p. 204–206°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.28; H, 5.81.

Naphthalene-1,2-diacetic Acid.—The action of ethereal diazomethane on the unsaturated dicarboxylic acid IXc or the monomethyl ester IXa gave a liquid dimethyl ester IXb. Dehydrogenation of 2 g. of the diester by sulfur followed by hydrolysis as described for IIIb gave 1.2 g. of crude naphthalene-1,2-diacetic acid; m. p. 180–190°. A sample after four recrystallizations from a mixture of benzene and acetone formed colorless prisms; m. p. 216–218°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.89; H, 5.11.

1′-(or 3′)-Carbomethoxy-2′-keto-1,2-cyclopentenonaphthalene.—Esterification of 2.9 g. of the diacid with methanol and sulfuric acid gave 3 g. (92%) of the **dimethyl ester of naphthalene-1,2-diacetic acid**; m. p. 89–91°. A sample after three recrystallizations from methanol formed colorless leaflets; m. p. 91–92°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.66; H, 5.96.

A Dieckmann cyclization of 1 g. of the dimethyl ester carried out as described for VI gave 0.8 g. of 1′-(or 3′)-carbomethoxy-2′-keto-1,2-cyclopentenonaphthalene; m. p. 130–135°. Crystallization of a sample from a mixture of acetone and methanol formed fine colorless needles; m. p. 145–146.5°. The compound gave a deep blue-green color with alcoholic ferric chloride.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.98; H, 5.04. Found: C, 75.03; H, 5.38.

Heating a solution of 0.4 g. of the β-keto ester in 40 ml. of glacial acetic acid, 20 ml. of concentrated hydrochloric acid and 2 ml. of water for four hours resulted in a nearly black solution from which was isolated only 0.04 g. of an unstable ketone (colorless needles from petroleum ether; m. p. 98–100°) which gave a 2,4-dinitrophenylhydrazone (orange-yellow prisms from chloroform–alcohol; m. p. 214–216° dec.) for which satisfactory analyses were not obtained. Varying the concentrations of acetic acid and water and the time of heating gave the same results or unreacted material.

$\Delta^{1-1'}$-2′-Keto-3,4-dihydro-1,2-cyclopentenonaphthalene.—The Dieckmann cyclization of the dimethyl ester IXb gave a 82% yield of β-keto ester (m. p. 100–108°). Hydrolysis and decarboxylation of 0.88 g. of the keto ester with a mixture of hydrochloric acid and acetic acid gave 0.46 g. of $\Delta^{1-1'}$-2′-keto-3,4-dihydro-1,2-cyclopentenonaphthalene; m. p. 57–68°. After four recrystallizations from 60–75° petroleum ether the ketone formed colorless prisms; m. p. 72–73.5° (reported,[6] 74–75°).

The 2,4-dinitrophenylhydrazone was treated with hot acetic acid. The material soluble in acetic acid precipitated in fine dark red needles on addition of water; m. p. 251–253° dec. The material insoluble in acetic acid formed lighter red prisms; m. p. 252–254° dec. (reported,[6] dark red needles; m. p. 250.5–251° dec., and lighter red plates; m. p. 247.5–248° dec. from a mixture of benzene and toluene). The ultraviolet absorption was measured on a 0.0005% solution of the ketone in methanol; log ϵ = 4.38 at 287 mμ (reported,[4a] log ϵ = 4.38).

1,2,3,4-Tetrahydronaphthalene-1,2-diacetic Acid.—A mixture of 60 g. of 2% sodium amalgam and a solution of 4.47 g. of the unsaturated acid IXc in 40 ml. of *M* sodium hydroxide was shaken vigorously for thirty minutes; excess alkali was neutralized with hydrochloric acid and the mixture was shaken with another 60 g. of amalgam for thirty minutes. The isolated acid (3.61 g., m. p. 134–136°) consisted of a mixture of the *cis* and *trans* forms. By repeated recrystallizations from benzene and from aqueous acetone it was possible to obtain one of the forms (m. p. 145–146°; called the α-form since its configuration is not known) in a pure state in 20% yield. Both forms were isolated by the method used by Drake and McVey[14] on a mixture of different acids. A mixture of the crude isomeric acids (2.44 g.) was shaken with 32.8 ml. of 0.1 *N* sodium hydroxide for twenty-four hours. After the removal of the insoluble acid by filtration, the filtrate was acidified and the acid which precipitated was recrystallized five times from acetone–water and five times from benzene–petroleum ether (60–75°). The **β-1,2,3,4-tetrahydronaphthalene-1,2-diacetic acid** formed colorless needles; m. p. 142–143°.

The insoluble portion from the previous operation was again shaken with 32.8 ml. of the alkali for twenty-four hours and the acid which remained undissolved was recrystallized as above, yielding the **α-1,2,3,4-tetrahydronaphthalene-1,2-diacetic acid** as colorless rods; m. p. 146–147°. A mixture of the pure α- and β-forms of the acid melted at 137–140°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: (α-acid) C, 67.78; H, 6.86, 6.66; (β-acid) C, 68.20; H, 6.75.

Cyclization of the Stereoisomeric Acids.—A Dieckmann cyclization of the dimethyl ester from 1.53 g. of the α-form

(13) Hershberg, *Ind. Eng. Chem.*, **8**, 313 (1936).

(14) Drake and McVey, *J. Org. Chem.*, **4**, 464 (1939).

of 1,2,3,4-tetrahydronaphthalene-1,2-diacetic acid, carried out as described for VI, yielded 1.24 g. of α-1'-(or 3')-carbomethoxy-2'-keto-1,2,3,4-tetrahydro-1,2-cyclopentenonaphthalene, which after three recrystallizations from methanol formed colorless prisms; m. p. 108–109°.

Similarly from the ester of 1.29 g. of the β-acid 0.98 g. of the β-form of the keto ester was obtained, which after three recrystallizations from methanol formed fine colorless needles; m. p. 113–115°. A mixture of the two pure forms melted at 90–95°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: (α-form) C, 73.94; H, 6.74; (β-form) C, 73.70; H, 6.82.

The cyclic keto esters can be separated from each other more readily and in better yield than can the original acids. Cyclization of the dimethyl esters prepared from 1.66 g. of the mixture of acids yielded 1.48 g. of a mixture of the two forms of the keto esters; m. p. 70–91°. The mixture was dissolved in the minimum of hot methanol and a one-third excess of the solvent was added. On chilling, the β-form of the keto ester precipitated in nearly pure state. When the filtrate was concentrated to one-half its volume and chilled, a small amount of the mixed isomers separated; from the concentrated filtrate the nearly pure α-form of the keto ester separated. Two recrystallizations from methanol yielded the pure compounds. About equal amounts of the two forms were obtained.

Hydrolysis and decarboxylation of 0.7 g. of the α-form of the cyclic keto ester by a mixture of acetic acid and hydrochloric acid gave a quantitative yield of the α-form of 2'-keto-1,2,3,4-tetrahydro-1,2-cyclopentenonaphthalene (X); m. p. 83–85°. It crystallized from methanol in colorless rectangular plates; m. p. 85–86°.

Similarly, the β-form of X was obtained in 94% yield (m. p. 48–49°) from the isomeric keto ester; it crystallized from methanol in colorless needles; m. p. 51–52°.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: (α-form) C, 83.74; H, 6.64; (β-form) C, 83.94; H, 7.71.

The 2,4-dinitrophenylhydrazones were recrystallized from methanol–chloroform; α-form, yellow needles with m. p. 260–261°; β-form, orange-yellow needles with m. p. 240–241° dec.

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: N, 15.29. Found: (α-form) N, 15.11; (β-form) N, 15.12.

The semicarbazones of both forms crystallized in very fine colorless plates; α-form, m. p. 254–256° dec.; β-form, m. p. 220–222° dec.

Anal. Calcd. for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: (α-form) C, 69.43; H, 6.94; N, 17.34; (β-form) C, 69.09; H, 7.34; N, 16.81.

A suspension of 0.25 g. of the semicarbazone (α- or β-form) in ethanolic sodium ethoxide from 0.46 g. of sodium and 13 ml. of absolute alcohol was heated at 170° for twenty hours in a bomb tube. The isolated yellow liquid was heated with 0.2 g. of 10% palladium-charcoal catalyst at 300–320° for forty-five minutes. The product formed a picrate, which after two recrystallizations from ethanol melted at 106–107°, alone and when mixed with an authentic specimen of the picrate of 1,2-cyclopentenonaphthalene.

Summary

Three 3-ketohydrophenanthrenes and two 2'-ketohydro-1,2-cyclopentenonaphthalenes were synthesized by methods involving the Reformatsky and Dieckmann reactions.[15]

(15) A similar series of ketones has been prepared from 2-carbomethoxy-1-keto-1,2,3,4-tetrahydrophenanthrene by L. E. Miller in this Laboratory. These results will be published soon.

ANN ARBOR, MICHIGAN RECEIVED JUNE 20, 1949

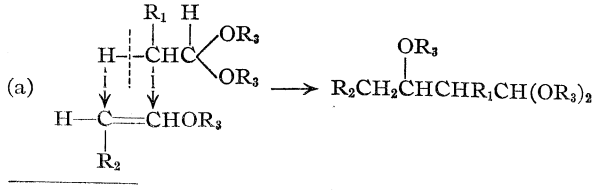
[CONTRIBUTION FROM THE PROCESS DEVELOPMENT LABORATORY, CARBIDE AND CARBON CHEMICALS CORPORATION]

Reaction of Acetals and α,β-Unsaturated Ethers

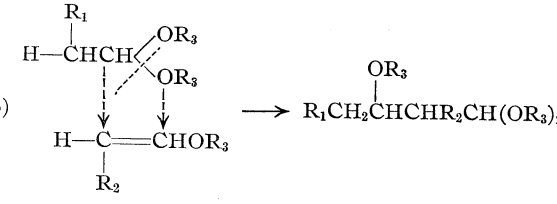
BY R. I. HOAGLIN AND D. H. HIRSH

During the course of an investigation of the chemistry of vinyl ethers the reaction of acetals and α,β-unsaturated ethers was studied. Examples of this reaction were reported by Mueller-Cunradi and Pieroh in a U. S. patent[1] which describes the condensation of acetaldehyde acetals and vinyl ethers in the presence of catalysts capable of effecting the polymerization of vinyl ethers.

A priori the reaction of an acetal with an α,β-unsaturated ether could involve a splitting of either an alpha hydrogen, as suggested by Mueller-Cunradi and Pieroh, or an alkoxy group from the acetal with addition of the corresponding resulting fragments to the double bond of the unsaturated ether as shown in reactions (a) and (b).

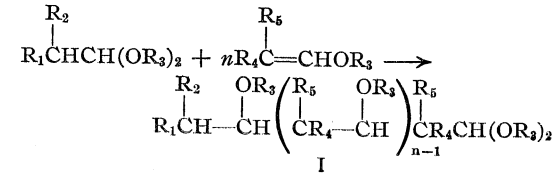


(1) Mueller-Cunradi and Pieroh, U. S. Patent 2,165,962 (1939).



R_1 and R_2 may be hydrogen atoms or alkyl radicals; R_3 is an alkyl radical.

The present study showed that an alkoxy group is split from the acetal molecule and that the course of reaction indicated in (b) is correct. The investigation also showed that the reaction could be extended to include acetals of aldehydes other than acetaldehyde and also α,β-unsaturated ethers other than those derived from vinyl alcohol. The results may be generalized by the following equation, where R_1, R_2, R_4 and R_5 may



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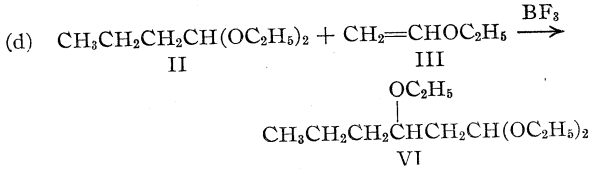
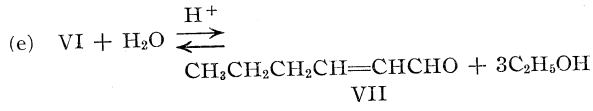
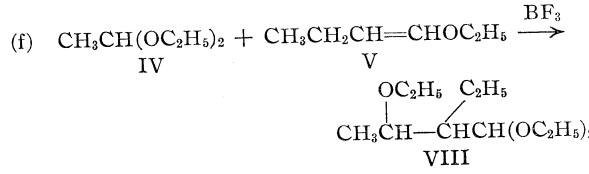
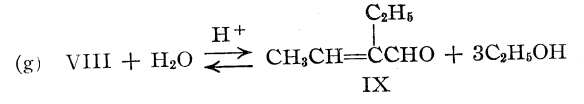
be hydrogen atoms or alkyl radicals, R_3 is an alkyl radical and n is a whole number.

The manner in which acetals and α,β-unsaturated ethers react was determined by means of two syntheses, the first involving the condensation of diethyl butyral (II) and vinyl ethyl ether (III), reaction (d), while the second entailed the addition of diethyl acetal (IV) to 1-butenyl ethyl ether (V), reaction (f). The product of the first reaction, 1,1,3-triethoxyhexane (VI), was simultaneously hydrolyzed and de-ethanolated with a mineral acid, reaction (e), to give 2-hexenal (VII), a known compound. The product of the second reaction, 1,1,3-triethoxy-2-ethylbutane (VIII), was similarly treated, reaction (g), giving 2-ethyl-2-butenal (IX), also a known compound.



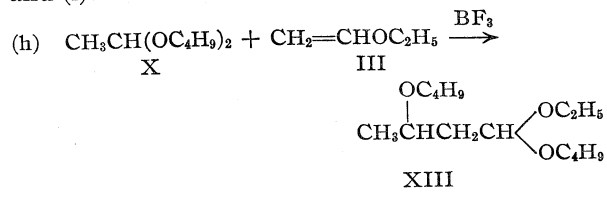


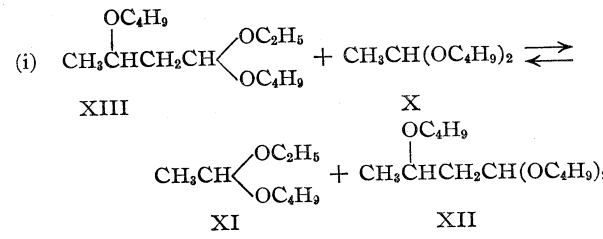




Had the mechanism indicated by Mueller-Cunradi and Pieroh been correct, the structures of VI and VIII would have been reversed and the products of reactions (e) and (g) would also have been the reverse of those actually observed. Because of the fact that acetals of only acetaldehyde and ethers of only vinyl alcohol were used in the examples of the patent, the error in the mode of reaction was not observed by the inventors.

Examination of the general reaction shown in equation (c) shows that the alkoxy radicals in the acetal and unsaturated ether molecules are identical (OR_3). The reaction occurs with equal ease when reactants are used in which the alkoxy radicals are not identical, although the products are so numerous that isolation of pure compounds is difficult. For example, dibutyl acetal (X) reacted with vinyl ethyl ether (III) to give a mixture of products, two of which, 1-ethoxy-1-butoxyethane (XI) and 1,1,3-tributoxybutane (XII), were isolated. These compounds were assumed to have been formed by an alkoxy interchange between dibutyl acetal and 1,3-dibutoxy-1-ethoxybutane (XIII). These transformations are shown in equations (h) and (i).

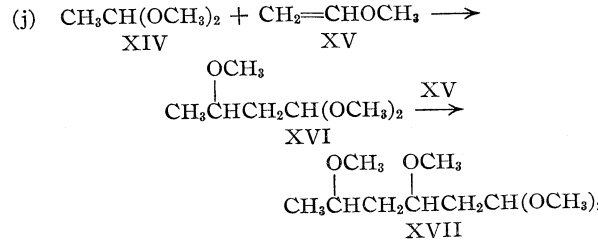




Compound XIII was not isolated but was believed to be present in intermediate fractions obtained in the distillation of the reaction product.

Several new alkoxyacetals were prepared which further illustrate the mechanism of the reaction and its versatility in the synthesis of compounds of specific structure. In Table I are presented yields and some physical properties of several of these alkoxyacetals prepared from acetals and α,β-unsaturated ethers.

The reaction of acetals and α,β-unsaturated ethers is similar to the addition of alcohols to ethylene oxide in that several products are formed, the distribution of which depends primarily on the mole ratio of the reactants. In Fig. 1 are shown graphically the data from several experiments in which the mole ratio of dimethyl acetal (XIV) to vinyl methyl ether (XV) was varied between 1:1 and 5:1. The main products of this reaction are 1,1,3-trimethoxybutane (XVI) and 1,1,3,5-tetramethoxyhexane (XVII) at the mole ratios employed.



Because these experiments were carried out batchwise, the mole ratios shown merely indicate a ratio of moles of acetal used to the total moles of vinyl ether added. Actually, the mole ratio varied between infinity and the finite value indicated. The data show, as expected, that the yield, based on vinyl methyl ether, of 1,1,3-trimethoxybutane increases and that of 1,1,3,5-tetramethoxyhexane decreases with an increase in the acetal:vinyl ether mole ratio.

Differences in reactivity between various acetals and vinyl ethers are also illustrated by the

TABLE I

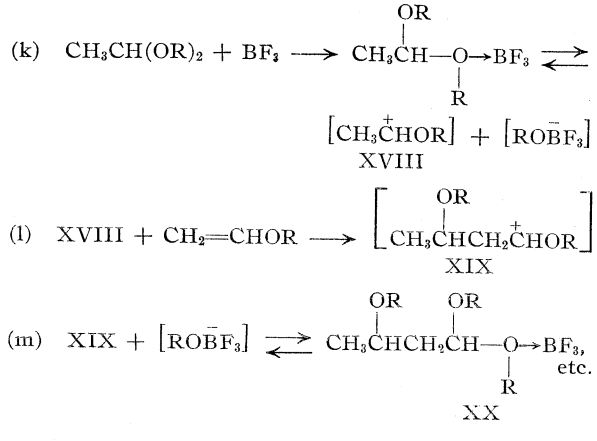
PREPARATION OF ALKOXYACETALS FROM ACETALS AND α,β-UNSATURATED ETHERS

Acetal	Unsaturated ether	Mole ratio of acetal to unsaturated ether	Product isolated	Yield of product based on ether	Physical properties: Boiling point, °C.[a]	Sp. gr., 20/15.6°C.	$n^{20}D$	Molecular refractivity Calcd.	Obs.
Dimethyl acetal	Vinyl methyl ether	3	1,1,3-Trimethoxybutane	79	157 (760) 46 (10)	0.921	1.4030	39.37	39.3
			1,1,3,5-Tetramethoxyhexane	10	83–85 (5)	.958	1.4206	54.86	54.6
Diethyl acetal	Vinyl ethyl ether	3	1,1,3-Triethoxybutane	67	190 (760) 68 (10)	.878	1.4069	53.19	53.3
			1,1,3,5-Tetraethoxyhexane	18	107 (5)	.902	1.4200	73.28	73.5
			1,1,3,5,7-Pentaethoxyoctane	..	110–116 (0.5)	.917	1.4281	93.21	93.6
Diethyl butyral	Vinyl ethyl ether	3	1,1,3-Triethoxyhexane	72	84–86 (5)	.873	1.4138	62.85	62.4
			1,1,3,5-Tetraethoxyoctane	16	100–105 (1)	.896	1.4258	82.48	82.7
1,1-Diethoxy-2-ethylhexane	Vinyl ethyl ether	5	1,1,3-Triethoxy-4-ethyloctane	67	93–95 (1)	.872	1.4277	80.80	81.0
Diethyl acetal	1-Propenyl ethyl ether	3	1,1,3-Triethoxy-2-methylbutane	71	69 (5)	.880	1.4115	57.9	57.7
Dimethyl acetal	1-Butenyl methyl ether	5	1,1,3-Trimethoxy-2-ethylbutane	74	65 (10)	.918	1.4171	48.58	48.3
Diethyl acetal	1-Butenyl ethyl ether	3	1,1,3-Triethoxy-2-ethylbutane	48	76–78 (5)	.880	1.4172	62.35	62.4
1,1-Diethoxy-2-ethylbutane	1-Butenyl ethyl ether	3	1,1,3-Triethoxy-2,4-diethylhexane	54	81–84 (1)	.881	1.4306	80.80	80.4
1,1-Diethoxy-2-ethylhexane	1-Butenyl ethyl ether	3	1,1,3-Triethoxy-2,4-diethyloctane	40	105–107 (1.5)	.878	1.4342	90.00	89.7
Diethyl acetal	2-Ethyl-1-hexenyl ethyl ether	3	1,1,3-Triethoxy-2-butyl-2-ethylbutane	24	87–90 (1)	.886	1.4343	80.80	80.7

[a] Boiling points uncorrected.

data shown in Fig. 1. These data show a distinct difference in the yields of products obtained when dimethyl acetal and diethyl acetal were treated with vinyl methyl ether and vinyl ethyl ether, respectively. Apparently the difference in reactivity between dimethyl acetal and trimethoxybutane with vinyl methyl ether is greater than the difference in reactivity between diethyl acetal and triethoxybutane with vinyl ethyl ether.

The ease with which boron trifluoride forms complexes suggested that the catalyst plays a role as shown in the equations



The activated forms XVIII and XIX are thus the points attacked by the unsaturated ether and a higher boiling alkoxyacetal is formed when a molecule of unsaturated ether reacts with the active form shown in XIX. In this manner the reaction proceeds indefinitely, resulting in products of the general type indicated in formula I.

A detailed catalyst study was not made for the acetal–α,β-unsaturated ether reaction. However, a single experiment was carried out in which zinc chloride was found to be just as effective as boron trifluoride in the reaction of diethyl acetal and vinyl ethyl ether.

The reaction of acetals and α,β-unsaturated ethers represents a new method of increasing the length of a carbon chain and the products obtained are similar in structure to those obtained by the aldol condensation. For example, for the synthesis of 1-hexanol by the acetal–unsaturated ether reaction, diethyl butyral and vinyl ethyl ether may be used. These intermediates are prepared from butyraldehyde and acetaldehyde, respectively, which raw materials are also involved in the synthesis of 1-hexanol *via* the aldol condensation. The aldol reaction, however, results in the formation of several unsaturated aldehydes because of the ability of each of the raw materials to condense with itself or with

another aldehyde. A complex mixture of aldehydes, consisting of both straight and branched chains, is obtained requiring precise rectification for its resolution. The alkoxyacetals, formed in the acetal–unsaturated ether reaction, are straight- or branched-chained compounds, but both types are not obtained from the same reaction product. The alkoxyacetals are easily separated by distillation because of their difference in molecular weight, this difference being the molecular weight of the unsaturated ether used.

From the alkoxyacetals, obtained by the reaction of acetals and α,β-unsaturated ethers, may be prepared a multitude of chemical intermediates. Although publication of the details of the preparation of these intermediates is not in the scope of this paper the names of a few of the compounds derived from the reaction products of diethyl acetal and vinyl ethyl ether will serve to illustrate the potential utility of these alkoxyacetals. From 1,1,3-triethoxybutane may be obtained by hydrogenolysis 1,3-diethoxybutane (diethyl ether of 1,3-butanediol). Hydrolysis of triethoxybutane with mineral acid gives 3-ethoxybutanal or crotonaldehyde, the product obtained depending on the concentration of acid used.[2] From 3-ethoxybutanal may be obtained, by standard procedures, 3-ethoxybutanol and its esters and 3-ethoxybutanoic acid and its esters. Simultaneous dehydration and de-ethanolation of 3-ethoxybutanol gives butadiene.[1]

By analogous reactions 1,1,3,5-tetraethoxyhexane gives 1,3,5-triethoxyhexane, 3,5-diethoxyhexanal, 3,5-diethoxyhenanol and its esters, 3,5-diethoxyhexanoic acid and its esters, 2,4-hexadienal, hexanal, 1-hexanol, hexanoic acid, sorbic acid, hexyl ether, hexylamine and others. Analogous compounds can be prepared from alkoxyacetals derived from various acetals and α,β-unsaturated ethers.

Experimental[3]

The preparation of a few alkoxyacetals and unsaturated aldehydes is described and will serve to illustrate the experimental procedures employed.

Preparation of Reactants

Acetals used were prepared in the usual way, by the acid-catalyzed reaction of the appropriate aldehydes and alcohols. The unsaturated ethers were obtained by the catalytic vapor-phase decomposition of acetals.

Condensations

(a) **1,1,3-Trimethoxybutane and 1,1,3,5-Tetramethoxyhexane.**—Dimethyl acetal, 1943 g. (21.58 moles), was placed in a 5-l., 3-necked flask equipped with stirrer, brine-cooled condenser, gas diffuser and thermometer. Three and seven-tenths grams of boron trifluoride etherate (25% boron trifluoride in ethyl ether), was added to the acetal solution (0.05% of boron trifluoride based on the weight of acetal). This solution was warmed to 34° and

(2) Halbig and Kaufler, U. S. Patent 1,902,070 (1933).

(3) Boiling points and melting points are uncorrected.

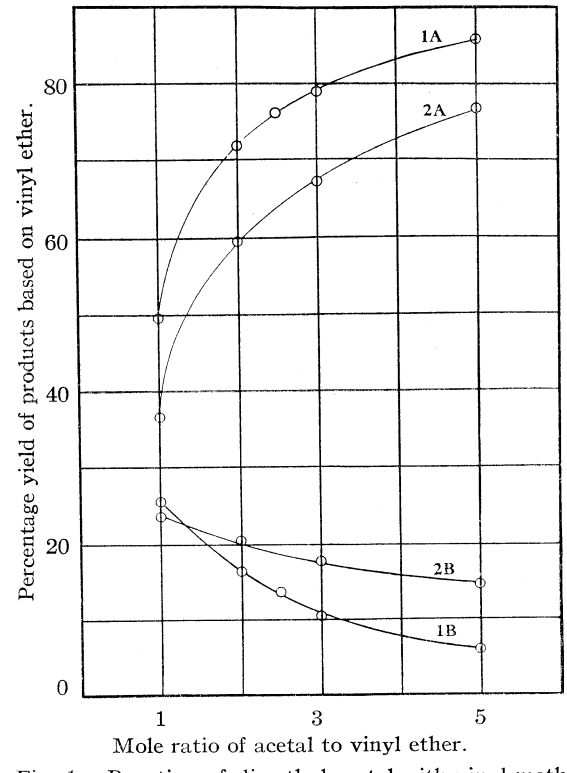


Fig. 1.—Reaction of dimethyl acetal with vinyl methyl ether and diethyl acetal with vinyl ethyl ether. Mole ratio of acetal to vinyl ether *vs.* yield of products based on vinyl ether: 1A, 1,1,3-trimethoxybutane; 2A, 1,1,3-triethoxybutane; 1B, 1,1,3,5-tetramethoxyhexane; 2B, 1,1,3,5-tetraethoxyhexane.

422 g. (7.19 moles) of vinyl methyl ether (99%) was vaporized into the agitated solution. Reaction took place at once with the evolution of heat. The temperature was maintained at 35 to 40° by regulation of the rate of addition of vinyl ether and by external cooling with water. The addition of vinyl methyl ether was completed in one hour and twenty minutes after which the reaction mixture was stirred another hour. The catalyst was then neutralized with 15 g. (400% excess) of anhydrous powdered sodium carbonate. The mixture was agitated four hours and then filtered to remove salts. Fractionation of the filtrate in the presence of a small amount of sodium carbonate gave 1,1,3-trimethoxybutane and 1,1,3,5-tetramethoxyhexane in yields of 79 and 10%, respectively, based on the vinyl methyl ether used. By-products, 1,1-dimethoxy-2-butene and 1,1,3-trimethoxy-4-hexene, were obtained in yields of 0.1 and 0.8%, respectively, although the former compound was not isolated in a pure form. The positions of the methoxy groups and double bond in trimethoxyhexene were indicated by mass spectrometric data. Trimethoxyhexene was obtained in 98% purity by redistillation of intermediate fractions composited from several similar reaction products: b. p. 72–74° (10 mm.); d^{20}_{20} 0.926; $n^{20}D$ 1.4261; *MR*, observed 48.2, calcd. 48.18.

(b) **1,1,3-Triethoxyhexane and 1,1,3,5-Tetraethoxyoctane.**—A mixture of 3070 g. (21 moles) of diethyl butyral and 6 g. of boron trifluoride etherate (25% boron trifluoride in ethyl ether) was stirred and warmed to 49°. To this mixture was added with good agitation 511 g. (7 moles) of vinyl ethyl ether (98.8%). The rate of addition was regulated, so that by cooling the reaction flask with water a reaction temperature of 49 to 50° was maintained. The addition of vinyl ether required forty-five

minutes, after which the catalyst was neutralized by agitation with 72 g. of 10% alcoholic sodium hydroxide solution. The reaction product was distilled under vacuum to recover the unreacted diethyl butyral and the products, 1,1,3-triethoxyhexane and 1,1,3,5-tetraethoxyoctane, which were obtained in yields of 72 and 16%, respectively, based on vinyl ethyl ether.

(c) **1,1,3-Triethoxy-2-ethylbutane.**—Three hundred grams (3 moles) of 1-butenyl ethyl ether was added dropwise to 1063 g. (9 moles) of diethyl acetal containing 1 cc. of an ethyl ether solution of boron trifluoride etherate (35% boron trifluoride). The mixture was stirred constantly during the addition of the ether and the temperature was maintained between 45 and 48° with slight cooling of the reaction flask. The addition of the ether was complete in fifteen minutes, although the reaction continued for another fifteen minutes. The catalyst was neutralized by agitation with 5 g. of anhydrous, powdered sodium carbonate for a period of three hours. Distillation of the reaction product gave 1,1,3-triethoxy-2-ethylbutane in 48% yield, based on 1-butenyl ethyl ether.

Hydrolysis and De-alkanolation

(a) **2,4-Hexadienal and 5-Methoxy-2-hexenal.**—One mole (206.2 g.) of 1,1,3,5-tetramethoxyhexane was distilled with 220 g. of 5.0% aqueous sulfuric acid solution. Methanol was removed as fast as formed until the vapor temperature could no longer be maintained at 65°. The removal of methanol (110 g.) required three and one-half hours. Distillation was stopped and the kettle residue was cooled to room temperature. This product consisted of a lower layer containing 5.75% sulfuric acid and 6.0% of aldehyde (as 5-methoxy-2-hexenal), and an upper layer containing essentially 2,4-hexadienal and 5-methoxy-2-hexenal. The upper layer was distilled under vacuum in the presence of 0.5 g. of sodium acetate. The yields of 2,4-hexadienal and 5-methoxy-2-hexenal were 47 and 38%, respectively. Physical properties of 2,4-hexadienal: b. p. 43° (5 mm.); d^{20}_{20} 0.898; $n^{20}D$ 1.5384. Physical properties of 5-methoxy-2-hexenal: b. p. (approx.) 58° (5 mm.); d^{20}_{20} 0.931; $n^{20}D$ 1.4615; *MR*, observed 36.1; calcd. 35.8.

(b) **2-Hexenal and 2-Ethyl-2-butenal.**—1,1,3-Triethoxyhexane, 327 g. (1.5 moles), was distilled with 375 cc. of 2% aqueous hydrochloric acid solution. After refluxing this mixture ten minutes the vapor temperature dropped to 77.5° and an ethanol fraction was removed. After five hours the removal of ethanol was essentially complete, water was added to the kettle and crude 2-hexenal (94% purity) was recovered as the upper layer of the 2-hexenal–water steam distillate. The yield of 2-hexenal was 94%. Physical properties of 2-hexenal: b. p. 50–51° (20 mm.); d^{20}_{20} 0.845; $n^{20}D$ 1.4464. 1-Hexanol was prepared from the aldehyde by hydrogenation; 3,5-dinitrobenzoate, m. p. 58°.

Using the same procedure, 2-ethyl-2-butenal was prepared in 95% yield from 1,1,3-triethoxy-2-ethylbutane. Physical properties of 2-ethyl-2-butenal: b. p. 58° (50 mm.); d^{20}_{20} 0.858; $n^{20}D$ 1.4478. 2-Ethyl-1-butanol was prepared from the aldehyde by hydrogenation; 3,5-dinitrobenzoate, m. p. 50°.

Acknowledgment.—The authors wish to acknowledge the helpful suggestions made by other members of the Process Development Laboratory and Research Laboratory of this Corporation and also the assistance of Dr. Samuel F. Clark who was formerly associated with this project.

Summary

1. The reaction of acetaldehyde acetals and vinyl ethers was extended to include acetals of other aldehydes and α,β-unsaturated ethers of alcohols other than vinyl alcohol.

2. The manner in which acetals and α,β-unsaturated ethers react was shown to be in disagreement with that suggested by Mueller-Cunradi and Pieroh.

3. The utility of the acetal–α,β-unsaturated ether reaction is discussed.

SOUTH CHARLESTON, W. VA. RECEIVED MAY 12, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

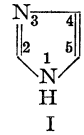
Studies of Imidazole Compounds. II. The Structure of Certain Simple Imidazole Derivatives

BY ROBERT A. TURNER

Although the structures of several aromatic nuclei have been discussed extensively in the chemical literature, the structure of the imidazole nucleus has been given scant attention. In this paper we discuss the structure of imidazoles, as revealed by the spectrophotometric data of certain simple derivatives.

Discussion

Imidazole (I) possesses an aromatic sextet (II) and thus satisfies one of the known requirements for aromatic character.



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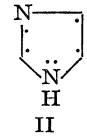


II

The nitrogen atom in position 3 has an electron pair, not included in the sextet, and which may be donated to a proton. Imidazole is a basic substance which readily forms salts with acids. Since the two unshared electrons of the nitrogen atom in position 1 are needed to form the sextet, they may not be donated to a proton, and consequently imidazole is a monoacid base.[1]

When the imidazole nucleus has acquired a proton, the charged molecule has the resonance forms III and IV.

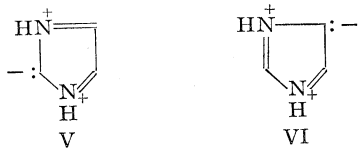


III IV

(1) The structure of pyrrole is, by contrast, enlightening in this connection. It loses its aromatic stability in the presence of hydrogen ions because the sextet is destroyed when the two unshared electrons of the nitrogen atom are donated. Not only is pyrrole a weak base, but it is unstable in the presence of acids.

This resonance is the same as that of an amidine salt and is very similar to that of an imido ester salt. Like amidine salts, imidazole salts are uncolored. The resonance of salts of amidines and of imido esters contributes stability to these substances, but this resonance does not extend through a sufficiently long conjugated system, nor are the resonating forms sufficiently polarized so that the salts are colored.

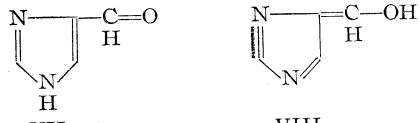
If the electrons of the carbon-to-carbon double bond of III could enter into the resonance between the nitrogen atoms, the resonance of an imidazole salt would not be that of an amidine salt but would be of a more complex kind. However, if the electrons of the carbon-to-carbon double bond do enter into the resonance, structures such as would



V VI

contribute to the total structure of imidazole. These structures would not have much significance, for well substantiated reasons.

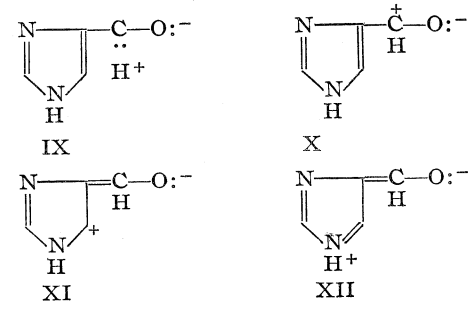
Imidazole-4-aldehyde is a colorless, crystalline substance, of molecular weight 96.09 and m. p. 174°. It is not easily oxidized, contrary to the expected behavior of aldehydes. On the basis of



VII VIII

properties such as these, and others, *e. g.*, the extreme reluctance with which the aldehyde enters into most condensation reactions, Hubball and Pyman[2] postulated that the aldehyde existed chiefly in the enol form VIII rather than in the aldehyde form VII.[3] However, this proposition is simply that VII and VIII are in equilibrium, with the equilibrium shifted so that the enol form VIII preponderates greatly over the aldehyde. It seems unlikely that such a state would effectuate the masking of aldehyde properties in the absence of steric factors, for special steric conditions must usually exist in order to quench the lability which is known to attend the equilibrium between an aldehyde and its enol. In view of this and the evidence to be discussed below we believe the explanation of Hubball and Pyman[2] to be untenable.

Besides the usual structure VII for imidazole-4-aldehyde there are others for which evidence exists if we accept certain premises of modern structure theory. The variable amount of ionic character in the C–H bond makes IX a contributory structure. The strongly electronegative oxygen atom causes the C–O bonding to have considerable ionic character so that X is also a contributory structure. Related to X are structures such as XI and XII. Of these we regard XII as having special significance and contributing to a greater degree to the total structure of imidazole-4-aldehyde than any of the corresponding structures for benzaldehyde contribute to its total structure, because of the stability of quadrivalent, positively charged nitrogen.



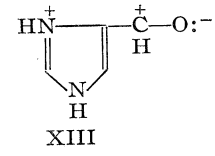
IX X

XI XII

The structures X, XI and XII are very probably those responsible for the absorption of imidazole-4-aldehyde in the ultraviolet region (Fig. 1). Since imidazole does not absorb light in either the visible or near ultraviolet region, this absorption of imidazole-4-aldehyde is attributable only to the (conjugated) aldehyde group.[4]

An interesting phenomenon appears when acid is added to imidazole-4-aldehyde: the absorption peak at 256 mμ is obliterated. The change occurs immediately, for it does not matter whether the aldehyde is dissolved in acid before its spectrum is measured, or whether a drop is added just prior to the determination of absorption at 256 mμ. We explain the phenomenon as follows.

Addition of a proton to VII causes its stabilization in forms corresponding to III and IV. Either of the nuclear nitrogen atoms has a charge of +1. Thus electrons would be drawn toward the nucleus, and forms corresponding to X, XI and XII would be very improbable. For example, XIII,



XIII

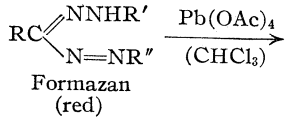
the structure which corresponds to X after the addition of a proton, is very unlikely. We say, then, that the addition of a proton to imidazole-4-aldehyde reduces the contribution of forms such as X, XI and XII to a negligible amount. Since only these forms absorb in the ultraviolet region, absorption *in that region* is eliminated.

(2) Hubball and Pyman, *J. Chem. Soc.*, 21 (1928).

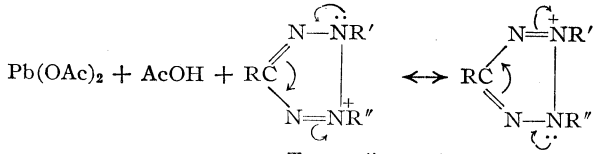
(3) Imidazole-4-aldehyde forms a cyanohydrin, a phenylhydrazone, an anil, an oxime, a sodium bisulfite addition compound and a semicarbazone; it condenses with pyruvic acid and β-naphthylamine to form 2-(imidazol-4-yl)-benzo-f-quinoline-4-carboxylic acid. It does not undergo the Cannizzaro reaction, or the Perkin reaction; it gives a negative Schiff test; it does not form an acetal; and it is not oxidized either by air or by ammoniacal silver nitrate.

(4) 4-Hydroxymethylimidazole, the alcohol corresponding to imidazole-4-aldehyde, has no absorption peak in the ultraviolet region.

In this connection it is interesting to compare the structure and absorption characteristics of a formazan with those of the tetrazolium salt formed from the formazan by oxidation.[5] It is to



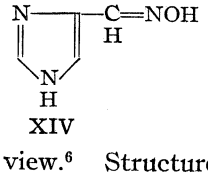
Formazan
(red)



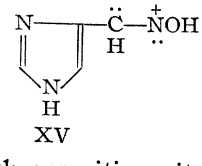
Tetrazolium salt
(colorless)

be noted that the tautomerism which is present in the formazan is not present in the tetrazolium salt, which exhibits resonance. Imidazole-4-aldehyde has, like the formazan, a tautomerism in which a hydrogen atom migrates from one nitrogen atom to another; in acid solution imidazole-4-aldehyde is no longer tautomeric but possesses a resonance very similar to that of the tetrazolium salt. A formazan has large absorption peaks in the regions 290 and 420 mμ. Tetrazolium salts have a single, broad peak near 300 mμ, the peak at the longer wave length having been eliminated. Thus the analogy between imidazole-4-aldehyde and a formazan, on one hand, and between imidazole-4-aldehyde hydrochloride and a tetrazolium salt, on the other, is accountable in structure theory and is further supported by the absorption spectra of the several compounds.

The absorption of imidazole-4-aldehyde oxime (Fig. 2) in alcohol solution, and in alcohol solution containing hydrochloric acid, parallels that of the aldehyde. The oxime absorbs strongly, with a peak at 249 mμ; in the presence of hydrochloric acid the peak is shifted to 240 mμ. Thus the effect found to occur in the aldehyde also occurs in the oxime, but to a lesser extent. We account for this as follows. The oxime XIV has a contribution to its structure of the form XV. Data from dipole moment determinations support

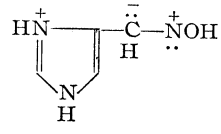


XIV



XV

this view.[6] Structures with a positive nitrogen contribute to the total structure, whereas in the analogous oxygen compound the related form with positive oxygen is unimportant. Furthermore, we may expect that addition of a proton to XV to yield XVI would not depress the absorption at all, but rather augment it, inasmuch as the positive charge in the nucleus would mobilize the electron pair which shifts when XV is formed from XIV.



XVI

We now turn to the evidence derived from infrared spectrometry which bears upon the structure of imidazole-4-aldehyde and related compounds. Generally, aldehydes exhibit a peak, which may be quite broad, in the region 1640 to 1690 cm.$^{-1}$. Aldehydes which are conjugated with a double bond, whether it is part of a chain or in an aromatic ring, have peaks which are shifted toward shorter wave lengths; the peaks of these aldehydes are near 1700 cm.$^{-1}$ and are large. The infrared spectrum of imidazole-4-aldehyde is shown in Fig. 3. It will be noticed that the peak which extends from 1654 to 1696 cm.$^{-1}$ is typical of an aromatic aldehyde. While the spectrometric evidence for the aldehyde group is satisfactory, there is no certain evidence of an alcohol group. We consider that this evidence, which shows that imidazole-4-aldehyde exists as the aldehyde, or that at least a large fraction of it so exists, negates the postulate of Hubball and Pyman[2] that imidazole-4-aldehyde exists chiefly in the enol form VIII.

The comparison of the spectrum of imidazole-4-aldehyde with the spectrum of 4-hydroxymethyl-imidazole (Fig. 4) reveals two easily discernible features. First, the broad band from 1654 to 1696 cm.$^{-1}$, present in the spectrum of the aldehyde, is absent from the spectrum of the alcohol. Second, the spectrum of the alcohol in the region 3000 to 3500 cm.$^{-1}$ (the region of vibrations of hydroxyl groups) shows more absorption than does the spectrum of the aldehyde. Comparison of the spectrum of the aldehyde with those of several blank determinations of mineral oil in the region near 2900 cm.$^{-1}$ has shown that the absorption of the aldehyde is almost identical with the absorption of mineral oil in that region.

If the aldehyde existed in the enol form VIII, either wholly or partly, it would exhibit some absorption in the region 3100 to 3500 cm.$^{-1}$. Thus the evidence from infrared spectrometry shows that the aldehyde is not enolated.[7]

The infrared spectrum of the aldehyde oxime (Fig. 5) now becomes of interest. From what has been stated in the foregoing discussion it might be expected that the oxime would have a peak at

(5) Kuhn and Jerchel, *Ber.*, **74**, 941 (1941).

(6) Hurdis and Smyth, THIS JOURNAL, **65**, 89 (1943), have adduced evidence from dipole moment measurements which strongly indicates a structure with positive nitrogen to be contributory in the case of certain nitriles. It is reasonable to expect the same structure in an oxime, which is a hydrated nitrile.

(7) It may be remarked that both the data from Raman spectra and from polarographic reduction indicate that pyrrole-2-aldehyde exists as the aldehyde and not as the enol, and is slightly more difficult to reduce than benzaldehyde. *Cf.* Bonino and Scaramelli, *Ricerca sci.*, **6**, II, 111–112 (1935); *C. A.*, **30**, 8208 (1936).

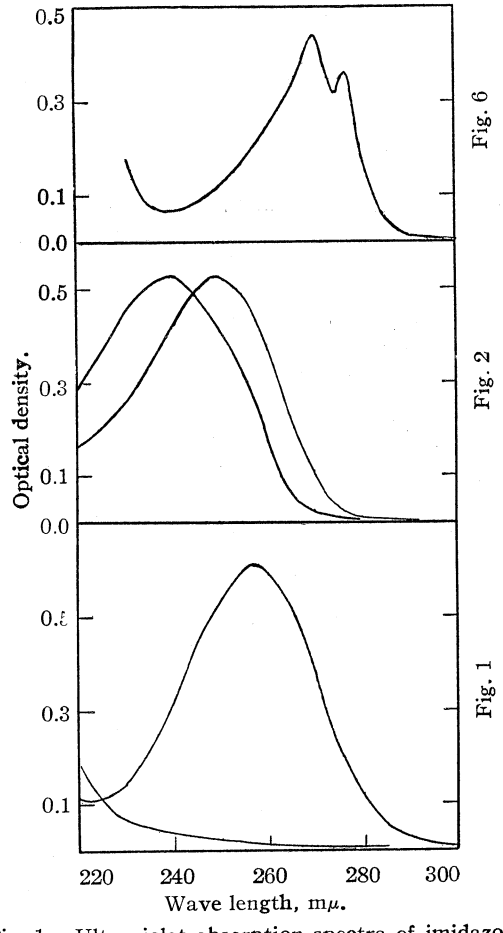


Fig. 1.—Ultraviolet absorption spectra of imidazole-4-aldehyde: upper curve, 0.0050 mg. per ml. in 95% ethanol; peak at 256.5 mμ with ε equal to 11,700. Lower curve, 0.0050 mg. per ml. in 96% ethanol which was 0.040 *N* in hydrochloric acid.

Fig. 2.—Ultraviolet absorption spectra of imidazole-4-aldehyde oxime: right curve, 0.0050 mg. per ml. in 95% ethanol; peak at 249 mμ with ε equal to 11,600. Left curve, 0.0050 mg. per ml. in 95% ethanol which was 0.040 *N* in hydrochloric acid; peak at 240 mμ with ε equal to 11,710.

Fig. 6.—Ultraviolet absorption spectrum of imidazole-4-carboxylic acid: 0.050 mg. per ml. in 95% ethanol; peaks at 270.5 mμ, with ε equal to 980, and at 277 mμ with ε equal to 810.

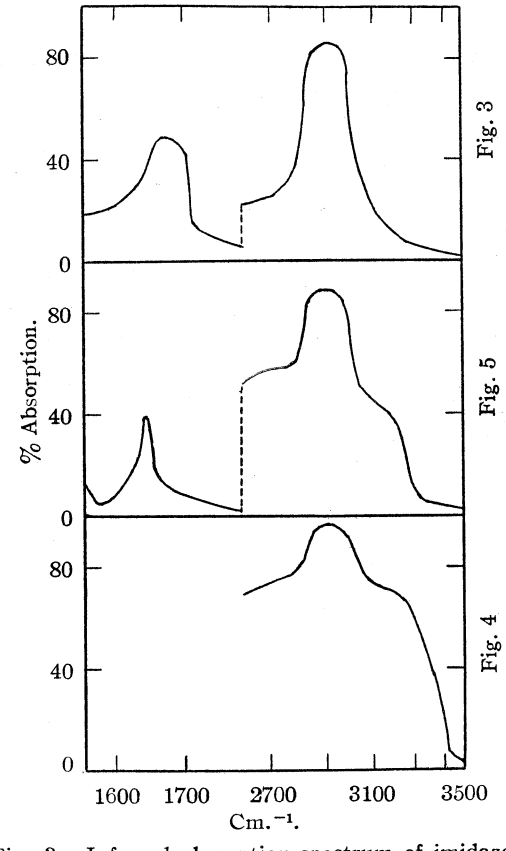


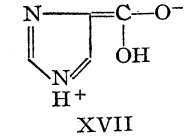
Fig. 3.—Infrared absorption spectrum of imidazole-4-aldehyde: regions 1570 to 1800 cm.$^{-1}$ (left curve) and 2650 to 3350 cm.$^{-1}$ (right curve).

Fig. 4.—Infrared absorption spectrum of 4-hydroxymethyl-imidazole: region 2400 to 3600 cm.$^{-1}$.

Fig. 5.—Infrared absorption spectrum of imidazole-4-aldehyde oxime regions 1570 to 1800 cm.$^{-1}$ (left curve) and 2650 to 3350 (right curve).

the usual place for absorption due to the group C-N of an oxime (1650 cm.$^{-1}$), and also that the spectrum of the oxime would exhibit absorption in the high frequency region on account of the O–H group. The spectrum shows how well these expectations are fulfilled. There is a peak at 1653 cm.$^{-1}$, and there is considerable absorption in the high-frequency region.

Imidazole-4-carboxylic acid presents an absorption spectrum in the ultraviolet (Fig. 6) which has two peaks: at 270.5 mμ, ε = 980; and at 277 mμ, ε = 810. Because the values of these peaks are so much lower than the value for imidazole-4-aldehyde, the electronic transitions to which they are attributable are much less probable. However, there is no certainty that the transitions for both compounds are the same, or even similar. The two peaks must be the result of interaction between the carboxyl group and the imidazole ring since neither moiety alone absorbs radiation in this region. We postulate the structure XVII, corresponding to XII for imidazole-4-aldehyde,



XVII

as the one to which the absorption at 277 mμ is due.[8]

(8) The peak at 270.5 mμ is such a peak, both with respect to position and to intensity, as would be expected for an aromatic acid. Benzoic acid, for example, exhibits a peak at 270 mμ with ε = 800; *cf.* Kumler and Strait, THIS JOURNAL, 66, 2352 (1943).

Experimental

The samples of compounds used in the experiments reported here were prepared as described by Turner and Scholz[9] and had the melting points and properties recorded by them.

Ultraviolet spectrophotometric measurements were made with solutions of the compounds studied, in 95% ethanol. The instrument used was a Beckman Quartz Spectrophotometer, made by the National Technical Laboratories.

Infrared spectrophotometric measurements were made with crystals of the compound, mulled in mineral oil. The mineral oil suspension was held between two sodium chloride plates. A stream of dry nitrogen was allowed to sweep through the carriage holding the salt plates, so that the absorption spectrum of air (due to water and carbon dioxide, chiefly) was greatly diminished. Small absorption bands due to water remained in the spectrophotometric tracings in the region below 1600 cm.$^{-1}$. The instrument used was a Perkin–Elmer Infrared Spectrometer, Model 12A, equipped with a Brown automatically recording potentiometer, and with an adjustable attenuator to oppose and counterbalance the irregularities of emission of infrared radiation from the source (Globar).

The infrared curves are tracings of photographs of the original recording obtained from the spectrometer. The spectra in all cases were determined in the region 650 to 4000 cm.$^{-1}$ but only pertinent regions are shown in the figure. Values of bands given in the discussion were taken from the original recording and are accurate to about ± 5 cm.$^{-1}$ in the region near 1700 cm.$^{-1}$. The per cent. of absorption is only approximate.

Acknowledgment.—The author takes pleasure in expressing his appreciation to Professor Charles P. Smyth of Princeton University, who kindly read and criticized this paper before it was submitted for publication. The author wishes to acknowledge his debt to Professor du Vigneaud for his interest and encouragement in this work. The author also wishes to express his thanks to Dr. Julian R. Rachele for many helpful consultations in relation to the infrared determinations; and to Dr. Caesar R. Scholz of Ciba Pharmaceutical Products, Inc., for samples of imidazole derivatives.

(9) Turner and Scholz, THIS JOURNAL, **71**, 2801 (1949).

Summary

The general properties of imidazoles are discussed, taking into consideration resonance and tautomerism. Comparisons with similar open-chain and ring systems are made.

The structure of imidazole-4-aldehyde is discussed in detail in the light of ultraviolet and infrared spectrophotometric data. These data reveal that, contrary to the postulate of Hubball and Pyman,[2] the aldehyde does not exist as an enol. Its peculiar properties must be explained on the basis of its aldehyde structure.

In connection with the structure theory of the aldehyde related compounds such as the oxime, the corresponding alcohol, and the corresponding acid are discussed.

NEW YORK 21, N. Y. RECEIVED FEBRUARY 25, 1949

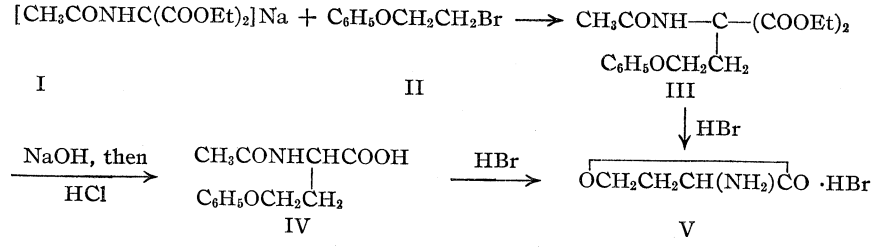
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Studies of Imidazole Compounds. III. Synthesis of 4-(2-Chloroethyl)-imidazole

BY ROBERT A. TURNER

In a previous paper of this series[1,2] the synthesis of certain derivatives of 4-methyl-imidazole was described. These derivatives were made from 4-chloromethyl-imidazole, and in order to prepare related derivatives of 4-ethyl-imidazole, 4-(2-chloroethyl)-imidazole was required.

4-(2-Chloroethyl)-imidazole hydrochloride IX has been synthesized in small amounts by Garforth and Pyman[3] through a long series of reaction steps. For our purpose a more practicable and reliable synthesis was needed. In order to achieve this a requisite intermediate was α-amino-γ-butyrolactone hydrobromide V, of which a preparation was recently described.[4] However, this preparation depends on the availability of γ-butyrolactone, and an alternate synthesis of V was devised according to the scheme



Ethyl acetylaminomalonate I and phenoxyethyl bromide II were condensed to the ester III. The latter was not isolated, but was saponified directly to the sodium salt of the corresponding dicarboxylic acid. In aqueous solutions this acid spontaneously released carbon dioxide, and when decarboxylation was complete, the α-acetylamino-γ-phenoxybutyric acid IV was isolated by continuous extraction with chloroform. Conversion of IV into V was performed through long boiling in 48% hydrobromic acid. It was also found

(1) Turner, Huebner and Scholz, THIS JOURNAL, **71**, 2801 (1949).

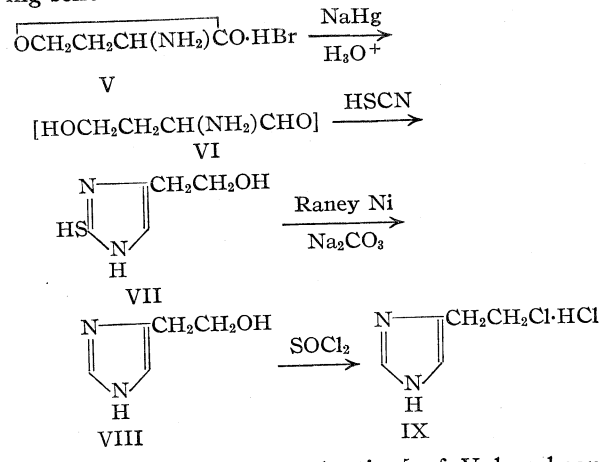
(2) For the second paper of this series, see Turner, *ibid.*, **71**, 3472 (1949).

(3) Garforth and Pyman, *J. Chem. Soc.*, 489 (1935).

(4) Livak, Britton, Vander Weele and Murray, THIS JOURNAL, **67**, 2219 (1945).

that the malonic ester derivative III could be hydrolyzed directly into V by means of hydrobromic acid; however, the procedure involving separation of the intermediate IV gave a purer product.

The synthesis of the hydrochloride IX from the lactone V was performed according to the following scheme



The Neuberg–Fischer reduction[5] of V has been reported,[3] but the method was found to be unreliable. We have devised a procedure for the Neuberg–Fischer reduction which gives a consistently good yield of the thiol VII (VI was not isolated). It was found that the success of the reduction depended on careful control of several variables, chief among which were the temperature and *p*H. An acidic reaction mixture was necessary in order to prevent the reduction of the amino-aldehyde VI to the corresponding alcohol, as well as the self-condensation of VI to a dihydropyrazine.

Treatment of the acidic solution of VI with ammonium thiocyanate yielded VII, which was isolated in crystalline form. Since VII bears a primary alcohol group, we sought a method of desulfurization differing from the usual[6] addition of a 2-thiolimidazole to boiling 10% nitric acid, and it was found that the desulfurization of VII could be performed smoothly by the action of Raney nickel catalyst suspended in sodium carbonate solution.[7] Attempts to crystallize VIII, either as the base or as the hydrochloride failed.[8] This did not prove to be a serious mischance as the sirupy hydrochloride of VIII was smoothly converted by means of thionyl chloride into 4-(β-chloroethyl)-imidazole IX, which crystallized readily.

Experimental

Condensation of Diethyl Acetylaminomalonate with Phenoxyethyl Bromide.—In a flask equipped with stirrer, dropping funnel, and reflux condenser, was prepared a solution of sodium ethoxide from 10.3 g. of sodium and 250 ml. of anhydrous ethanol. To this solution were added in turn 105 g. of diethyl acetylaminomalonate,[9] 200 ml. of anhydrous ethanol, a solution of 103 g. of phenoxyethyl bromide[10] in 200 ml. of anhydrous ethanol, and 2 g. of potassium iodide. When the reaction mixture had been stirred under reflux for forty-eight hours, the solvent was distilled. A solution of 120 g. of sodium hydroxide in 500 ml. of water was added, and after warming for a time to remove a little ethanol which remained, the mixture was boiled under reflux for two hours, cooled, and made just acid to congo paper with about 250 ml. of concentrated hydrochloric acid. During the acidification the solution seethed as carbon dioxide was evolved, and it was extracted continuously with chloroform for five hours. Following evaporation of the chloroform *in vacuo* a brown sirup remained which was dissolved in a mixture of 250 ml. of benzene and 200 ml. of methanol. The solution was concentrated until crystallization commenced in the hot. After having stood in the cold the crystals were filtered. The filtrate was concentrated to obtain another crop; total yield of **α-acetylamino-γ-phenoxybutyric acid (IV)**, 68 g. (64%); m. p. 131.5–132°.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.74; H, 6.37; N, 5.90. Found: C, 60.33; H, 6.27; N, 5.74.

Concentration of the aqueous layer after the extraction with chloroform gave a crystallizate which was a mixture of sodium chloride and **α-amino-γ-phenoxybutyric acid.** Recrystallization from water gave 5.30 g. (6.1%) of this acid; m. p. 229°; reported,[11] 233°. After admixture with an authentic specimen of the acid the melting point was not depressed. In preliminary experiments on a small scale IV was isolated as an oil which later crystallized; m. p. 116–120°. After two recrystallizations the melting point was 122.5–123°, unchanged by further recrystallization.

Anal. Found: C, 60.71; H, 6.32; N, 5.72.

After a few experiments in which IV was isolated as a substance of m. p. 122.5° a preparation was performed which yielded IV as a substance of m. p. 131.5–132°. Subsequent to the appearance of this higher-melting, dimorphic modification the other form was never obtained.

α-Amino-γ-phenoxybutyric Acid from IV.—To 2.68 g. of IV was added 17 cc. of concentrated hydrochloric acid and 11 cc. of water. The mixture was heated for fifteen hours on the steam-bath and then distilled *in vacuo* to dryness. The residue was dissolved in 30 cc. of water and again taken to dryness. Solution of the residue in a little water, neutralization with lithium hydroxide solution, and acidification with dilute hydrochloric acid gave a precipitate of the product; yield, approximately quantitative; m. p. 231° (decomposition); after recrystallization, 233° (decomposition).

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.65; H, 6.67; N, 6.95.

α-Amino-γ-butyrolactone Hydrobromide. (V).—A solution of 6.85 g. of IV in 25 g. of 48% hydrobromic acid was boiled under reflux in a stream of nitrogen for four and one-half hours. Then 20 ml. of hydrobromic acid was added, and 20 ml. of solution was distilled (to remove phenol). After two hours more under reflux the solution was distilled *in vacuo* to dryness. The semi-crystalline mass was digested with anhydrous ethanol until the sirup dissolved, then left in the cold, and finally filtered. By reworking the mother liquor a total of 2.70 g. (61%) of the lactone hydrobromide was obtained; m. p. 224–226° (dec.). Five grams of the oily malonic ester III was boiled eight hours with 50 g. of 48% hydrobromic acid. Isolation as described above gave 1.20 g. of lactone; m. p. 227° (decomposition); after recrystallization the melting point was somewhat lower, 224–226°.

(5) *Cf.* Neuberg, *Ber.*, **41**, 956 (1908); Fischer, *ibid.*, 1019 (1908).

(6) *Cf.* Gabriel and Pinkus, *ibid.*, **26**, 2199 (1893); Gabriel and Posner, *ibid.*, **27**, 1037 (1894).

(7) *Cf.* Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943).

(8) The base has been reported to crystallize after several months (ref. 2). Since the preparation of this paper it has been noticed that a sample of VIII has crystallized after having stood for approximately two years.

(9) Prepared by the procedure of Snyder and Smith, THIS JOURNAL, **66**, 351 (1944).

(10) Prepared according to "Organic Syntheses," Coll. Vol. I, p. 436 (1941).

(11) Fischer and Blumenthal, *Ber.*, **40**, 108 (1907).

Anal. Calcd. for $C_4H_8O_2NBr$: C, 26.39; H, 4.43; N, 7.70; Br, 43.91. Found: C, 26.54; H, 4.34; N, 7.96; Br, 44.45.

α-Amino-γ-butyrolactone Hydrobromide (V) from γ-Butyrolactone.—γ-Butyrolactone was brominated to α-bromo-γ-butyrolactone by the method of Livak, *et al.*[4] Amination of the bromolactone was performed essentially by their procedure, but the isolation of α- and amino-γ-butyrolactone hydrobromide V was greatly facilitated with the use of anhydrous propanol. The mixture of crystalline hydrobromide and brown sirup which was first obtained was partially dried at 100° and 20 mm. and then treated with hot, anhydrous propanol until the sirup dissolved. The first crop of the crystalline hydrobromide, which formed in the cold, was filtered; treatment of the mother liquor in the manner just described gave a second crop; total yield, 64%; m. p. 212–220°.

The lactone hydrobromide was recrystallized by solution in 95% ethanol, addition of an equal volume of benzene, and distillation of ethanol–benzene–water azeotrope through a column. The cooled solution yielded colorless crystals; m. p. 228–231° (dec.), with emollescence at 221°; recovery, 90%.

Anal. Calcd. for $C_4H_8O_2NBr$: N, 7.70; Br, 43.91. Found: N, 7.89; Br, 44.32.

2-Thiol-4-(2-hydroxyethyl)-imidazole (VII).—To a three-necked, 250 ml. flask, equipped with stirrer, dropping funnel and thermometer, and set in a dry ice-cellosolve-bath, were added 18.2 g. (0.10 mole) of α-amino-γ-butyrolactone hydrobromide V and 50 ml. of water. When the lactone had dissolved, 50 ml. of alcohol was poured in, and as soon as the temperature had fallen below −20°, simultaneous addition of 230 g. of 3% sodium amalgam and of 60 ml. of 5 *N* hydrochloric acid from the dropping funnel was begun. The amalgam was added in seven portions at intervals of six minutes, and the acid was allowed to flow in at such a rate that the reaction mixture was maintained just acid to congo paper. After the last portion of amalgam had been introduced the mixture was stirred and kept acid for ten minutes longer. During the whole reaction period the temperature was regulated to the range −16 to −20°.

Following decantation of the supernatant solution and washing of the mercury with 50 ml. of water, the combined solution and washing were filtered, treated with 16.2 g. of ammonium thiocyanate, and, after one-half hour, distilled *in vacuo* to dryness. The yellow, semi-crystalline residue was extracted four times with 50-ml. portions of warm ethanol, and the united extracts were treated with 30 ml. of water and concentrated *in vacuo* until crystallization commenced. After refrigeration overnight the product was filtered; yield, 12.5–14.6 g. (87–100%); m. p. 176° (incomplete). This crude material contained sodium and ammonium halides; after three recrystallizations from water a pure sample was obtained; m. p. 191–192°. After two recrystallizations the melting point was 188–190°; yield, 60–71%. Material of this purity was employed in desulfurization.

Anal. Calcd. for $C_5H_8OSN_2$: C, 41.64; H, 5.59; S, 22.20; N, 19.43. Found: C, 41.67; H, 5.28; S, 21.87; N, 19.32.

4-(2-Chloroethyl)-imidazole Hydrochloride IX. Desulfurization of 2-Thiol-4-(2-hydroxyethyl)-imidazole VII.—A solution of 21.6 g. of VII (m. p. 188° or higher) in 300 ml. of water, containing 23 ml. of saturated aqueous sodium carbonate solution, was distilled to remove traces of ammonia and then added to a suspension of 80 g. of Raney nickel catalyst[12] in 50 cc. of alcohol. The mixture was then stirred and heated under reflux for five and one-half hours.

The nickel was filtered, returned to the flask with 50 ml. of water and stirred and heated for one-half hour. After repetition of the extraction the combined filtrates were acidified with 40 ml. of concentrated hydrochloric acid, and distilled to dryness *in vacuo*. The residue of **4-(2-hydroxyethyl)-imidazole hydrochloride** and inorganic salts was treated with 80 cc. of anhydrous propanol and warmed until the sirup dissolved. After filtration of the salts the solvent was distilled *in vacuo*. The hydrochloride remained as 18.4 g. (83%) of yellow sirup.[13]

The hydrochloride was mixed with 23 ml. of purified thionyl chloride until solution was effected. The mixture was warmed under gentle reflux for one-half hour with exclusion of moisture, treated with an equal volume of benzene, and distilled to dryness *in vacuo*. On cooling, the residue formed a mass of sticky crystals; m. p. 106–110°. Recrystallization from anhydrous propanol–ethyl acetate gave 16.5 g. (79% based on 4-(β-hydroxyethyl)-imidazole hydrochloride) of light yellow platelets; m. p. 118–121, raised to 124° by another recrystallization.

Anal. Calcd. for $C_5H_8N_2Cl_2$: C, 35.95; H, 4.83; Cl, 42.45. Found: C, 35.60; H, 5.02; Cl, 42.03.

Acknowledgment.—We wish to acknowledge the capable assistance of Mrs. Kathryn Oney in these experiments. We are grateful to the Cliffs Dow Chemical Co. for a sample of γ-butyrolactone.

Summary

4-(2-Chloroethyl)-imidazole has been synthesized through this series of steps: α-amino-γ-butyrolactone was reduced to α-amino-γ-hydroxybutyraldehyde, which was converted to 2-thiol-4-(2-hydroxyethyl)-imidazole with ammonium thiocyanate; desulfurization of the thiol led to 4-(2-hydroxyethyl)-imidazole; the latter was converted to 4-(2-chloroethyl)-imidazole hydrochloride with thionyl chloride.

A new synthesis of α-amino-γ-butyrolactone, starting from diethyl acetylaminomalonate has been described.

RECEIVED APRIL 19, 1949

(12) Prepared according to Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).

(13) Attempts to prepare crystalline salts were unsuccessful, with the exception of the picrate, which was more soluble in water than picric acid and could not be isolated in pure form.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTH TEXAS STATE COLLEGE]

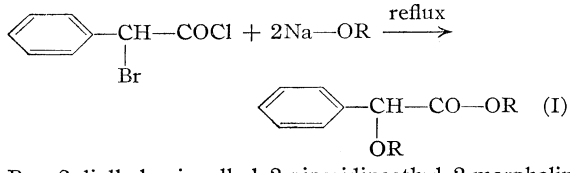
2-Dialkylaminoalkyl α-(2-Dialkylaminoalkoxy)-phenylacetates and Related Amides. II[1]

BY PRICE TRUITT, E. E. RICHARDSON,[2] LOREN M. LONG[3] AND WILLIAM J. MIDDLETON[4]

In the first paper of this series[5] a number of compounds structurally related to 2-dimethylaminoethyl benzhydryl ether hydrochloride, Benadryl,[6] were reported. These compounds were alkyl esters of α-(2-dialkylaminoalkoxy)-phenylacetic acid. Although this substitution of the alkyl carboxyl group for one of the phenyl groups of Benadryl completely eliminated the antihistaminic activity, some antispasmodic activity was noted.[7]

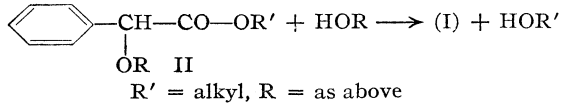
Since numerous reports of physiologically active compounds containing the dialkylaminoalkyl ester linkage have been recorded,[8] we deemed it worthwhile to prepare some 2-dialkylaminoalkyl esters of the α-2-dialkylaminoalkoxy)-phenylacetic acids in order to compare their physiological activity with that of the previously reported alkyl α-(2-dialkylaminoalkoxy)-phenylacetates.[5] Also to obtain a still broader view of the effect of changes in structure on physiological activity, the preparation of several amide derivatives of the α-(2-dialkylamino-alkoxy)-phenylacetic acids was desirable.

The reactions utilized in the preparation of the esters reported in this paper are



R = 2-dialkylaminoalkyl, 2-piperidinoethyl, 2-morpholinoethyl

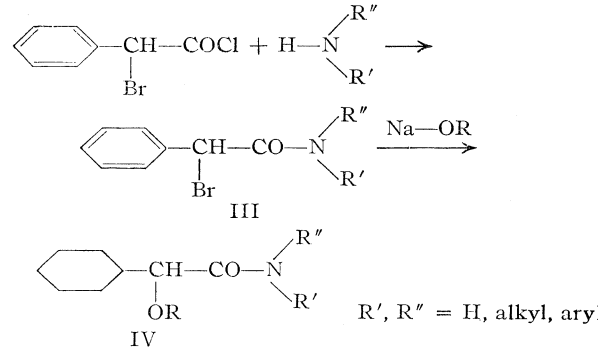
In the preceding paper mention was made of the fact that compound I was formed by ester exchange, thusly



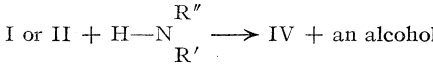
R′ = alkyl, R = as above

The latter method will give a satisfactory yield (60–80%) of I but it is not a useful method of preparation since compound II is obtained in poor yield in two steps from bromophenylacetyl chloride. The method utilized for the synthesis of the esters reported in this paper involves only one step in addition to the preparation of α-bromophenylacetyl chloride.

The amides corresponding to the above esters were obtained via the reactions



Attempts to prepare compound IV by the following reaction were not satisfactory. The yields of desired products were very low.



None of the compounds reported in this paper exhibited anti-histaminic activity; however, all of those tested showed some antispasmodic action.

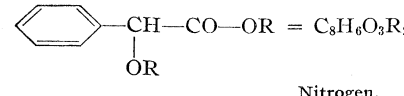
Experimental

The dialkylaminoalkanols used in these experiments were obtained from Eastman Kodak Company and distilled before use.

The α-bromophenylacetyl chloride was prepared as previously reported.[5]

2-Dialkylaminoalkyl α-(2-Dialkylaminoalkoxy)-phenylacetates (Table I).—Two moles of potassium metal was added to 2.2 moles of dialkylaminoalkanol dissolved in

TABLE I



R	Yield, %	B. p., °C.	Mm.	$n^{20}D$	Nitrogen, % Calcd.	Found	Anti-spas.[c] 1	2
$(CH_3)_2NC_2H_4$	77	215	20	1.5011	9.49	9.36	12	5
$(C_2H_5)_2NC_2H_2$	75	200	12	1.4943	8.60	8.80	8	20
$C_4H_8NOC_2H_4$[a]	38	155	3	1.5170	7.22	6.94	10	5
$(C_2H_5)_2NC_3H_6$	71	145	3	1.4948	7.41	7.46		
$C_5H_{10}NC_2H_4$[b]	73	160	6	....	7.48	7.31		
n-$(C_4H_9)_2NC_2H_4$	43	230	5	....	6.06	6.27		

[a] 2-Morpholinoethyl. [b] 2-Piperidinoethyl. [c] Anti-spasmodic action on (1) the rabbit, (2) the guinea pig as % of that of papaverine.

(1) This work was aided by a grant from the Graduate School of North Texas State College. Some of the material in this paper was presented before the Regional meeting of the American Chemical Society at Houston in December, 1947.

(2) Research Fellow 1947, Faculty Research Grant. Present address: Department of Chemistry, Kansas State College, Manhattan, Kansas.

(3) Research Chemist, Parke, Davis and Company, Detroit, Michigan.

(4) Research Fellow 1947–1948, Faculty Research Grant.

(5) Truitt, Mark, Long and Jeanes, THIS JOURNAL, **70**, 4214 (1948).

(6) Rieveschl and Huber, Paper 41, Division of Medicinal Chemistry, American Chemical Society Meeting, Atlantic City, 1946.

(7) Recent tests indicate that one of these compounds, benzyl α-(2-diethylaminoethoxy)-phenylacetate had an antispasmodic activity of 200% of papaverine with barium chloride induced spasms and 300% with acetylcholine.

(8) Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

dry toluene. When all of the potassium had reacted, 1 mole of freshly distilled α-bromophenylacetyl chloride dissolved in an equal volume of dry toluene was added dropwise with constant stirring. When the initial reaction had subsided, the mixture was refluxed with continuous stirring for four to ten hours. Apparently little reaction occurred after the four hours heating period but no decrease in yield was noted when the longer reflux time was used.

The reaction mixture was filtered to remove the precipitated sodium salts and the toluene was subsequently distilled under a water-pump vacuum. The residual liquid was distilled *in vacuo* and further purified by two fractional distillations. The hydrochlorides of these esters were too hydroscopic to handle conveniently.

α-Bromophenylacetamide.—A concentrated solution of 2 moles of ammonium hydroxide was cooled to −10°. This solution was stirred vigorously while 1 mole of α-bromophenylacetyl chloride was added dropwise. Care was taken to keep the temperature of the reaction mass below 0°. After stirring for two hours at this temperature the reaction was allowed to warm to room temperature. The crystals which had formed were collected and recrystallized from alcohol to give glistening white crystals of α-bromophenylacetamide.

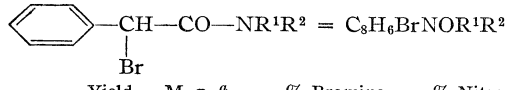
N,N-Diethyl α-Bromophenylacetamide.—A solution of 1 mole of α-bromophenylacetyl chloride in an equal volume of carbon tetrachloride was cooled to −10° and a solution of 2 moles of diethylamine in carbon tetrachloride added dropwise with constant stirring so as to keep the temperature below 0°. After stirring for two hours at this temperature, water was added to dissolve the diethylamine hydrochloride. The organic layer was separated, dried and the carbon tetrachloride distilled *in vacuo*. The liquid residue was fractionated at reduced pressure to give N,N-diethyl-α-bromophenylacetamide.

The remaining amides were prepared in an analogous manner. Data for all of the amides are given in Table II.

α-(2-Piperidinoethoxy)-phenylacetamide.—One mole of α-bromophenylacetamide was refluxed with 1 mole potassium 2-piperidinoethoxide suspended in xylene for two hours. The product was extracted from the xylene with 5% hydrochloric acid. Neutralization of this acid extract gave a white precipitate. Recrystallization from alcohol gave white flakes of the expected α-(2-piperidinoethoxy)-phenylacetamide.

Other amides were prepared in the same manner and data concerning these are given in Table III. N,N-Diphenyl-α-bromophenylacetamide failed to give the expected product. The yields in all other cases were approximately 50%.

TABLE II

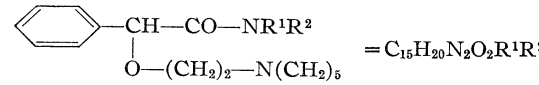


$= C_8H_6BrNOR^1R^2$

R^1	R^2	Yield, %	M. p.,[a] °C.	% Bromine Calcd.	% Bromine Found	% Nitrogen Calcd.	% Nitrogen Found
H	H	92	148[b]	37.34	37.49	6.55	6.54
C_2H_5	C_2H_5	49	155–160[c]	29.59	29.68	5.18	5.22
H	C_6H_5	40	123	27.53	27.65	4.83	4.90
C_6H_5	C_6H_5	32	140	21.82	21.95	3.82	3.87
H	CH_3	68	74	35.07	35.17	6.15	6.23

[a] Corrected. [b] First prepared by Darapsky, *J. prakt. Chem.*, **96**, 285 (1917). [c] B. p. at 6 mm.

TABLE III



$= C_{15}H_{20}N_2O_2R^1R^2$

R^1	R^2	Yield, %	M. p.,[a] °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Antispas.[b] 1	Antispas.[b] 2
H	H	165–167	155–157	10.69	10.77	20	80
CH_3	H	51	133–134	10.15	10.26	15	10
C_6H_5	H	43	171–172	6.39	6.48		
C_2H_5	C_2H_5	47	[c]	8.80	8.91		

[a] Corrected. [b] Tests as given in Table I. [c] An oily solid that melted slightly above room temperature.

Summary

Six dialkylaminoalkyl α-(2-dialkylaminoalkoxy)-phenylacetates have been prepared and characterized. In addition six N- and N,N-disubstituted α-bromophenylacetamides have been synthesized and four of these converted to the corresponding N- and N,N-substituted α-(2-piperidinoethoxy)-phenylacetamides. A partial evaluation of the physiological properties for some of these compounds is given.

DENTON, TEXAS RECEIVED MARCH 25, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of Certain 2-Alkoxyethyl Phenyl Ketones[1]

BY ROBERT EDWARD LESLIE[2] AND HENRY R. HENZE

In connection with another problem, certain alkoxyethyl ketones, especially the 2-propoxyethyl phenyl and 2-(1-methylethoxy)-ethyl phenyl ketones, were needed. Initially, it was visualized that these ketones might be prepared from interaction of Grignard reagents and appropriately substituted alkoxypropionitriles. Attempts to develop this method were not successful, but the desired substances were obtained as a result of reactions between diphenylcadmium and certain β-alkoxypropionyl chlorides. The latter were synthesized through the following sequence: (a) addition of appropriate alcohols to acrylonitrile[3] forming β-alkoxynitriles; (b) hydrolysis of the latter to the corresponding β-alkoxypropionic acids; (c) subsequent conversion into β-alkoxypropionyl chlorides.

Preparation of the ketones was tried first by the method of Cason,[4] namely, addition of the acyl halide to the solution of diphenylcadmium, but the reaction complexes formed very heavy precipitates. Before reaction was complete, agglutination of the suspended matter made stirring practically impossible and thus homogenization of the reaction mixtures was not attained. However, by reversing the sequence of addition of reactants, clumping of the addition products was avoided and

(1) From the M.A. thesis of R. E. Leslie, June, 1948.

(2) Present address: Guatemala City, Guatemala, C. A.

(3) Utermohlen, THIS JOURNAL, **67**, 1505 (1945).

(4) Cason, *ibid.*, **68**, 2078 (1946)

TABLE I

β-ALKOXYPROPIONIC ACIDS R—O—CH_2CH_2COOH

—R	B. p., °C.	Mm.	Yield, %	$n^{20}D$	d^{20}_4	Equiv. wt. Calcd.	Equiv. wt. Found	Molec. refraction Σ	Molec. refraction Calcd.
C_2H_5	107	10	58	1.4216	1.1490	118.1	118.2	28.47	28.54
C_3H_7	117	8	65	1.4238	1.0148	132.2	134.1	33.09	33.20
$CH(CH_3)_2$	101	4	62	1.4208	1.0074	132.2	137.9	33.09	33.25
C_4H_9	112	3	55	1.4280	0.9908	146.2	146.2	37.70	37.95

the yields of ketones were increased. It was found preferable, also, to use ether as the solvent and diluent, rather than to employ benzene, as described by Cason. Five β-alkoxyethyl phenyl ketones (alkyl = CH_3, C_2H_5, C_3H_7, $CH(CH_3)_2$ and C_4H_9) were prepared.

Experimental

Preparation of β-Propoxypropionitrile.[4a]—One hundred and seventy grams of acrylonitrile was added dropwise to a solution of 3 g. of sodium methoxide in 120 g. of propanol with maintenance of the temperature below 70°. Two hundred five grams (77% yield) of product was obtained; b. p. 92° (24 mm.), $n^{20}D$ 1.4128, d^{20}_4 0.8969, Σ *MR* 31.30, *MR* calcd. 31.44.

Preparation of β-Alkoxypropionic Acids.—In general, one mole of a β-alkoxypropionitrile was added slowly dropwise with stirring to 50 ml. of 75–80% sulfuric acid, resulting in the formation of a homogeneous solution. The latter, with stirring, was heated for approximately ten minutes at which time a sudden increase in the rate of reflux was observed.[5] Heating was discontinued for twenty minutes, then 60 ml. of water was added and the mixture was subjected to gentle warming, at the reflux temperature, and stirring for ninety minutes longer. The reaction mixture was cooled, the organic layer was removed and added with stirring to a cooled solution of one mole of sodium hydroxide in 300 ml. of water. Upon cooling, the insoluble, upper layer of organic material was removed. The lower layer was acidified, and the additional organic matter which separated was added to the previously collected main fraction of the alkoxy acid. The crude product was dried over anhydrous sulfate before fractionation *in vacuo*. Data obtained for these four acids are listed in Table I.

Preparation of β-Alkoxypropionyl Chlorides.—The acid (1 mole) was added dropwise to the stirred thionyl chloride (1.5 moles) which was warmed since the reaction was notably endothermic. After stirring the mixture for one hour without further heating, the material was fractionated *in vacuo*. Certain data concerning the five acid chlorides prepared are given in Table II.

TABLE II

β-ALKOXYPROPIONYL CHLORIDES R—O—$CH_2CH_2CO{\cdot}Cl$

—R	B. p., °C.	Mm.	Yield, %	d^{20}_4	Chlorine, % Calcd.	Chlorine, % Found[a]
CH_3[b]	64	44	85	1.1256	28.92	29.03
C_2H_5	77.5	52	96	1.0594	25.97	26.10
C_3H_7	77	25	92	1.0424	23.53	23.58
$CH(CH_3)_2$	73.5	30	91	1.0343	23.53	23.82
C_4H_9	86	20	94	1.0157	21.53	21.62

[a] Weighed sample was warmed with dilute sodium hydroxide solution before completing the gravimetric analysis. [b] The sample of β-methoxypropionic acid was donated by The B. F. Goodrich Co., Akron, Ohio.

Preparation of 2-Alkoxyethyl Phenyl (or Alkyl) Ketones.—One-fourth mole of β-ethoxypropionitrile in 250 ml. of anhydrous ether was added dropwise with stirring to a solution of three-fourths mole of ethylmagnesium bromide in 550 ml. of ether. The evolution of heat was quite noticeable, and a dark green precipitate separated from solution. A small sample of the addition-product was removed and dried to yield a very fine yellow powder which reacted vigorously with water to form a yellow gum. Upon treatment of the small sample with water, ammonia was evolved. Hydrolysis of the main portion was attempted with ice-cold hydrochloric acid; an insoluble, red gum resulted. From the ether solution, upon distillation, there was obtained only a small volume of low-boiling liquid which failed to exhibit typical ketone function. The red gum, also, failed to give a carbonyl test. After fusion of the gummy material with sodium, tests for the presence of magnesium and chlorine were positive, but for nitrogen was negative.

The attempted preparation of a ketone was repeated, except that the solution of ethylmagnesium bromide was added to that of β-ethoxypropionitrile. Similar results were obtained.

A solution of β-methoxypropionitrile in ether was added to a very dilute ether solution of phenylmagnesium bromide (4 equivalents); reaction was vigorous, a viscous gummy mass was formed and was treated with ice-cold, concentrated hydrochloric acid. Again, no identifiable product was isolated.

A similar negative result was obtained when β-ethoxypropionitrile in butyl ether was added to 2.5 equivalents of phenylmagnesium bromide in butyl ether solution.

Attempts were then made to prepare alkoxyethyl phenyl ketones using Cason's procedure.[4] Phenylmagnesium bromide, in 6–7 volumes of absolute ethyl ether, was treated with finely divided, anhydrous cadmium chloride; heat was evolved, the solution darkened in color and suspension of a white precipitate was noted. After addition of the cadmium chloride was complete, usually in five to ten minutes, the reaction mixture was stirred for ninety minutes. Upon discontinuing the stirring, the mixture separated into three layers; the two upper, liquid layers were decanted into a separatory funnel for dropwise addition to the appropriate β-alkoxypropionyl chloride diluted with 5–6 volumes of anhydrous benzene. An approximate ratio of 0.6 mole (estimated) of diphenylcadmium to 1 mole of acyl chloride was employed. As the reactions were exothermic, cooling of the mixture was necessary. A gray precipitate formed and was in such finely divided condition as to offer little resistance to the stirrer. Stirring was continued for one hour.

The mixture was hydrolyzed with ice-cold, concentrated hydrochloric acid. Initially a gray, viscous gum formed, but disappeared after about five minutes, and a clear upper layer formed and was separated. After removal of ether and benzene, the organic material was washed with an aqueous solution of sodium bicarbonate, dried over anhydrous calcium chloride, subjected to a pressure of 4 mm. at room temperature before being distilled at less than 1 mm. pressure. Unless distilled at this low pressure the ketones tended to decompose forming acrylophenone and the corresponding alcohols. Data, secured from characterization of the ketones, have been placed in Table III.

(4a) After completion of all the Experimental and after deposit of the M.A. thesis (March, 1948), Christian and Hixon (THIS JOURNAL, **70**, 1333 (1948)) reported the synthesis in 84% yield of β-propoxypropionitrile; b. p. 84° (19 mm.), $n^{20}D$ 1.4131, d^{20}_{20} 0.9006.

(5) In hydrolysis of β-alkoxypropionitriles by the action of concentrated sulfuric acid, precaution needed to be taken so as to avoid excessive heating in the preliminary course of the reaction. The reaction is so exothermic as to be difficult to control. Overheating resulted in loss of material and possibly could bring about personal injury.

TABLE III

2-ALKOXYETHYL PHENYL KETONES R—O—$CH_2CH_2COC_6H_5$

—R	Yield, %	$n^{20}D$	d^{20}_4	Molec. refrac. Σ	Molec. refrac. Calcd.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3[a]	90	1.5250	1.0602	46.96	47.46	73.14	73.12	7.37	7.36
C_2H_5[b]	82	1.5190	1.0356	51.57	52.23	74.13	73.93	7.92	7.73
C_3H_7	82	1.5193	1.0300	56.19	56.68	74.97	74.30	8.39	7.83
$CH(CH_3)_2$	89	1.5083	1.0108	56.19	56.73	74.97	74.39	8.39	8.30
C_4H_9	91	1.5036	0.9976	60.81	61.19	75.69	74.98	8.80	8.78

[a] Straus and Berkow (ref. 7, p. 144) reported b. p. 125–126° (16 mm.), d^{15}_4 1.020. [b] Kohler (ref. 6, p. 388), who obtained this ketone as a by-product in the preparation of phenyl vinyl ketone from α,β-dibromopropiophenone, reported b. p. 135° (18 mm.), m. p. about 12°.

These alkoxyethyl phenyl ketones readily formed 2,4-dinitrophenylhydrazones; the melting points of the latter are given in sequence to the appropriate alkyl group: CH_3, 175.5–176.5°; C_2H_5, 161.0–161.5°; C_3H_7, 158.0–158.5°; $CH(CH_3)_2$ 174.5–175.0°; C_4H_9, 152.5–153.0°.

In one instance, the impure 2-(1-methylethoxy)-ethyl phenyl ketone, obtained by distillation as described above, was redistilled through a six-inch column from an oil-bath at 140–155°. Several fractions of constant refractive index were removed at 106–107° (18 mm.)[6,7] and were found to possess the following physical properties: $n^{20}D$ 1.5440; d^{20}_4 1.0350; Σ MR[8] 40.35; MR calcd. 40.31. The product, acrylophenone, formed (a) a 2,4-dinitrophenylhydrazine derivative [or 1-(2,4-dinitrophenyl)-3-phenyl-Δ²-pyrazoline], m. p. 155–156° and (b) a phenylhydrazine derivative [or 1,3-diphenyl-Δ²-pyrazoline],[9,10,11] m. p. 153°.

(6) Kohler, *Am. Chem. J.*, **42**, 375 (1909), reported b. p. 118° (18 mm.).

(7) Straus and Berkow, *Ann.*, **401**, 121 (1913), reported b. p. 115° (18 mm.).

(8) Includes 0.65 correction for exaltation of C_6H_5CO– compounds; *cf.* Auwers, *Ber.*, **45**, 2765 (1912).

Summary

1. Certain β-alkoxypropionitriles, obtained by the interaction of acrylonitrile and various alcohols, were hydrolyzed to yield β-alkoxypropionic acids which, in turn, were converted into the corresponding acid chlorides.

2. The β-alkoxypropionyl chlorides reacted with diphenylcadmium to yield 2-alkoxyethyl phenyl ketones, three of which have not previously been reported. These ketones tend to be unstable upon distillation and decompose to produce acrylophenone.

(9) Straus and Berkow, ref. 7, reported m. p. 152°.

(10) Schafer and Tollens, *Ber.*, **39**, 2181 (1906), reported m. p. 152–153°.

(11) Young and Roberts, THIS JOURNAL, **68**, 649 (1946), reported m. p. 154–155°.

AUSTIN, TEXAS RECEIVED FEBRUARY 19, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

A Proposed Mechanism of the Alkylation of Benzyl Halides with Nitro Paraffin Salts[1]

BY H. B. HASS[2] AND MYRON L. BENDER[3]

It was shown in the preceding paper[4] that, of nine para-substituted benzyl halides, only *p*-nitrobenzyl chloride gave carbon-alkylation with sodium 2-propanenitronate whereas the other eight benzyl halides gave oxygen-alkylation in 68–77% yield as illustrated in the equations

$$p\text{-}NO_2C_6H_4CH_2Cl + (CH_3)_2CNO_2^-Na^+ \longrightarrow p\text{-}NO_2C_6H_4CH_2C(CH_3)_2NO_2$$

$$p\text{-}CH_3C_6H_2CH_2Br + (CH_3)_2CNO_2^-Na^+ \longrightarrow p\text{-}CH_3C_6H_4CHO + (CH_3)_2C{=}NOH$$

These facts led us to seek some explanation for the anomalous behavior of *p*-nitrobenzyl chloride in this reaction.

The anions of nitroparaffin salts have been represented as resonance hybrids involving forms with the negative charge on oxygen or on carbon.[5] Carbon-alkylation may then be considered[6] to involve a nucleophilic displacement by the resonating anion at carbon while oxygen-alkylation may be considered to involve a displacement by the resonating anion at oxygen. The compounds resulting from oxygen-alkylation, nitronic esters, have been isolated in several cases similar to the present work[7] and have been prepared by a different synthesis[8]; they are thermally instable and decompose spontaneously even at room temperature into carbonyl compounds and oximes. While the mechanisms discussed above account for the possibility of the two modes of alkylation, they furnish no basis of explaining the anomalous behavior of *p*-nitrobenzyl chloride.

(1) An abstract of a thesis by Myron L. Bender, submitted to the Faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, August, 1948. Presented before the Division of Organic Chemistry, 114th American Chemical Society meeting, St. Louis, Missouri, September 6, 1948.

(2) Present address: General Aniline and Film Corp., New York, N. Y.

(3) E. K. Lilly Fellow, 1947; American Cyanamid Company Fellow, 1947–1948; present address: Harvard University, Cambridge 38, Massachusetts.

(4) Hass and Bender, THIS JOURNAL, **71**, 1767 (1949).

(5) Kornblum, Lichtin, Patton and Iffland, *ibid.*, **69**, 307 (1947).

(6) Hauser, *ibid.*, **60**, 1957 (1938).

(7) Thurston and Shriner, *J. Org. Chem.*, **2**, 183, 560 (1937–1938); Weisler and Helmkamp, THIS JOURNAL, **67**, 1167 (1945), and other references cited therein.

(8) Arndt and Rose, *J. Chem. Soc.*, 1 (1935).

The second-order rates of the four alkylation reactions involving lithium 2-propanenitronate and *o*-nitrobenzyl chloride, *m*-nitrobenzyl chloride, *p*-nitrobenzyl chloride and benzyl chloride have been determined at 30 ± 0.3°; the experimental results are shown in Fig. 1. The relative rates of these four halides in this reaction are compared in Table I with the relative rates of the

TABLE I

COMPARISON BETWEEN RATES OF ALKYLATION AND POTASSIUM IODIDE REACTIONS

Halide	Alkylation[a]	Lithium 2-propanenitronate in ethanol at 30° $k_2 \times 10^4$ (l./mole sec.)	Lithium 2-propanenitronate in ethanol at 30° Relative k_2	KI in acetone[9,10] at 50° Relative k_2
o-Nitrobenzyl chloride	C(46%) + O(30%)	1.37	9.2	9.2
p-Nitrobenzyl chloride	C(83%) + O(1%)	1.05	7.1	7.0
m-Nitrobenzyl chloride	O(73%)	0.64	4.3	4.0
Benzyl chloride	O(73%)	0.29	1.9	1.0

[a] See Table III for experimental evidence.

halides in another second-order reaction, the reaction with potassium iodide in acetone. The correlation between the rates of these two reactions implies that the rate-determining step is the same for all four halides in the reaction with lithium 2-propanenitronate (as it is assumed to be in the potassium iodide reaction). Previous evidence indicates that the rate-determining

TABLE II

PARALLELISM BETWEEN CARBON-ALKYLATION AND STILBENE FORMATION

Benzyl halide	Alkylation: alcoholic sodium 2-propanenitronate Carbon	Oxygen	Williamson reaction: alcoholic sodium hydroxide or sodium alkoxide Stilbene	Ether	Reference
p-CH_3		X		X	*a*
p-Br		X		X	*b*
Unsubstituted		X		X	*c*
p-CO_2CH_3		X		X	*h*
p-$COCH_3$		X		X	*i*
p-CN		X		X	3
m-NO_2		X		X	*d*
p-CF_3		X		X	*j*
o-NO_2	X	X	X	X	*e*
p-NO_2	X	X	X	X	*f*
2,4-DiNO_2	X		X	X	*g*

[a] Radzizewski and Wispek, *Ber.*, **15**, 1745 (1882). [b] Errera, *Gazz. chim. ital.*, **17**, 203 (1887). [c] Cannizzaro, "Jahresbericht uber die Fortschritte der Chemie," 1856, p. 581. [d] Errera, *Gazz. chim. ital.*, **18**, 234 (1888). [e] Bischoff, *Ber.*, **21**, 2072 (1888). [f] Romeo, *Gazz. chim. ital.*, **35**, I, 111 (1905). [g] Krassuski, *J. Russ. Phys.-Chem. Soc.*, **27**, 339 (1895). [h] Methyl ether: b. p. 95–96° (2.5 mm.); $n^{20}D$ 1.5217. *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.66; H, 6.75. Found: C, 66.4; H, 6.61. [i] Methyl ether: b. p. 104–106° (3 mm.); $n^{20}D$ 1.5274; lit. b. p. 107–109° (3.5 mm.); $n^{20}D$ 1.5287[3]. [j] Ethyl ether: b. p. 59–61° (5 mm.); $n^{20}D$ 1.4380. *Anal.* Calcd. for $C_{10}H_{11}F_3O$: C, 58.78; H, 5.43. Found: C, 58.5; H, 5.47.

(9) Bennett and Jones, *J. Chem. Soc.*, 1815 (1935).

(10) Conant, Kirner and Hussey, THIS JOURNAL, **47**, 488 (1925).

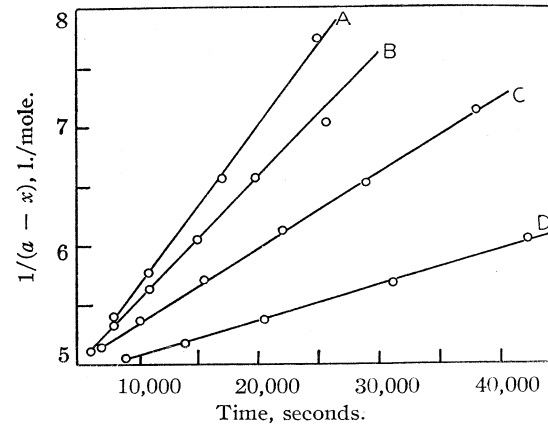


Fig. 1.—Reaction of lithium 2-propanenitronate with benzyl halides at 30 ± 0.3°, $a = a' = 0.200$ *M*: (A) *o*-nitrobenzyl chloride; (B) *p*-nitrobenzyl chloride; (C) *m*-nitrobenzyl chloride; (D) benzyl chloride. Each line represents one run.

step in oxygen-alkylation is the formation of a nitronic ester.[8,7] Since the four halides illustrate both oxygen- and carbon-alkylation, this study leads to the conclusion that the rate-determining step in both oxygen- and carbon-alkylation is the formation of a nitronic ester intermediate.

The reactions of *o*-nitro-, *m*-nitro, *p*-nitro- and 2,4-dinitrobenzyl chlorides with sodium 2-propanenitronate compiled in Table III show that carbon-alkylation occurs with both *o*- and *p*-nitrobenzyl chlorides but not with *m*-nitrobenzyl chloride.

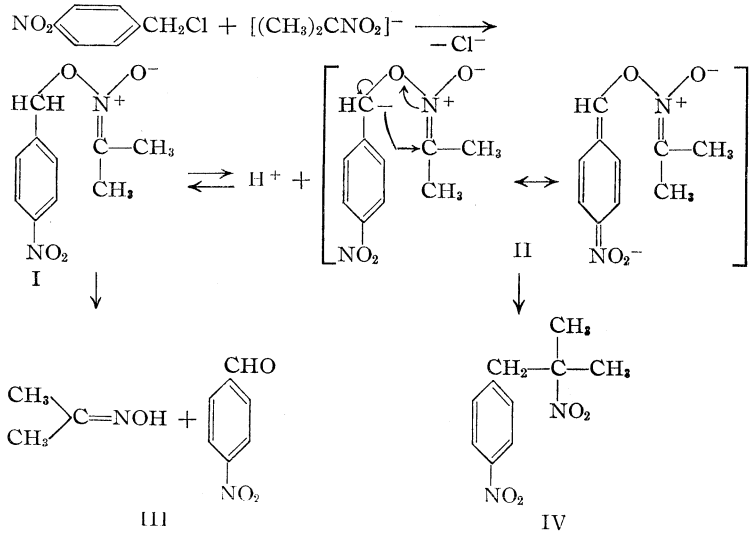
Table II presents a parallelism between those benzyl halides showing carbon-alkylation with sodium 2-propanenitronate and those exhibiting stilbene formation in the Williamson reaction. The mechanism proposed for stilbene formation[10] involves the ready removal of a benzylic hydrogen facilitated by the presence of an ortho- or para-nitro group.

It is therefore proposed that the ease of removal of a benzylic hydrogen is an important factor in the production of carbon-alkylation. The following experiments substantiate this conclusion. The effect of a methyl group on the carbon alpha to the benzene ring would be to reduce the ionization of the benzylic hydrogen and, therefore, to favor oxygen-alkylation. This has been borne out by experiment: 1-(α-bromoethyl)-4-nitrobenzene gave a 60% yield of *p*-nitroacetophenone. The effect of increasing the acidity of the medium would be to hinder the ionization of the benzylic hydrogen and, therefore, to favor oxygen-alkylation. Two parallel runs were made with *p*-nitrobenzyl chloride and sodium 2-propanenitronate except that in one run an additional equivalent amount of 2-nitropropane was added. This increased the acidity of the medium (as

(11) Plisov, *Ukrainsku. Khem. Zhur.*, **4**, Sci. Pt., 241 (1929); Kleucker, *Ber.*, **62**, 2587 (1929); Kharasch, Nudenberg and Fields, THIS JOURNAL, **66**, 1276 (1944).

any acid would) and increased the oxygen-alkylation from 1% (no free nitroparaffin) to 6% (with free nitroparaffin).

The mechanism shown is suggested to explain the foregoing experiments.



The first step in both oxygen- and carbon-alkylation is the formation of the nitronic ester, I. When oxygen-alkylation occurs, *p*-nitrobenzaldehyde and acetoxime, III, are produced by thermal cleavage of the nitronic ester, I, at (a) together with a hydrogen shift. When carbon-alkylation occurs, the resonance-stabilized carbanion, II, is formed by the ionization of a benzylic hydrogen of I. Following the ionization, an internal nucleophilic displacement reaction by II occurs, producing the carbon-alkylation product, IV. An examination of the Fischer–Hirschfelder model of II shows that the spatial requirements for this rearrangement are satisfied since the two carbon atoms forming a new bond are adjacent to each other. Thus, there are two competing reactions of a nitronic ester such as I. The relative amounts of the final products are determined by the relative rates of the competing cleavage and ionization reactions. Since the rate of the ionization reaction is a function of the position of the ionization equilibrium, those factors in the structure of the reactants and in the reaction medium which shift the equilibrium of the ionization reaction will shift the direction of alkylation.

That the foregoing mechanism is not the only one possible in the alkylation of nitroparaffin salts is illustrated by the reaction of 1-(β-bromoethyl)-4-nitrobenzene with sodium 2-propanenitronate to produce 3-methyl-3-nitro-1-(*p*-nitrophenyl)-butane. By the preparation of a possible intermediate, *p*-nitrostyrene, and its conversion to the final product under the original reaction conditions, this reaction seems to proceed in two steps. The first step is dehydrobromination effected by the 2-propanenitronate ion acting as a base. The second step is a Michael addition catalyzed by the basic reaction conditions.

Experimental[12]

1-(α-Bromoethyl)-4-nitrobenzene.—Seven-hundreths mole of 1-ethyl-4-nitrobenzene (n^{20}D 1.5454) was brominated in carbon tetrachloride. A procedure of Cumming, Hopper and Wheeler[13] was followed. A 92% yield of 1-(α-bromoethyl)-4-nitrobenzene was obtained; b. p. 152–153° (5 mm.); n^{20}D 1.6028.

Anal. Calcd. for $C_8H_8BrNO_2$: N, 6.09. Found: N, 6.27.

Reaction of Halides and Sodium 2-Propanenitronate.—These alkylations which were run as described in a previous paper[3] are summarized in Table III.

Preparation of *p*-Nitrostyrene.—1-(β-Bromoethyl)-4-nitrobenzene (m. p. 67–68°) was converted to *p*-nitrostyrene according to the method of Strassburg, Gregg and Walling[14]; m. p. 19–20°; lit. m. p. 21°.[14]

Condensation of *p*-Nitrostyrene and 2-Nitropropane.—*p*-Nitrostyrene (2.0 g., 0.013 mole), 2-nitropropane (1.2 g., 0.013 mole), and 10 drops of methanolic sodium methoxide dissolved in 10 ml. of methanol were refluxed for forty hours; after cooling the crystals were filtered. A 72% yield of 3-methyl-3-nitro-1-(*p*-nitrophenyl)-butane was obtained; m. p. 81–82°.

Proof of Structure of 2-Methyl-2-nitro-1-(*o*-nitrophenyl)-propane. a. Reduction.—2-Methyl-2-nitro-1-(*o*-nitrophenyl)-propane was reduced with Raney nickel and hydrogen as described by Hass, Berry and Bender.[15] An 82% yield of 1-(*o*-aminophenyl)-2-methyl-2-propylamine was obtained; b. p. 107–109° (3.5 mm.); n^{20}D 1.5577.

Anal. Calcd. for $C_{10}H_{16}N_2$: N, 17.05. Found: N, 17.11.

(b) **Selective Deamination.**—1-(*o*-Aminophenyl)-2-methyl-2-propylamine was treated with 50% hypophosphorous acid according to the method of Kornblum and Iffland,[16] to produce 2-methyl-1-phenyl-2-propylamine in 85% yield; b. p. 80° (15 mm.); n^{20}D 1.5122; benzoyl derivative, m. p. 112–113°; lit. b. p. 94° (15 mm.); n^{20}D 1.5132; benzoyl derivative, m. p. 112.5–113°.[16]

Proof of Structure of 3-Methyl-3-nitro-1-(*p*-nitrophenyl)-butane. a. Reduction.—3-Methyl-3-nitro-1-(*p*-nitrophenyl)-butane was reduced with Raney nickel and hydrogen as described by Hass, Berry and Bender.[15] A 79% yield of 1-(*p*-aminophenyl)-3-methyl-3-butylamine was obtained; b. p. 120–122° (1 mm.); m. p. 36–37°.

Anal. Calcd. for $C_{11}H_{18}N_2$: N, 15.72. Found: N, 15.7.

(b) **Selective Deamination.**—4-(*p*-Aminophenyl)-2-methyl-2-butylamine was treated with 50% hypophosphorous acid according to Kronblum and Iffland[16] to produce 2-methyl-4-phenyl-2-butylamine in 72% yield; b. p. 98–100° (10 mm.); n^{20}D 1.5061.

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.8; H, 10.8; N, 8.55.

(c) **Exhaustive Methylation.**—2-Methyl-4-phenyl-2-butylamine was converted to the corresponding methiodide with methyl iodide and potassium hydroxide in 73% yield using the directions of Plattner[17]; m. p. 202° dec.

(12) All melting points are corrected. Microanalyses by Mr. H. Galbraith and Miss L. Roth.

(13) Cumming, Hopper and Wheeler, "Systematic Organic Chemistry," Constable & Co., Ltd., London, England, 1937, p. 351.

(14) Strassburg, Gregg and Walling, THIS JOURNAL, **69**, 2142 (1947).

(15) Hass, Berry and Bender, *ibid.*, **71**, 2290 (1949).

(16) Kornblum and Iffland, *ibid.*, **71**, 2137 (1949).

(17) Plattner, *Helv. Chim. Acta*, **27**, 229 (1944).

TABLE III

REACTION OF HALIDES WITH SODIUM 2-PROPANENITRONATE

Halide	Moles of halide	Moles of sodium 2-propane-nitronate	Time, hours	Temp., °C.	Product	M. p. of product °C.	Yield %
o-Nitrobenzyl chloride[a]	0.19	0.2	18	25	2-Methyl-2-nitro-1-(*o*-nitrophenyl)-propane[j]	54–55	46
					o-Nitrobenzaldehyde[f]	41–42	30
m-Nitrobenzyl chloride[b]	.05	.05	0.25	80	*m*-Nitrobenzaldehyde[g]	55–57	73
p-Nitrobenzyl chloride[c]	.059	.059	1	80	2-Methyl-2-nitro-1-(*p*-nitrophenyl)-propane	64–66	83
					p-Nitrobenzaldehyde[h]	104–106	1
p-Nitrobenzyl chloride[c]	.059	.059[m]	1	80	2-Methyl-2-nitro-1-(*p*-nitrophenyl)-propane	64–66	76
					p-Nitrobenzaldehyde[h]	104–106	6
1-(α-Bromoethyl)-4-nitrobenzene	.03	.03	15	25	*p*-Nitroacetophenone[i]	79–80	60
1-(β-Bromoethyl)-4-nitrobenzene[d]	.05	.05	3	80	3-Methyl-3-nitro-1-(*p*-nitrophenyl)-butane[k]	81–82	54
2,4-Dinitrobenzyl chloride[e]	.05	.05[e]	15	25	1-(2,4-Dinitrophenyl)-2-methyl-2-nitropropane[l]	68–69	33

[a] M. p. 47–49°. [b] M. p. 45–46°. [c] M. p. 70–71°. [d] M. p. 67–68°. [e] M. p. 33–34°. [f] Phenylhydrazone, m. p. 154°. [g] Semicarbazone, m. p. 240°. [h] Semicarbazone, m. p. 220°; the aldehyde was separated by sodium bisulfite extraction. [i] Phenylhydrazone, m. p. 132°. [j] Calcd. for $C_{10}H_2O_4$: C, 53.56; H, 5.40; N, 12.49. Found: C, 53.5; H, 5.44; N, 12.49. [k] Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.6; H, 6.04; N, 11.70. [l] Calcd. for $C_{10}H_{11}N_3O_6$: C, 44.61; H, 4.12; N, 15.61. Found: C, 44.4; H, 4.27; N, 15.8. [m] 0.059 mole of 2-nitropropane added to increase the acidity. This experiment was reproduced three times.

Anal. Calcd. for $C_{14}H_{24}IN$: C, 50.45; H, 7.26; N, 4.20. Found: C, 50.5; H, 7.25; N, 4.28.

The methiodide was converted to 3-methyl-2-phenyl-2-butene according to the procedure of Cope and Overberger[18] in 78% yield; b. p. 85–86° (16 mm.); $n^{20}D$ 1.5060.

(d) **Preparation of Isoamylbenzene.**—3-Methyl-1-phenyl-2-butene in ethanol solution was treated with Raney nickel and hydrogen at 50 p. s. i. and 25° for twenty hours. A 78% yield of isoamylbenzene was obtained; b. p. 83–84° (16 mm.); $n^{20}D$ 1.4862; lit. b. p. 84° (16 mm.); $n^{20}D$ 1.4835.[19] 2,4-Diacetaminoisoamylbenzene was prepared according to method of Ipatieff and Schmerling[19]; m. p. 212–213°. The melting point of a mixture of this sample and an authentic sample showed no depression.

Rate Study. Materials.—Commercial absolute ethanol was used as solvent. 2-Nitropropane ($n^{20}D$ 1.3940) was a re-rectified Commercial Solvents Corp. product. *p*-Nitrobenzyl chloride (m. p. 70–70.5°) was a recrystallized Eastman Kodak Co. product. *m*-Nitrobenzyl chloride (m. p. 45–46°) and *o*-nitrobenzyl chloride (m. p. 47–49°) have been described previously.[3] Benzyl chloride was a Baker C. P. product.

Method.—Fifty ml. of an ethanolic solution containing 0.02 mole of lithium 2-propanenitronate[20] was placed in the reaction vessel and equilibrated in the constant-temperature bath. A fifty-ml. portion of an ethanolic solution containing 0.02 mole of halide was equilibrated in the constant-temperature bath and then pipetted into the reaction vessel. The reaction mixture was shaken and the timer was started.

The rates of reaction were determined by titration of the free chloride ion by the Volhard method. Ten-ml. aliquots were removed from the reaction mixture at intervals and drowned in ice-cold dilute nitric acid in a glass-stoppered bottle. An excess of standard silver nitrate solution and a few ml. of nitrobenzene was added, and the mixture was vigorously shaken. The excess silver nitrate was then titrated against standard potassium thiocyanate solution using ferric alum as indicator. This modification of the Volhard procedure gave reproducible results accurate to within 3% when tested on known synthetic reaction mixtures.[21]

Results.—Figure 1 gives the experimental results of these rate studies. Since the initial concentrations of the reacting substances in these second-order reactions were the same, the rate expression may be written as $k_2t = [1/(a - x)] - (1/a)$ so that the plot of $1/(a - x)$ against t should be linear, the slope being equal to k_2. Table I gives the values of the second-order rate constant calculated in this manner.

Acknowledgment.—Several stimulating discussions with Drs. Herbert C. Brown and Nathan Kornblum on various phases of this theory are gratefully acknowledged.

Summary

A kinetic study of the reactions of four benzyl halides with lithium 2-propanenitronate indicates that the rate-determining step in both oxygen- and carbon-alkylation is the formation of a nitronic ester intermediate. A comparison of the alkylation and Williamson reactions of benzyl halides indicates that the ease of removal of a benzylic hydrogen by a base is an important factor in determining the direction of the alkylation reaction. A mechanism is suggested to explain these results.

LAFAYETTE, INDIANA RECEIVED JUNE 8, 1949

(18) Cope and Overberger, THIS JOURNAL, **70**, 1433 (1948).

(19) Ipatieff and Schmerling, *ibid.*, **60**, 1476 (1938).

(20) The lithium salt was used since a homogeneous reaction mixture was needed.

(21) This method is essentially that of Beste and Hammett, THIS JOURNAL, **62**, 2482 (1940).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

A Static Low Temperature Method for Determining Small Residual Fields Accurately in Magnetic Experiments

BY W. F. GIAUQUE AND J. W. STOUT

The technique of adiabatic demagnetization experimentation in this Laboratory has been developed around the iron-free solenoid type of magnet. In this way the complications due to considerable residual fields and hysteresis which interfere with precise measurements, when iron yoke magnets are used, have been largely avoided. However even the earth's field is large enough to interfere with some measurements and the iron in a typical reinforced concrete building will increase the field which remains when the current through a solenoid is reduced to zero.

For example, when a substance has been demagnetized adiabatically to a low temperature, it is desirable to apply some test to determine if any net directed magnetic moment remains. A very simple method of measuring any residual magnetic moment was used by Giauque and MacDougall.[1] They measured the e. m. f. induced in a coil surrounding the sample, while the substance was slowly warmed to temperatures above 1°K., in which region the magnetic properties were comparatively ideal. In such an experiment, the considerable change of magnetic susceptibility with temperature, will, in the presence of a residual field, produce an e. m. f. due to the changing magnetic moment induced by the residual field. The above authors found such an effect with gadolinium phosphomolybdate tridecahydrate and were able to explain it quantitatively by means of residual field measurements made with a flip-coil at a later date. Residual field measurements should be available at the same time as any other measurements which have a field dependence at small fields. It is undesirable to complicate an already complicated measuring system by operating a flip-coil or other rotating device in the proximity of the sample, and we prefer not to use methods which are based on the properties of ferromagnetic materials of high and variable permeability since the presence of such material should be avoided if possible. We have used a simple static method which avoids the above effects.

A convenient and well known method of measuring magnetic field strength at ordinary temperatures is based on the change of electrical resistance of bismuth with field. The ordinary instruments based on this effect are nowhere near sensitive enough for our present purpose. However, measurements of Beckman[2] have shown that the increase of resistance of bismuth with field is greatly enhanced at low temperatures. The bismuth coils used at ordinary temperatures are calibrated and are expected to retain their calibration for considerable periods. It is very improbable that such a coil would retain a low temperature calibration with sufficient accuracy after warming to ordinary temperatures, followed by recooling to the temperature of liquid helium. The following methods avoid the necessity of precalibration.

Some bismuth wire was made by heating the metal and extruding it through a die with a diameter of 0.024 in., under a pressure of 7000 atmospheres. A coil of twelve turns, with a diameter of 2 in. and a length of 1.5 in., was wound non-inductively. It was mounted in a dewar vessel near the center of, and co-axial with, a vertical solenoid magnet.[3] We have supported such coils in grooves cut in micarta, or etched in Pyrex tubing and both leave something to be desired in preventing breakage of the brittle bismuth wire. Potential and current leads were attached to each end of the wire. All measurements were made with the coil immersed in liquid helium at its boiling point 4.22°K.

A steady current of about 2.58×10^{-4} ampere was passed through the coil and the resistance was found to be 21.8645 ohms A small current was then passed through the solenoid magnet and the change in resistance was observed. The current through the magnet was then reversed and the quite different change in resistance of the bismuth was recorded. The procedure was repeated with several other small values of solenoid current. The relationship between field and the current through the solenoid is easily computed from its dimensions.

Since the change of resistance of the bismuth should depend on the magnitude and not the sign of the net magnetic field, a plot of ΔR against applied field should be symmetrical about a line parallel to the ΔR axis, and displaced from it by the amount of the component of the residual field along the axis of the solenoid. Such a plot is shown in Fig. 1. The method is independent of the character of the dependence of ΔR on the applied field.

It is, however, a matter of some interest to inquire concerning the relationship between the change in resistance and the absolute value of the vertical component of the magnetic field. The data are given in Table I. Values of the quantities A and B in Fig. 1 were selected to give a smooth function of $(R_H - R_{H=0})/H^2$ against H.

It is evident that ΔR is proportional to H^2 at fields of the order of 0–20 oersteds and that the rate of change then decreases rapidly and appears to approach a condition in which it depends very little on the applied field.

(1) Giauque and MacDougall, THIS JOURNAL, **60**, 376 (1938).
(2) Beckman, Comm. Phys. Lab. Leiden, No. 130a (1912).
(3) Giauque and MacDougall, THIS JOURNAL, **57**, 1175 (1935).

TABLE I

CHANGE OF RESISTANCE OF BISMUTH WITH MAGNETIC FIELD AT 4.22°K.

$H = H$(applied) $+ A$ oersteds; $A = 2.03$; $R_{H=0} = R(H \text{ applied} = 0) - B$ ohms; $B = 2.40 \times 10^{-3}$; $\Delta R = R_H - R_{H=0}$

H	$\Delta R \times 10^3$	$\Delta R \times 10^3/H^2$
+ (2.03)	(2.40)	0.582
− 2.87	4.76	.578
+ 6.93	27.53	.573
+11.83	79.74	.570
− 7.77	35.32	.585
−14.30	118.12	.578
+18.36	191.94	.569
	ΔR ohms	
+50.7	1.204	0.468
−46.5	1.022	.473
+50.8	1.181	.458
+93	1.630	.188
203	5.356	.130
391	12.72	.0832
671	25.45	.0565
1210	47.76	.0326
1618	61.33	.0234
3218	90.57	.0088
6206	112.1	.0029
8409[a]	120.5	.0017

[a] Reading at limit of ammeter and thus probably a little low.

The principal source of error in the data in Table I is due to the fact that the applied field was determined by reading an ammeter. ΔR was determined by means of an accurate potentiometer. More accurate results could have been obtained had the magnet current also been determined by a potentiometric method. However the results are such that a residual field of 2.03 oersteds gives considerably better internal consistency of all the data than 2.05 oersteds. Thus we conclude that the vertical component of the residual field was 2.03 ± 0.02 oersteds. This may be compared with the result of Giauque and MacDougall,[1] 2.0 ± 0.1 oersteds, determined with a flip-coil under approximately the same conditions.

During the period of the above experiments all large currents through the magnet produced a field which was in the same direction as the vertical component of the earth's field. In order to find out if the residual field was somewhat greater immediately after the full field of about 8000 oersteds was turned off, an experiment was tried to test this point. It was found that there was no observable change in the resistance of the bismuth coil after a field of about 8400 oersteds had been applied for three-fourths of a minute. In order to improve the sensitivity of the above test an applied field of 16.28 oersteds was used in the direction of the residual field both immediately before and after the large field was applied. This measurement showed that any change in the residual field was less than 0.01 oersted. The magnet was not used for an hour prior to this test.

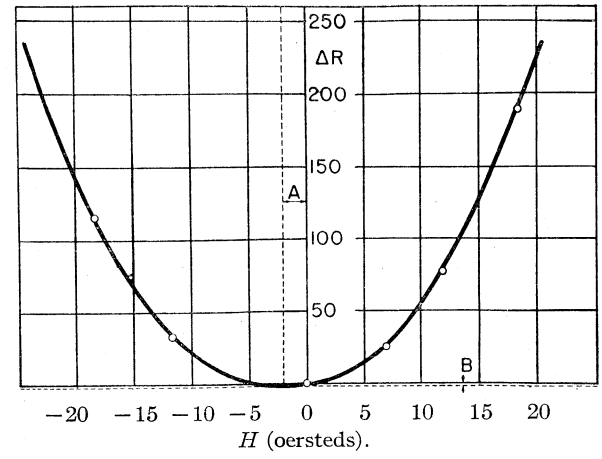


Fig. 1.—Measurement of a small residual magnetic field with a bismuth coil: ΔR = ohms $\times 10^{-3}$; A, residual field along solenoid axis; B, resistance due to the residual field.

Although the above accuracy was sufficient for the investigation of which it was a part, the sensitivity and simplicity of the method could be greatly increased and the result made available in a very short time by the following procedure: Send an accurately measured current through the solenoid and read the potential drop due to the current used in the bismuth coil. Reverse the solenoid current and adjust its value until the potential drop across the bismuth coil returns to the original value, thus restoring its resistance to the initial value. The component of the residual field will be equal to the field produced in the solenoid by one-half the difference in the direct and reverse solenoid currents. We have estimated that with an applied solenoid field of about 20 oersteds, and a current of some 5×10^{-3} ampere through the bismuth coil mentioned above, a potentiometer scale reading of about 1 cm. would be equivalent to 0.001 oersted in the residual field.

For some purposes it will be desirable to know the other components of the residual field. These could be determined with the assistance of auxiliary coils, which, while of necessity must be located at some distance in adiabatic demagnetization experiments, could produce a calculated field, in the desired direction at the location of the bismuth coil.

Summary

A method utilizing the electrical resistance of a bismuth coil at liquid helium temperature to measure accurately a small residual magnetic field has been described.

This static method has been devised to avoid the use of ferromagnetic materials, flip-coils and other rotating or oscillating devices, which are considered to provide undesirable complications during adiabatic demagnetization experiments at temperatures below 1°K.

BERKELEY, CALIFORNIA RECEIVED MAY 17, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC COMPANY]

The Mass Spectrum of Monoisotopic $B_2^{10}H_6$

BY FRANCIS J. NORTON

The dissociation of complex molecules by electron impact presents many features of theoretical and practical interest. This is particularly so in the cases where isotopes occur in the molecular structure. The availability of stable separated isotopes from the Atomic Energy Commission renders possible the construction of molecules with altered isotope ratios. This paper is to report the investigation of one of these, $B_2^{10}H_6$, by the mass spectrometer, and the determination of its molecular fragmentation pattern under electron impact. Normal B_2H_6 with its pattern was also studied.

Normal boron consists of two stable isotopes, about 20% B^{10} and 80% B^{11}. From the Isotopes Division, U. S. Atomic Energy Commission, was obtained the complex $BF_3 \cdot CaF_2$. In this the boron is 96% of the B^{10} isotope and 4% of B^{11}. Through the kindness of Dr. Edith Boldebuck and Dr. J. R. Elliott of our laboratory, $B_2^{10}H_6$ was synthesized from this enriched isotopic material and was used in these experiments.

The mass spectrum of normal polyisotopic diborane has been studied by J. A. Hipple[1] and by Vernon H. Dibeler and Fred L. Mohler.[2] From its mass spectrum they made calculations for the ion distribution of the monoisotopic material. The present work renders possible a comparison between such a calculation and an experimental determination on essentially monoisotopic diborane. Further interest lies in the fact that the mass spectrometers used in references,[1,2] and in the present work were made by three different manufacturers.

Experimental

(a) The synthesis of $B_2^{10}H_6$ was from the complex $B^{10}F_3 \cdot CaF_2$ (the boron consisting of 96% B^{10}). This was heated to 350° in a stream of purified nitrogen. The $B^{10}F_3$ evolved was collected in cooled ether and reacted with lithium hydride. The diborane was separated from the ether and subjected to several low temperature vacuum distillations. It was kept stored at −20°. From mass spectrometer analyses higher boron hydrides and normal B_2H_6, if present at all, were under 0.05%. Diethyl ether was under 0.1%, and a small amount, under 0.1%, of SiH_4, was also found. Normal B_2H_6 was furnished by Dr. L. V. McCarty of our laboratory and was of very high purity.

(b) The mass spectrometer used was the 60° type, single focussing with 6-inch radius of curvature. It is manufactured by the General Electric Company. The accelerating voltage was 2000, ionizing voltage 70. The filament current was 4.5 amperes, total emission current 1.0 ma., trap current (electrons collected at end of ionizing chamber) 0.28 ma. Positive ion currents at the collector were measured by a 954 preamplifier tube in a direct current feedback amplifier circuit. The initial voltage drop to ground was through an IRC resistor of 2×10^9 ohms. The amplifier output was recorded on a General Electric photoelectric recorder with appropriate resistances for selecting sensitivity ranges. The range of masses was covered by sweeping the magnetic field. This could be done either automatically or manually. For precise measurement, the desired peak was selected and held at maximum value on the recorder by manual control. It was focussed to maximum value by manipulating the focussing, drawing out and beam centering voltages.

It should be pointed out that with this type of instrument, to obtain the maximum peak height as is done with these manual measurements reported, refocussing is needed particularly at the lower end of the mass scale, for each mass peak. This means that the scan does not represent the maximum height of peak attainable. The peak heights for a given focus do remain reproducible, and the scans in the lower mass regions especially, should be regarded as recognition patterns. On automatic sweep, changes in focus were made for peaks in the 1, 2, 10–13 and 20–28 mass regions, to give them maximum values possible with fewest focus changes.

The height could be read to ±1% for deflections of the recorder pen from one-half to full scale. For measurements, readings were made in the region of 80 to 100% full scale deflection. This could be chosen by using appropriate, known values of resistance in the measuring circuit.

The gas to be measured was fed into the spectrometer through an orifice type leak. This was so small that 40 mm. gas pressure on the high side gave 2×10^{-7} mm. on the ion gage at the spectrometer tube outlet. The gas used during analysis was minute in amount. With that leak, the change in pressure in a 1 liter reservoir was under 2% per twenty-four hours.

Measurements were made keeping the B_2H_6 on the leak at 25°. I had found in previous work that with very pure, normal diborane handled with good vacuum practice so that the amount of water present is exceedingly small, the following rates of decomposition were observed at an initial pressure of 33 mm. This extrapolated to 25° on a log

°C.	Rate of pressure increase dp/dt (mm./min.)
120	0.045
110	.020
100	.005

rate *vs.* $1/T$ plot gives about 10^{-6} mm./min., or under 0.005% per twenty-four hours.

Before introduction, the hydride was held in a trap at −190° and any traces of gaseous hydrogen pumped away; it was then taken over to the leak reservoir with the trap at −78°. After the mass spectrum was run, the remaining B_2H_6 was taken back into the trap, put at −190° and any hydrogen measured. It was under 0.1%. Hence, it is believed the hydrogen ion peaks found are from B_2H_6 dissociation in the mass spectrometer only.

Results

The isotopic constitution of the gas molecules entering the spectrometer can be calculated very simply from statistical considerations alone. The general expression from simple probability for the abundance distribution of isotopic species of molecules is given by $(a + b)^n(c + d)^m$ where a and b are the relative abundances of the isotopes of one atom, in this case boron isotopes 10 and 11, and c and d are the relative abundances of the stable

(1) J. A. Hipple, Jr., *Phys. Rev.*, **57**, 350 (1940).

(2) V. H. Dibeler and F. L. Mohler, THIS JOURNAL, **70**, 987 (1948).

TABLE I

ISOTOPIC CONSTITUTION OF THE MOLECULAR GASES USED

Molecular type	Normal B_2H_6 (20% B^{10}) (80% B^{11}) Proportion calculation	Per cent.	"Monoisotopic" B_2H_6 (96% B^{10}) (4% B^{11}) Proportion calculation	Per cent.
$B^{11}B^{11}H_6$	$0.8 \times 0.8 = 0.64$	64.0	$0.04 \times 0.04 = 0.0016$	0.16
$B^{11}B^{10}H_6$	$2(0.2 \times 0.8) = 0.32$	32.0	$2(0.04 \times 0.96) = 0.0768$	7.68
$B^{10}B^{10}H_6$	$0.2 \times 0.2 = 0.04$	4.0	$0.96 \times 0.96 = 0.9216$	92.16

hydrogen isotopes 1 and 2. The exponents n and m represent the number of atoms in the molecule. Taking the relative isotopic abundances as: $B^{10} = 0.2$, $B^{11} = 0.8$, $H^1 = 0.998$, H^2 (deuterium) $= 0.02$, the expression becomes for B_2H_6: $(0.2 + 0.8)^2(0.9998 + 0.02)^6$. For normal deuterium abundances, the second term may be taken as unity. If for the normal B_2H_6 a ratio of $B^{11}/B^{10} = 4.0$ is assumed, the following Table I gives the constitution for the two types of B_2H_6.

In the mass spectrometer these molecules are broken up by the impact of 70 volt electrons, and form positive ion fragments of various masses. The relative abundance of each of these is given by the positive ion current at each mass. This current is recorded as peak height, and the mass spectrum is a record of the peak heights or abundance plotted against mass. No way is known to calculate the theoretical abundance of the ion fragments from complicated molecules.

Figure 1 gives a record of the spectra of the two kinds of B_2H_6 used. Masses are recorded at the bottom, increasing from right to left, and the peak height is the magnitude of the positive ion current.

The measured values of the mass spectra are given in the following Table II. In each case, the dominant peak is taken = 100.

TABLE II

MEASURED MASS SPECTRA OF

Mass m/e	Monoisotopic $B_2^{10}H_6$ Observed in 96% B^{10} material	Monoisotopic $B_2^{10}H_6$ Corrected to 100% B^{10}	Normal B_2H_6 20% B^{10} 80% B^{11} average
28	...	...	(2.4)
27	0.5	(0.1)	100.0
26	9.4	1.5	96.2
25	100.0	100.0	52.5
24	46.9	46.5	78.7
23	28.6	24.5	38.3
22	61.0	63.0	8.5
21	5.1	5.1	1.3
20	1.9	1.9	0.1
14	...	...	0.5
13	0.9	0.5	12.6
12	9.7	9.9	8.0
11	4.6	4.7	16.0
10	11.5	12.0	3.65
2	45.7	45.7	71.6
1	1.6	1.6	2.4

A comparison of reproducibility may be of interest. The following spectra of normal B_2H_6 were taken; a, b, c on one day after the gas had run 1, 3 and 5 hours. Spectrum d was taken on another day and with another charge of gas.

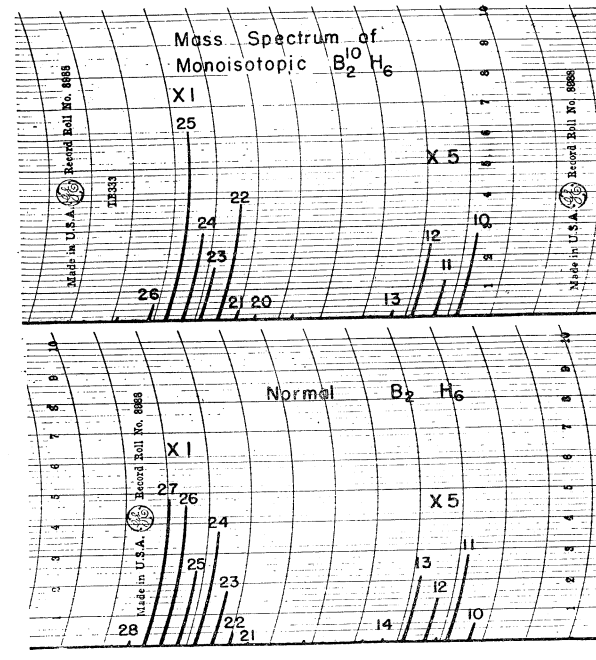


Fig. 1.—The mass spectra of monoisotopic $B_2^{10}H_6$ and of normal B_2H_6.

TABLE III

MEASURED MASS SPECTRA OF NORMAL B_2H_6

Mass	a	b	c	d	Av.
28	2.0	2.0	2.0	3.7	(2.4)
27	100	100	100	100	100
26	95.8	96.5	96.3	96.0	96.2
25	52.3	52.7	53.0	51.9	52.5
24	78.6	79.6	79.5	77.1	78.7
23	37.9	38.7	38.8	37.6	38.3
22	8.6	8.5	8.7	8.2	8.5
21	1.3	1.4	1.3	1.2	1.3
20	0.1	0.1	0.1	0.1	0.1
14	...	...	...	0.5	0.5
13	12.5	12.9	13.5	11.6	12.6
12	7.9	8.1	8.4	7.6	8.0
11	15.8	16.2	16.3	15.7	16.0
10	3.6	3.7	3.7	3.6	3.65

The measured spectrum for $B_2^{10}H_6$ needs correction for the presence of 4% B^{11} with the 96% B^{10} in the starting material. How this is done is illustrated by Table IV. Ions having the same constitution as regards the numbers of hydrogen attached to boron are connected by the slanting ar-

rows. These ions have similar, presumably identical, probabilities of formation by electron impact.

TABLE IV

CONSTITUTION OF MASS SPECTRUM OF B_2H_6

Mass	Constituent positive ions		
28	$B^{11}B^{11}H_6$		
27	$B^{11}B^{11}H_5$	$B^{10}B^{11}H_6$	
26	$B^{11}B^{11}H_4$	$B^{10}B^{11}H_5$	$B^{10}B^{10}H_6$
25	$B^{11}B^{11}H_3$	$B^{10}B^{11}H_4$	$B^{10}B^{10}H_5$
24	$B^{11}B^{11}H_2$	$B^{10}B^{11}H_3$	$B^{10}B^{10}H_4$
23	$B^{11}B^{11}H$	$B^{10}B^{11}H_2$	$B^{10}B^{10}H_3$
22	$B^{11}B^{11}$	$B^{10}B^{11}H$	$B^{10}B^{10}H_2$
21	.....	$B^{10}B^{11}$	$B^{10}B^{10}H$
20	.....	.....	$B^{10}B^{10}$
14	$B^{11}H_3$		
13	$B^{11}H_2$	$B^{10}H_3$	
12	$B^{11}H$	$B^{10}H_2$	
11	B^{11}	$B^{10}H$	
10	.....	B^{10}	
2	H_2		
1	H_1		

Hence, as we proceed downward along any slanting arrow, say from $B_2^{11}H_5$ mass 27, to $B^{10}B^{11}H_5$ mass 26, to $B_2^{10}H_5$ mass 25, the theoretical distribution of these three similar ions can be calculated directly, if the isotopic abundances of B^{10} and B^{11} are known, in the manner shown in Table I. The probability of $B^{11}B^{11}$ ion formation in the nearly monoisotopic material is only $0.04 \times 0.04 = 0.0016$. This is too low to be of any importance here, and the whole column of ions from $B_2^{11}H_x$ (x from 0 to 6) will be taken as zero for this case.

The ion at mass 20 of peak height 1.9 can be due only to B_2^{10}. From its 0.9216 probability, projected back up the arrow we arrive at the similar ion $B^{10}B^{11}$ of 0.0768 probability at mass 21. Its height can then be calculated as $(0.0768/0.9216) \times 1.9 = 0.16$. Then the measured mass 21 peak height minus this 0.16 gives 4.94 as the corrected peak height due to the ion $B_2^{10}H$ only. Proceeding up the table of constitution, Table IV, in this way, we arrive at the corrected values for 100% monoisotopic material, Table II, and put it on the new basis of Peak 25 = 100 = $B_2^{10}H_5$ ion, the most abundant ion.

In a similar manner, the normal B_2H_6 spectrum can be calculated to the monoisotopic spectrum, as did Hipple[1] and Dibeler and Mohler.[2] In agreement with the latter, I found that the best agreement with the observed spectrum, and with the monoisotopic spectrum here reported, was obtained by taking the normal distribution of boron isotopes as $B^{11}/B^{10} = 4.0$.

This is not in agreement with the ratio of 4.311 determined by Inghram[3] using BF_3 and $B(OCH_3)_3$; also Thode,[4] *et al.*, using BF_3 found the B^{11}/B^{10} ratio varied from 4.27 to 4.42 depending on the source of the boron. It is conceivable that either the preparation and repeated vacuum distillation of the B_2H_6 resulted in some enrichment of the light B^{10}, or that the probabilities of ion formation involving B^{10} and B^{11} are not identical as I assumed.

However, a calculation of sensitivities (that is, peak height as a function of the abundance of each type of molecule in terms of its partial pressure on the leak), checks the assumption that the ionization probability is very nearly identical for ions of similar type as $B^{11}B^{11}H_5$, $B^{10}B^{11}H_5$ and $B^{10}B^{10}H_5$, in both the normal and in the monoisotopic material. This is also true for each other ion type, irrespective of its isotopic constitution.

There is one other possibility which could account for the low value of the B^{11}/B^{10} ratio which had to be assumed, compared to the more precise values of Inghram[3] and Thode, *et al.*[4] It may be that the dissociation probability of $B_2^{10}H_6$ is greater than that of the heavier molecules. This would give more B^{10} in the dissociation products than in the original gas, and might explain the low ratio assumed.

In calculating the monoisotopic spectrum from the observed normal spectrum, it seemed best to derive the value for $B_2^{11}H_6$ ion at mass 28, from the $B_2^{10}H_6$ value, in view of the possible contaminations which can accumulate at mass 28. Hence, the value of 1.5 was used for the normal B_2H_6 mass 28 peak height relative to mass 27 = 100.

Using the ratio $B^{11}/B^{10} = 4.0$ for the normal B_2H_6 which I used, a monoisotopic spectrum can be calculated. In Table V are given: (a) the observed monoisotopic spectrum from $B_2^{10}H_6$, corrected for the 4% B^{11} present; (b) the monoisotopic spectrum calculated from my measured normal B_2H_6 spectrum; (c) the monoisotopic spectrum calculated by Hipple[1] from his measured normal spectrum and (d) the monoisotopic spectrum calculated by Dibeler and Mohler[2] from their measured normal spectrum.

TABLE V

MONOISOTOPIC MASS SPECTRUM OF B_2H_6

Ion	(a) Observed spectrum this paper	(b) Calculated this paper	(c) Calculated Hipple[1]	(d) Calculated Dibeler and Mohler[2]
B_2H_6	1.5	1.5	0	0.64
B_2H_5	100.0	100.0	100.0	100.00
B_2H_4	46.5	47.0	44.8	52.6
B_2H_3	24.5	23.2	21.7	26.2
B_2H_2	63.0	64.8	63.7	76.8
B_2H	5.1	4.7	2.9	7.00
B_2	1.9	2.2	2.2	3.43
BH_3	0.5	0.5	...	0.62
BH_2	9.9	9.0	...	19.5
BH	4.7	5.8	0	10.6
B	12.0	14.6	40	21.0
H_2	45.7	(45.7)	...	2.71
H_1	1.6	(1.6)	...	3.98

(3) M. G. Inghram, *Phys. Rev.*, **70**, 653 (1946).

(4) H. G. Thode, J. Macnamara, F. P. Lossing and C. B. Collins, THIS JOURNAL, **70**, 3008 (1948).

The concordance, with the exception of H_2 ion, is rather good, considering the determinations were made on three different mass spectrometers, manufactured by different companies. The wide differences in hydrogen mass 2 peak heights are undoubtedly due mainly to thermal decomposition in the source region, where there existed different structures, temperatures and differential pumping rates out of the source region, in the case of the three different types of mass spectrometer.

The use of the monoisotopic material enables the origin of the small peak at mass 11.5 to be identified unambiguously. This peak was noted by both Hipple[1] and Dibeler and Mohler.[2] The constitution of peak 23 is presented in the following Table VI. The figures are relative to the dominant peak = 100 in each spectrum.

It will be seen that peak 11.5 is proportional to the $B^{11}B^{10}H_2$ ion only. Hence, doubly ionized $B^{11}B^{10}H_2$ ion of mass 23 is responsible for this peak. The appearance potential of peak 11.5 was measured as approximately 23 volts (argon calibration), whereas the appearance potential for the singly ionized peaks was about 15 volts. Very small peaks of double ionization also were found at masses 12.5 and 13.5.

TABLE VI

CONSTITUTION OF PEAK 23

Ion	Normal B_2H_6	96% $B_2^{10}H_6$
$B_2{}^{11}H$	4.8	0
$B^{11}B^{10}H_5$	31.4	4.7
$B_2^{10}H_3$	1.4	23.9
Peak 23 height	37.6	28.6
Peak 11.5 height	0.66	0.075
Ratio 11.5 peak to $B^{11}B^{10}H_2$ ion contribution	0.021	0.017

Summary

The mass spectrum of the monoisotopic molecule $B_2^{10}H_6$ was determined. This was compared with the calculated monoisotopic spectrum from measurements on B_2H_6 of normal isotopic boron ratio.

SCHENECTADY, N. Y. RECEIVED APRIL 4, 1949

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 1250]

The Kinetics of the Acid-Catalyzed Hydrolysis of Amine Disulfonate Ion; The Third Ionization Constant of Amine Disulfonic Acid[1]

BY GEORGE J. DOYLE[2] AND NORMAN DAVIDSON

Amine disulfonate ion (imidodisulfonate ion) is known to hydrolyze irreversibly and quantitatively in dilute acid at a measurable rate according to the equation[3,4,5]

$$HN(SO_3)_2^{=} + H_2O \xrightarrow{H^+} HSO_4^- + H_2NSO_3^- \quad (1)$$

Wagner[6] in the course of his study of the kinetics of the hydrolytic decomposition of the sulfur–nitrogen acids did one experiment on the hydrolysis of amine disulfonate in dilute hydrochloric acid solution. On the basis of this meager evidence he concluded that the rate of hydrolysis is proportional to the product of the concentrations of hydrogen ion and amine disulfonate ion, and is therefore autocatalytic. Sisler and Audrieth[4] have presented valuable data on the hydrolysis of amine disulfonate and on the two-step hydrolysis of amine trisulfonate ion (nitrilo-sulfonate ion) to amine disulfonate and thence to amine monosulfonate ion (sulfamate ion) at several temperatures. This data is not, however, extensive enough for a kinetic analysis. Because of the lack of quantitative data, we have investigated more thoroughly the kinetics of reaction (1).

Materials.—The distilled water, standard base (0.02 *N* sodium hydroxide) and standard acid (0.02 *N* hydrochloric acid) were prepared and stored so as to be free of carbonate or carbon dioxide. A solution of sodium chloride used to adjust ionic strength was prepared from the C. P. salt which was dried four hours at 200°.[7] A solution of sodium sulfate used as a source of sulfate ion was prepared from the C. P. anhydrous salt which was ignited one and one-half hours at 700–800°.[8]

Potassium amine disulfonate was prepared by hydrolysis of potassium amine trisulfonate

$$N(SO_3)_3^{=} + H_2O \xrightarrow{H^+} HN(SO_3)_2^{=} + HSO_4^- \quad (2)$$

This in turn was prepared by reaction of a large excess of potassium bisulfite with potassium nitrite in hot aqueous solution (Sisler and Audrieth's modification[4,9] of Claus and Koch's[10] method)

$$NO_2^- + 3HSO_3^- \longrightarrow N(SO_3)_3^{=} + H_2O + OH^- \quad (3)$$

A preparation on a scale of about ten times greater than that used by Sisler and Audrieth gave a yield of potassium amine disulfonate, washed free of sulfate, of 64% based on potassium nitrite; Sisler and Audrieth report 51%. The

(1) A more detailed account of this research is contained in the thesis by George J. Doyle, submitted in partial fulfillment of the requirements for the degree of Master of Science at the California Institute of Technology.

(2) Present address: Department of Chemistry, University of Indiana, Bloomington, Indiana.

(3) Raschig, *Ann.*, **241**, 161 (1887).

(4) Sisler and Audrieth, THIS JOURNAL, **60**, 1947 (1938).

(5) Audrieth, Sveda, Sisler and Butler, *Chem. Rev.*, **26**, 49 (1940).

(6) Wagner, *Z. physik. Chem.*, **19**, 678 (1896).

(7) Sorensen, *Z. anal. Chem.*, **44**, 149 (1905).

(8) Remy and Siegmund, *ibid.*, **93**, 321 (1933).

(9) "Inorganic Syntheses," McGraw-Hill Book Co., New York N. Y., 1946, Vol. II, p. 182.

(10) Claus and Koch, *Ann.*, **152**, 336 (1869).

improvement in the yield is presumably due to the larger scale of operations. A slight modification of the procedure of these authors that was introduced was to wash the trisulfonate prior to hydrolysis with chilled, dilute ammonia (1:100) instead of water.

The salt was analyzed for sulfur, nitrogen and material not volatile on ignition with sulfuric acid (taken as potassium sulfate[8]). The analysis for nitrogen was done by a semi-micro Kjeldahl procedure according to E. C. Wagner,[11] using an apparatus of the type devised by Redemann.[12] Sulfur was determined as barium sulfate after hydrolysis and oxidation of the disulfonate with nitric acid containing a little hydrochloric acid as a catalyst.[13] To avoid coprecipitation of nitrate by barium sulfate, excess nitric acid was removed by repeated evaporation with hydrochloric acid. The results of the analysis, shown in Table I, indicate a purity of 97.6–98.5%.

TABLE I

ANALYSIS OF POTASSIUM AMINE DISULFONATE

K		N		S	
Found	Calcd.	Found	Calcd.	Found	Calcd.
30.43	30.87	5.55	5.53	24.74	25.31
30.38		5.50		24.75	
		5.44			

Another method of analysis was used to check the extent of deterioration, if any, with time. A weighed sample of the salt was dissolved in dilute base in order to neutralize any possible acid impurity and thus prevent premature hydrolysis. The solution was then adjusted to the equivalence point by adding acid. A known excess of acid was added and the disulfonate hydrolyzed completely by heating to 85–95° for an hour, and then titrated with standard base. The hydrolysis of sulfamic acid if it occurs to any extent during the heating will not affect the titer of the solutions. This analytical method indicated a purity of greater than 99% and showed no decomposition of the disulfonate, stored in a vacuum desiccator over anhydrous calcium sulfate, in a period of five months.

The Third Ionization Constant of Amine Disulfonic Acid.—A determination of the equilibrium constant for the reaction

$$HN(SO_3)_2^{=} \rightleftarrows H^+ + N(SO_3)_2^{\equiv} \qquad (4)$$

is in itself desirable and was necessary in order to select a suitable indicator for the acid titrations in the rate measurements. That the equilibrium constant for the reaction is not negligibly small is suggested by the fact that salts like $K_3N(SO_3)_2$ have been prepared.[5]

The value of the ionization function (classical ionization constant)

$$k_a = [H^+][N(SO_3)_2^{\equiv}]/[HN(SO_3)_2^{=}] \qquad (a)$$

with concentrations expressed in volume molal units, was determined at an ionic strength of 1.00 and 25° by measuring with an electronic (Beckman) *p*H meter and a glass electrode the *p*H's of dilute buffer solutions made by partially neutralizing the imide hydrogen of the disulfonate ion with sodium hydroxide and adjusting the ionic strength to 1.00 with sodium chloride. The *p*H's of dilute hydrochloric acid solutions adjusted to an ionic strength of 1.00 were also measured. In the latter solutions, the hydrogen ion concentration was taken equal to the stoichiometric concentration of hydrochloric acid, and the activity coefficient of hydrogen ion was taken to be the same as in the buffer solutions. The concentrations of hydrogen ion in the buffer solutions are then readily calculated and from this the value of the function (a).

In order to obtain some check on the method, the value of the ionization function $[H^+][HPO_4^{=}]/[H_2PO_4^-]$ was determined by the same method at ionic strengths of 1.00 and 0.15. The results of these measurements are contained in Table II. An average value of the ionization function for the disulfonate ion is about 3.2×10^{-9} at $\mu = 1$.

TABLE II

IONIZATION FUNCTIONS AT 25°

F		M				Ionization function $\times 10^{+9}$, moles/liter
Anion	NaOH	HCl	NaCl	*p*H	H^+, *M*	
Amine Disulfonate Ion: Ionic Strength,[14] 1.00						
0	0	0.01123	0.989	1.82	0.01123	
0	0	0.001123	.999	2.83	0.001123	
0.0200	0.00999		.910	8.39	3.02×10^{-9}	3.0
.0200	$.004995$		.925	7.91	$9.11 \times$	3.0
.0200	.01498		.892	8.82	$1.12 \times$	3.4
.0100	$.004995$		.955	8.34	$3.38 \times$	3.4
.0100	$.001998$		.964	7.78	$12.3 \times$	3.1
.0100	.00699		.949	8.68	$1.55 \times$	3.6
Dihydrogen Phosphate Ion: Ionic Strength,[14] 1.00						
0.0200	0.00999		0.960	6.20	4.67×10^{-7}	467
.0100	$.004995$		.980	6.20	$4.67 \times$	467
Dihydrogen Phosphate Ion: Ionic Strength,[14] 0.150						
0	0	0.001123	0.149	2.98	0.001123	
.0200	0.00999		.110	6.71	2.09×10^{-7}	210
.0100	$.004995$		.130	6.68	$2.24 \times$	220

In order to compare the observed values of the ionization function for the $H_2PO_4^-$ ion with the thermodynamic ionization constant we have used the approximate equation

$$\log f_i = -\frac{Az_i^2\mu^{1/2}}{1+\mu^{1/2}} + \beta_i\mu \qquad (b)$$

In this relation: f_i = activity coefficient of ith ion; A = Debye–Hückel coefficient; z_i = electronic charge of ith ion; μ = "ionic strength" = $\frac{1}{2}\Sigma c_i z_i^2$ where c_i's are in volume molal units[14]; β_i = a constant characteristic of the ith ion and of the medium.

Application of equation (b) to the results for the ionization functions of the $H_2PO_4^-$ ion leads to a value of 6.1×10^{-8} for the ionization constant of the $H_2PO_4^-$ ion, in excellent agreement with the value of 6.226×10^{-8} determined by Nims.[15] Probably equation (b) is not very accurate for ionic strengths as high as 1.0. Therefore, this excellent agreement suggests merely that the method of measurement can be used to obtain values of ionization functions that can be extrapolated to an

(11) Wagner, *Ind. Eng. Chem., Anal. Ed.*, **12**, 771 (1940).
(12) Redemann, *ibid.*, **11**, 635 (1939).
(13) Cupery, *Ind. Eng. Chem.*, **30**, 627 (1938).
(14) In this article, all concentrations are expressed in volume molal units. The "ionic strength," μ, is therefore not strictly that originally defined by Lewis and Randall (THIS JOURNAL, **43**, 1140 (1911)) using concentrations in weight-molalities, but is one-half the "ional concentration," Γ, used by Harned and Owen (Ref. 19, p. 33).
(15) Nims, THIS JOURNAL, **55**, 1946 (1933).

ionic strength of zero with some accuracy but it does not prove that the measured ionization functions at ionic strength 1.0 are reliable.

Rate Determination Procedure.—The reaction (1) was followed by titrating samples of the reaction mixture for total strong acid. It may be calculated from the value of the ionization function for the disulfonate ion that an indicator changing in the *p*H range of 5.0–6.0 is desirable for the titration of bisulfate ion in the presence of disulfonate ion. Brom cresol green–methyl red mixed indicator (endpoint 5.1) was used.

A reaction mixture was prepared by rapidly dissolving a known quantity of solid disulfonate in a thermostated solution of the other components in a 250-ml. volumetric flask, adding a small amount of water to adjust the volume and agitating again. The solution was then emptied into a 500-ml. glass-stoppered Erlenmeyer flask immersed in the thermostat. Two 10-ml. samples were taken with calibrated pipets and analyzed to determine the initial hydrogen ion concentration. In some runs, two final samples were hydrolyzed completely by heating to 80–90° for one hour, as a check on the disulfonate concentration. For the rate measurements at 25°, the samples were rapidly titrated with 0.02 *N* base. For the reactions at higher temperature, where the rate of hydrolysis was greater, the samples were run into excess base and back titrated with acid.

Initial Rate Studies at 25.00° at an Ionic Strength of 1.00.—To establish the kinetics of the reaction, a series of experiments was done with the ionic strength[14] fixed at 1.00. An ionic strength of about this magnitude is recommended to minimize the variations due to the salt effect on the rate of an ionic reaction.[16,17]

To establish tentatively the rate law, the average initial rates over the first 10% of hydrolysis for several series of experiments were obtained from graphically smoothed values of the reaction variable (amount of acid produced by the hydrolysis at time $t = x$) and the dependence of initial rates on initial concentrations of reactants determined. The dependence of initial rate on initial hydrochloric acid concentration for two initial disulfonate concentrations (0.0500 and 0.0200 *F*) is shown in Fig. 1. The dependence of initial rate on initial disulfonate concentration for two initial hydrochloric acid concentrations (0.099 and 0.0593 *F*) is exhibited in Fig. 2.

These results suggest the rate equation

$$-\mathrm{d}[\mathrm{HN(SO_3)_2^{=}}]/\mathrm{d}t = k[\mathrm{H^+}][\mathrm{HN(SO_3)_2^{=}}] \quad (c)$$

In an experiment for 34,000 min. at a *p*H of 8 in which $[\mathrm{HN(SO_3)_2^{=}}] = 0.045\ M$ and $[\mathrm{N(SO_3)_2^{\equiv}}] = 0.005\ M$, the observed change in titer of the solution corresponded to hydrolysis of 0.2% of the disulfonate and a calculated average rate of 3×10^{-9} mole/liter × minute. There was therefore no significant uncatalyzed hydrolysis in the experiments at moderate acidities.

In order to establish whether the hydrolysis of disulfonate is specifically catalyzed by hydronium ion (H_3O^+), or is also catalyzed by other acids, in particular by the bisulfate ion formed during the reaction, a series of experiments was performed (at 25.00° and $\mu = 1.00$) at constant initial disulfonate concentration and constant initial hydrochloric acid formality, but with varying initial amounts of added sulfate. In the hydronium ion concentration range with which we are concerned the disulfonate ion is not appreciably converted to $\mathrm{N(SO_3)_2^{\equiv}}$. We assume further that it is not appreciably converted to $\mathrm{HN(SO_3)/(SO_3H)^-}$. Evidence bearing on this point will be discussed more fully in a later section. In addition, the amine monosulfonic acid formed on hydrolysis is completely ionized.[13]

To determine the concentration of hydronium ion [H^+], in the presence of added sulfate, it was necessary to know the ionization function of

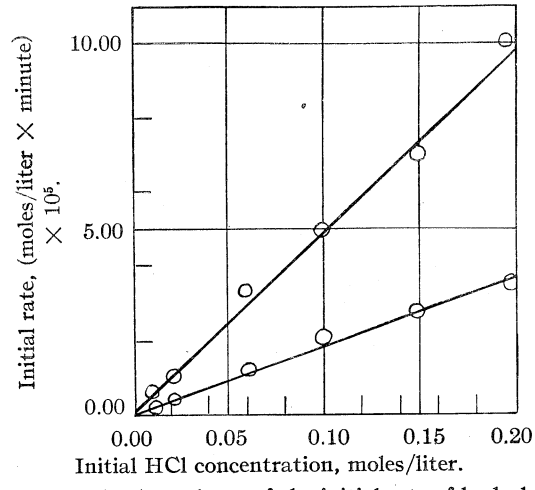


Fig. 1.—The dependence of the initial rate of hydrolysis of amine disulfonate on hydrochloric acid concentration at an ionic strength of 1.00 and at 25.00°; upper curve, $[\mathrm{HN(SO_3)_2^{=}}] = 0.0500$; lower curve, $[\mathrm{HN(SO_3)_2^{=}}] = 0.0200$.

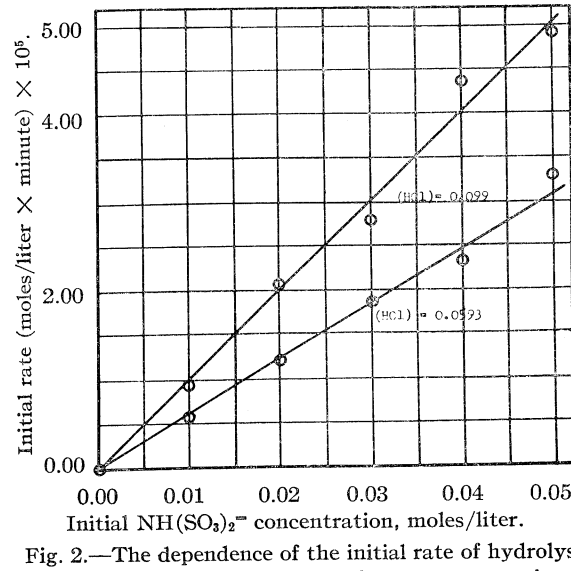


Fig. 2.—The dependence of the initial rate of hydrolysis of amine disulfonate on amine disulfonate concentration at an ionic strength of 1.00 and at 25.00°.

(16) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 94, 129.

(17) Brønsted and Pedersen, *Z. physik. Chem.*, **103**, 307 (1922).

HSO_4^- at an ionic strength of 1.00. This was calculated from the ionization constant[18] of HSO_4^- by multiplying by the ratio of the ionization function of $H_2PO_4^-$ at $\mu = 1.00$ measured by us to the ionization constant[15] of $H_2PO_4^-$

$$K(HSO_4^-, \mu = 1) = \frac{K(H_2PO_4^-, \mu = 1)}{K_0\,(H_2PO_4^-)} K_0\,(HSO_4^-) = \frac{4.67 \times 10^{-7}}{6.23 \times 10^{-8}} \times 1.20 \times 10^{-2} = 0.090$$

This calculation is based on the assumption that the ionic strength effects depend mostly on the charge types of the ions, and the small contributions of specific effects are nearly the same for the two acids. In treating the data, the procedure used above of calculating the average initial rate over the first 10% of hydrolysis was adopted. It is evident from the presentation of the data in Table III that the addition of sulfate decreases the rate of hydrolysis because it converts the hydronium ion to bisulfate. The hydrolysis is specifically catalyzed by hydronium ion.[19]

TABLE III

THE EFFECT OF INITIAL SULFATE CONCENTRATION ON INITIAL RATE AT 25.00° AND $\mu = 1.00$

Initial HCl volume molality, 0.0197; initial $HN(SO_3)_2^=$ volume molality, 0.02000

Na_2SO_4, F	NaCl, M	Initial rate, $\Delta x/\Delta t$ mole/liter × min. × 10^5	$[H^+]$, calcd.	$k = (\Delta x/\Delta t)/[H^+][HN(SO_3)_2^=]$ × 10^{+2}
0.0200	0.860	0.334	0.0166	1.005
.0400	.800	.288	.0143	1.005
.0500	.740	.260	.01250	1.04
.0800	.680	.222	.01107	1.00
.1000	.620	.190	.00985	0.965

The values of k, the specific rate constant at 25.00° and at $\mu = 1.00$, calculated from the slopes of Figs. 1 and 2 and from Table III, that is, from all the initial rate data, are presented in Table IV. Considering the approximate nature of initial rate calculations, the agreement amongst the various series of experiments is good, and tends to confirm the proposed rate equation (c).

The Course of the Reaction at 25.00° and $\mu = 1.00$.—To further confirm the validity of the rate equation (c), analysis of the progress of the reaction with time was carried out. These calculations are rather complicated because one must allow for the varying degree of dissociation of bisulfate (from sulfate added initially and from the hydrolysis of the disulfonate) during the course of the reaction.

(18) Hamer, THIS JOURNAL, **56**, 860 (1934).

(19) After carrying out the calculations outlined here, it was called to our attention that on p. 580 of "The Physical Chemistry of Electrolytic Solutions" (Reinhold Publishing Corp., New York, N. Y., 1943) Harned and Owen recommend the privately communicated value of 0.0101 for the ionization constant of HSO_4^- instead of the 0.0120 we have used. Since the correction to an ionic strength of 1.0 is uncertain, and since a difference of 20% would produce less than a 10% change in the calculated rate constants, we have not recalculated our results using the newer data.

TABLE IV

SPECIFIC RATE CONSTANT AT 25.00° AND AT $\mu = 1.00$ ESTIMATED FROM INITIAL RATE DATA

Description of experiments	k, liter/moles × min. × 10^2
Varying HCl concentration, $[HN(SO_3)_2^=] = 0.02000\ M$	1.00
Varying HCl concentration, $[HN(SO_3)_2^=] = 0.05000\ M$	0.93
Varying $HN(SO_3)_2^=$ concentration, $[HCl] = 0.0593\ M$	1.04
Varying $HN(SO_3)_2^=$ concentration, $[HCl] = 0.099\ M$	1.02
Varying $SO_4^=$ concentration, $[HCl] = 0.0197\ M$, $[HN(SO_3)_2]^= = 0.0200\ M$	1.01

The method chosen to treat most of the data is based on the equation (d)

$$k = \frac{2(x_2 - x_1)}{\int_{t_1}^{t_2} [((s + K - a)^2 + 4K(a + x))^{1/2} - (s + K - a)](d - x)dt} \quad \text{(d)}$$

In this relation: x = increase in acid titer due to the reaction (moles/liter) (reaction variable); K = ionization function of bisulfate ion; a = initial formality of hydrochloric acid (moles/liter); d = initial concentration of disulfonate; s = initial formality of sulfate. The equation (d) is derived in a straightforward manner from the rate equation (c). For the experiments at 25.00° and at $\mu = 1.00$, the integral in the denominator of (d) was evaluated by: (1) smoothing the data (x *vs.* t) graphically, (2) calculating the values of the integrand from the smoothed data, (3) plotting the integrand against time, and (4) evaluating the integral with a polar planimeter.

It should be mentioned that in the form $-d[HN(SO_3)_2^=]/[H^+][HN(SO_3)_2^=] = kdt$, the rate equation may be integrated analytically by applying the method of integration by partial fractions after suitable transformation. The cumbersome expressions resulting therefrom have been used in representative cases to check the method

TABLE V

VALUES OF THE RATE CONSTANT OBTAINED BY GRAPHICAL INTEGRATION

Temperature, 25.00°; ionic strength, 1.00

t_1, min.	t_2, min.	x_1, moles/liter	x_2, moles/liter	(k, liter/moles × min.) × 10^2
Run No. 28, $a = 0.01000$, $d = 0.02000$, $s = 0$ (NaCl) = 0.930				
0	2000	0	0.00440	1.05
1500	4000	0.00325	0.00855	1.02
3500	6000	.00760	.01205	0.97
5000	9000	.01040	.01575	0.98
Run No. 37, $a = 0.01970$, $d = 0.02000$, $s = 0.1000$, (NaCl) = 0.620				
0	3000	0	0.00575	1.01
2000	5000	.00380	.00920	1.05
4000	8000	.00760	.01305	0.99
7000	9000	.01190	.01400	0.95

described above.[1] Table V exhibits the results of representative experiments, analyzed by the graphical integration method.

For the experiments listed in the table and for most of the many other runs that were made, there was a definite downward trend in the calculated rate constants especially after about 50% of the disulfonate initially present had hydrolyzed. It is not known to what this was due. The trend could not be correlated with any of the known variables. In spite of these trends, the calculated constants are so nearly constant under a wide variety of initial conditions that, taken in conjunction with the results of the initial rate study, they indicate that the proposed rate equation (c) is essentially correct.

The fact that the calculated values of the rate constant, as exhibited in Tables IV and V, are constant and independent of the calculated concentrations of hydronium ion and disulfonate ion strongly suggests that no appreciable fraction of these ions reacts to form an acid-disulfonate ion [$H_2N(SO_3)_2^-$ or $HN(SO_3H)(SO_3)^-$] (that is, an isomer of the activated complex postulated in a later section). If as is indicated in Fig. 1 the rate constant calculated at an H^+ concentration of 0.20 mole/liter is the same within 10% as that at lower acidities so that less than 20% of the disulfonate has been converted to the acid-disulfonate ion in 0.2 M acid, a lower limit for the second ionization function of amine disulfonic acid is $0.2 \times 9 = 1.8$.

Dependence of the Specific Rate Constant on Ionic Strength at 25.00°.—The effect of varying the ionic strength is of interest because the theoretical interpretation gives a clue to the identity of the reacting species in the rate-controlling reaction, that is, it gives the sign and a good idea of the magnitude of the product of the charges of the reacting ions. As is well known, the use of equation (b) for the variation of activity with ionic strength in conjunction with Brønsted's theory yields the equation (e)

$$\log_{10} k = \log_{10} k_0 + \frac{2Az_1z_2\mu^{1/2}}{1 + \mu^{1/2}} + \beta\mu \qquad (e)$$

where z_1 and z_2 are the charges of the reacting ions, k_0 is the limiting specific reaction constant as the ionic strength approaches zero, and β is a constant at constant temperature.

To study this effect, experiments were done at a series of ionic strengths varying from 0.020 to 0.25. The hydrolysis was followed until more than 50% of the disulfonate had hydrolyzed. The data were smoothed and a rate constant calculated by a tabular integration method using the trapezoid rule. The time intervals of the integrals were taken over the first portion of the reaction but they did not include the region about $t = 0$, thus eliminating the effects of the disturbances involved in starting the reaction. The value of the ionization function of bisulfate ion at different ionic strengths, which is involved in the calculation, was estimated by assuming the validity of the equation (b), and that the value of K, 0.090, at $\mu = 1.00$ was accurate. This taken in conjunction with Hamer's value of K_0 at 25.00°[18] gives the equation

$$\log K = \log K_0 + \frac{4A\mu^{1/2}}{1 + \mu^{1/2}} + \gamma\mu \qquad (f)$$

where, at 25.00°, $K_0 = 0.0120$, $A = 0.5065$, and $\gamma = -0.137$ for sodium chloride solutions. The rate constants are shown in Table VI.

TABLE VI

DEPENDENCE OF THE RATE CONSTANT ON IONIC STRENGTH AT 25°

Moles/liter HCl	Moles/liter $HN(SO_3)_2^=$	Moles/liter NaCl	$\left(\frac{\mu}{\text{moles/liter}}\right)^{1/2}$	K, moles/liter	k, liter/moles × min.
0.00479	0.00500	0.00	0.1407	0.0212	0.0478
.00482	.00500	.0100	.1726	.0239	.0436
.00978	.01000	0.0	.1993	.0257	.0395
.00987	.01000	.0500	.3000	.0340	.0287
.00985	.01000	.1200	.400	.0431	.0233
.00985	.01000	.2100	.500	.0525	.0189
.01000	.02000	.930	1.000	.0900	.0102

In order to estimate the value of z_1z_2 in (e), log k was plotted against $0.5065\mu^{1/2}/(1 + \mu^{1/2})$ and a smooth curve drawn through the points as shown in Fig. 3. From smoothed data read from the

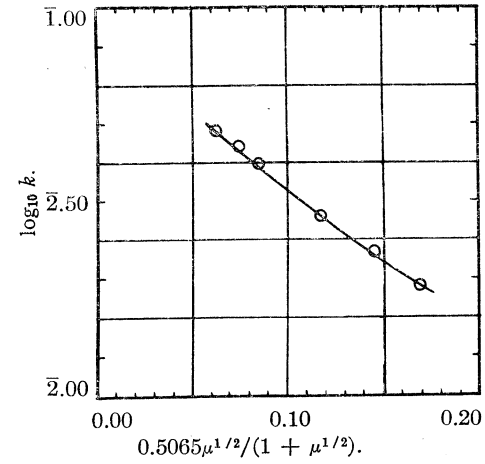


Fig. 3.—The dependence of the reaction constant on ionic strength at 25.00°.

curve, the slope of the curve was calculated, and divided by 2 to give an approximation to z_1z_2. The values thus obtained differed from −2 by about 5–10%. To fit equation (e) to the data, the value of −2 for z_1z_2 was assumed and log k + $[(4 \times 0.5065\ \mu^{1/2}/(1 + \mu^{1/2})]$ was plotted against μ, as shown in Fig. 4, to evaluate β. It was found that $\beta = +0.092$ and $k_0 = 0.0852$. This value of β is a reasonable one. The conclusion may be drawn that the most probable value of z_1z_2 is −2 which suggests a rate-determining reaction between amine disulfonate ion and hydronium ion. This is consistent with the experimental rate equation.

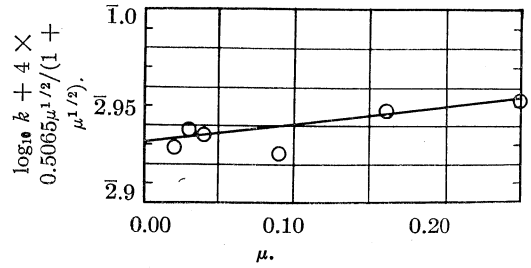


Fig. 4.—Graphical evaluation of k_0 and β of equation (e) at 25.00°.

The Effect of Temperature on the Rate.—To estimate the energy and entropy of activation, two additional series of experiments were done, one at 35°, the other at 45°. Each series consisted of three experiments at decreasing ionic strength to facilitate the extrapolation to μ = 0.00, two experiments to spot check the rate law at constant ionic strength, and one experiment in alkaline medium (added base equivalent to 10% of the disulfonate) to find if an uncatalyzed reaction with water becomes appreciable at the higher temperatures.

The results of these experiments are shown in Table VII. The rate constant was calculated by a tabular integration method utilizing the trapezoid rule over an early time interval which did not include the initial time. No attempt was made in these series to check the rate law by calculating the rate constant over different time intervals for the same experiment as the agreement of the values of the constant calculated for the two spot check experiments was taken as adequately showing the validity of the rate law at the temperature in question. No detectable reaction was found in alkaline media at these temperatures during time intervals comparable with the duration of the other experiments of the same series.

TABLE VII

DEPENDENCE OF REACTION CONSTANT ON TEMPERATURE AND IONIC STRENGTH

Moles/liter HCl	Moles/liter $HN(SO_3)_2^=$	Moles/liter NaCl	$\left(\frac{\mu^{1/2}, \text{moles}}{\text{liter}}\right)^{1/2}$	K for HSO_4^-	k, liter/moles × min.
		34.55°, K_0 = 0.0106			
0.00954	0.01000	0.0	0.1988	0.0234	0.143
.00974	.01000	.0225	.2495	.0275	.117
.00984	.01000	.0500	.2999	.0318	.101
.01962	.01000	.0400	.2997	.0318	.099
.00970	.02000	.0200	.2998	.0318	.100
		44.77°, K_0 = 0.00892			
.00469	.01000	.00500	.1991	.0205	.479
.00488	.01000	.0275	.2499	.0236	.416
.00488	.01000	.0350	.2642	.0246	.390
.00976	.01000	.0500	.2999	.0274	.364
.00469	.02000	.0250	.2998	.0274	.341

The values of the ionization function of bisulfate ion were estimated by neglecting the term linear in μ in the equation (f) previously derived from equation (b). This approximation is adequate because of the low ionic strengths and the relative intensitivity of the values of the rate constant to the value of the ionization function. Values of K_0 were taken from Hamer's values[18] and the very small corrections to the exact temperature of the experiments made using values of ΔH_i, the enthalpy of ionization, given by Hamer.

To extrapolate to μ = 0, the procedure used in the ionic strength studies at 25° was applied. The graphical evaluation of the constants β and log k_0 of equation (e) is shown in Fig. 5.

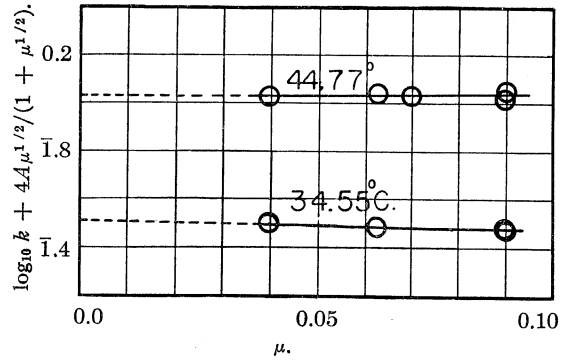


Fig. 5.—Graphical evaluation of k_0 and β at 34.55° and 44.77°.

In Table VIII the behavior of the rate constant with ionic strength and temperature is summarized. The values of A are the theoretical ones calculated from the expression given by the Debye–Hückel theory.

TABLE VIII

SUMMARY OF THE DEPENDENCE OF THE RATE CONSTANT ON IONIC STRENGTH AND TEMPERATURE

Temperature, °C.	A	β	k_0 liters/moles × min.
25.00	0.506	0.092	0.0852
34.55	.517	−.32	0.321
44.77	.528	.13	1.06

The Thermodynamics of the Activated Complex.—The variation of k_0 with temperature was interpreted by the activated complex theory. This theory yields the equation (g)[20]

$$k_0 = (\mathbf{k}T/h) \exp(-E^*/RT)\exp(\Delta S^*/R) \qquad (g)$$

for the specific rate constant of a reaction in solution. In this relation, **k** and h are Boltzmann's and Planck's constants, respectively, and the starred quantities are the internal energy and entropy of activation.

Figure 6 is a plot of log k_0/T *versus* $1/T$. From the slope of the straight line, ΔE^* = 23,500 cal., with an estimated error of the order of ±1000 cal.

Using this value for the activation energy, the values of $(\mathbf{k}T/h)$ exp $(\Delta S^*/R)$ (A in the Arrhenius equation, $k_0 = A \exp(-E^*/RT)$) and of the

(20) Glasstone, Laidler and Eyring "The Theory of Rate Processes," McGraw-Hill Book Co., New York, N. Y., 1941, pp. 198, 199: eqns. 167, 178.

entropy of activation listed in Table IX were calculated.

TABLE IX

VALUES OF THE ENTROPY OF ACTIVATION

T	k_0, ml./mole sec.	$(kT/h)\exp(\Delta S^*/R)$	ΔS^*, e. u.
25.00	1.42	2.4×10^{17}	21.2
34.55	5.18	2.67×10^{17}	21.6
44.77	17.66	2.55×10^{17}	21.1
	Av.	2.54×10^{17}	21.3

The frequency factor is about 10^3 times larger than that calculated on the basis of the simple collision theory for a bimolecular reaction.[21] This is to be expected for a reaction between two ions when $z_1z_2 = -2$. For if the results of Scatchard's arguments[22] based on a model of the activated complex consisting of two charged spheres at a distance r apart are used to calculate the contribution (ΔS^*_D) to the entropy of activation due to electrostatic interaction between dielectric medium and charged ion, it is found that

$$\Delta S^*_D = \frac{\epsilon^2 z_1 z_2}{rD}\left(\frac{\partial \ln D}{\partial T}\right)_p$$

Here, ϵ = electronic charge (e. s. u.); z_1,z_2 = charges of reacting ions; D = dielectric constant of medium; T = absolute temperature; p = pressure.[23] For water this yields

$$\Delta S^*_D = -20 z_1 z_2/r \text{ (A) e. u./mole} \qquad \text{(h)}$$

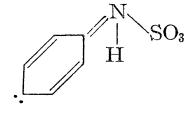
The value of $\mathbf{k}T/h$ is 1.7×10^{13} at $T = 298°K$. Since the collision factor has a value of *ca.* 2.8×10^{14} sec.$^{-1}$ when concentrations are expressed in moles/ml.,[23] a reaction with a "normal" collision factor has an entropy of activation of *ca.* 5.6 e. u. For the reaction in question, we may therefore attribute approximately 15.7 e. u. to the electrostatic interaction, corresponding on the basis of equation (*h*) to a separation of the charges in the activated complex of 2.5 Å. This argument is not presented to prove that in the activated complex, the charges of the reaction ions are separated by exactly 2.5 Å.; it does indicate that it is reasonable to expect a positive entropy of activation of the order of magnitude of that observed.

The Mechanism of the Reaction.—The kinetic evidence indicates that the reaction proceeds via the formation of an activated complex from hydronium ion and amine disulfonate ion which then decomposes to give the reaction products.

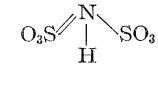
$$H_3O^+ + HN(SO_3)_2^= \rightleftarrows (H_3O, HN(SO_3)_2)^-$$

$$H_2O + (H_3O, HN(SO_3)_2)^- \longrightarrow HSO_4^- + H_2NSO_3^- + H_3O^+$$

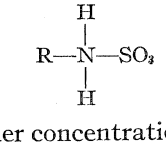
In speculating about the detailed mechanism of the reaction, it is pertinent to recall that N-alkyl sulfamic acids (*e. g.*, H_3CNHSO_3H) are quite resistant to hydrolysis, but that the N-aryl sulfamic acids (*e. g.*, $C_6H_5NHSO_3H$) have not been prepared because they hydrolyze readily in acid media; salts of the type $C_6H_5NHSO_3Na$ can be prepared.[24] The base strength of the electron pair on the nitrogen in disulfonate or phenylsulfamate is less than that of the corresponding electron pair in methyl sulfamate because the addition of a proton destroys the possibilities of resonance of the normal structure with structures of the type (I).



(I)

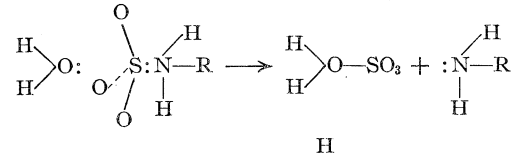


Consequently an activated complex of the type (II)

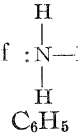


(II)

will exist in smaller concentration for R = C_6H_5 or SO_3 than for R = CH_3. However, in such an activated complex, the attack of a water molecule depicted in (III)



(III)

causes the liberation of  which is stabilized by resonance for R = C_6H_5 or $-SO_3^-$. The experimental evidence indicates that this latter ef-

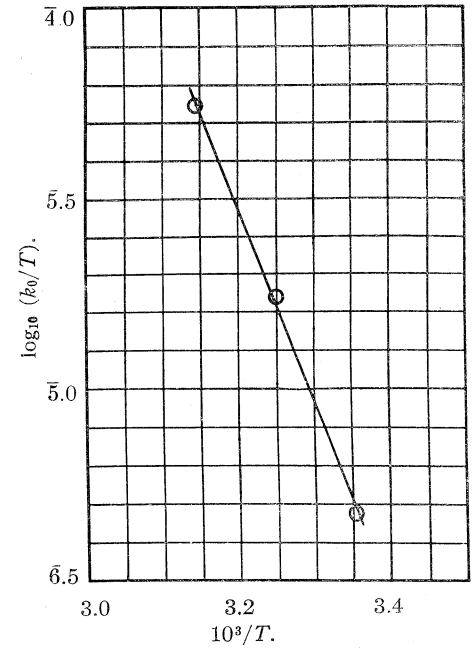


Fig. 6.—The dependence of k_0 on temperature.

(21) See, for example, Moelwyn-Hughes "Kinetics of Reactions in Solution," 2d edition, Oxford University Press, 1947, Chapter III.

(22) Scatchard, THIS JOURNAL, **52**, 52 (1930).

(23) Glasstone, Laidler and Eyring, *loc. cit.*, pp. 434–435. A similar equation is given in ref. 21, p. 93.

(24) Ref. 5, p. 69.

fect is greater than the effect of resonance on the acid strengths of the activated complexes. It is not necessary to think of the addition of a proton and the attack by a water molecule as steps taking place in series; in a single attack by a hydronium ion, the same factors would affect the relative reactivities of disulfonate, N-alkyl and N-aryl sulfamates.

An uncatalyzed reaction with water like (III) would require the liberation of the unstable ion; $:\overset{\overset{H}{|}}{\underset{\cdot\cdot}{N}}-R$ and hence does not take place. If the activated complex for the acid catalyzed reaction $\overset{H}{|}$ were $HO_3S-\overset{H}{\underset{\cdot\cdot}{N}}-R$ the same unfavorable factor would affect the reaction.

Acknowledgment.—We are indebted to Professor Don M. Yost for proposing this problem to us. Professors N. Kharasch and S. Winstein of the University of Southern California and The University of California, respectively, have made stimulating suggestions as to the mechanism of the reaction.

Summary

The rate of the acid catalyzed hydrolysis of amine disulfonate ion, $HN(SO_3)_2^{=}$, in water solution has been studied over the temperature range 25–45°. The results at constant ionic strength conform to the rate equation

$$-d[HN(SO_3)_2^{=}]/dt = k[H^+][HN(SO_3)_2^{=}]$$

if the equilibrium between sulfate ion and hydrogen ion is taken into account. The uncatalyzed hydrolysis was found to have an undetectable rate compared to the rate of the acid catalyzed reaction.

The variation of the rate constant with ionic strength implies that the charge product of the ions involved in the rate determining reaction is −2.

The variation of the rate constant at zero ionic strength with temperature is described by the equation

$$k_0(\text{ml./mole} \times \text{sec.}) = 2.54 \times 10^{17} \exp.\ (-23{,}500/RT)$$

The relatively large value of the frequency factor (as compared with that expected on the basis of collision theory for a bimolecular reaction between uncharged molecules) is explained on the basis of a large positive entropy of formation of the activated complex, due to its electrostatic interaction with the solvent.

A mechanism involving an activated complex of amine disulfonate ion and hydronium ion may be invoked to explain these results. A hypothesis to explain the relative stability toward hydrolysis of methyl sulfamic acid as compared with phenyl sulfamic acid or amine disulfonate is advanced.

In addition, the ionization function (classical ionization constant) for the equilibrium: $HN(SO_3)_2^{=} = H^+ + N(SO_3)_2^{=}$ in a sodium chloride solution at an ionic strength of 1.00 at 25° was measured as 3.2×10^{-9}.

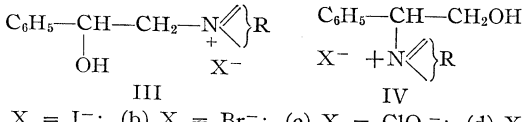
PASADENA, CALIF. RECEIVED JANUARY 3, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Reactions of 1,2-Epoxides with Salts of Organic Bases. I. Styrene Oxide[1,2]

BY L. CARROLL KING, NEIL W. BERST AND F. N. HAYES

Styrene oxide (I) reacts with strong acid salts of certain organic bases to give a mixture of quaternary salts. For example, I reacted with pyridine hydriodide (II) to give a mixture of 2-phenyl-2-hydroxyethylpyridinium iodide (IIIa) and 1-phenyl-2-hydroxyethylpyridinium iodide (IVa).



III IV

(a) X = I^-; (b) X = Br^-; (c) X = ClO_4^-; (d) X = $^-O_3SC_6H_4CH_3$; R = C_5H_5—

In a series of reactions between I and II the over-all yield of mixed salts was quite constant, with IVa the principal product. The yields of IIIa were consistently low, except in the case where I was in excess. The requisite reaction time was five to ten minutes. Prolonged heating had little effect on the total yield or distribution of isomers except when I was in excess. In this case the products became tarry and the isolable yield of IVa was smaller.

The structure of IIIa was determined by comparison with authentic 2-phenyl-2-hydroxyethylpyridinium iodide, prepared by the method of Krohnke.[3] Further proof was obtained by oxidizing[4] 2-phenyl-2-hydroxyethylpyridinium perchlorate (IIIc), prepared from IIIa, to the known phenacylpyridinium perchlorate.[5] The structure assigned to IVa follows from its non-identity with IIIa and from its formation from the reaction of 2-phenyl-2-iodoethanol[6] with pyridine.

The generality of the reaction was established by allowing I to react with a number of acid salts

(1) Presented before the Organic Division of the American Chemical Society, San Francisco, April, 1949.

(2) This investigation was supported in part by a research grant from the National Cancer Institute, U. S. Public Health Service,

(3) Krohnke, *Ber.*, **66**, 607 (1933).

(4) Krohnke, *ibid.*, **67**, 659 (1934).

(5) King, THIS JOURNAL, **66**, 894 (1944).

(6) Prepared by the method of Columbic and Cottle, *ibid.*, **61**, 996 (1939).

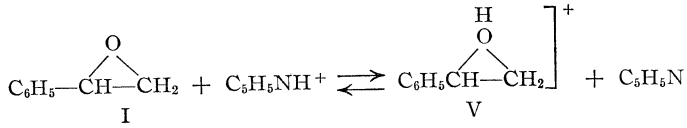
TABLE I[a]

Salt used in reaction	Yield, % III	Yield, % IV	M. p., °C. III	M. p., °C. IV	Formula of product	Carbon, % Calcd.	Carbon, % Found III	Carbon, % Found IV	Hydrogen, % Calcd.	Hydrogen, % Found III	Hydrogen, % Found IV
Pyridine hydriodide	6.7	68[e]	256–258	127–129	$C_{13}H_{14}ONI$	47.72	47.62	48.00	4.31	4.29[b]	4.40[d]
Pyridine hydrobromide	5.3[c]	73	230–232	134–135	$C_{13}H_{14}ONBr$	55.73	55.98	55.30	5.04	5.04	5.06
Pyridinium perchlorate	18[f]	56	217–218	[g]	.....	...	...	...	..	...	..
Pyridinium tosylate	11	52	212–213	[g]	$C_{20}H_{21}O_4NS$	64.67	64.60	...	5.70	5.50	..
Picoline hydriodide	10[h]	88	175–177	133–134	$C_{14}H_{16}ONI$	49.28	49.23	48.98	4.73	4.82[i]	4.73
3-Picolinium perchlorate	15	62	180–184	123–125	$C_{14}H_{16}O_5NCl$	53.57	53.80	53.15	5.14	5.22	4.82
Isoquinolinium perchlorate	21	60	214–215	132–133	$C_{17}H_{16}O_5NCl$	58.37	58.03	58.10	4.61	4.36	4.67
Isoquinoline hydriodide	99[j]	86[j]	173–176	146–147	$C_{17}H_{16}ONI$	54.12	54.36	54.27	4.28	4.41	4.34

[a] In this table, III and IV refer to the generalized ion as shown in the text. R and X are determined by the salt used in the reaction. [b] Iodide: calcd. 38.9; found, 38.2. [c] This compound was also prepared from 1-phenyl-2-bromoethanol. [d] Iodide: calcd. 38.9; found, 38.4. [e] This compound was also prepared from 2-phenyl-2-iodoethanol. [f] Identical with 1-(2-phenyl-2-hydroxyethyl)-pyridinium perchlorate, synthesized by Krohnke, *Ber.*, **66**, 607 (1933). [g] These salts were not isolated as such. The yields are based on the amount of IVa isolated after metathetical reactions with iodide ion (see experimental). [h] In the first run this compound was obtained in the yield shown by one of us, F. N. H. We were unable to repeat the experiment. The substance is readily obtained by action of β-picoline on 1-phenyl-2-bromoethanol followed by metathetical reaction with iodide ion. [i] Iodide: calcd. 37.2; found, 37.0. [j] When prepared by action of isoquinoline hydriodide on styrene oxide these compounds could not be separated. They were prepared in the yields shown by the reaction of isoquinoline with 1-phenyl-2-bromoethanol followed by metathetical reaction with iodide and from the reaction of isoquinoline with 2-phenyl-2-iodoethanol.

of pyridine and other heterocyclic tertiary amines. The results of these experiments along with the data for the products are listed in Table I. In the reactions employing pyridinium perchlorate and *p*-toluenesulfonate, IIIc and IIId were obtained in much larger yields than IIIa for the analogous reaction using II. Compounds IVc and IVd would not crystallize, but their identity was demonstrated, in each case, by a metathetical conversion to IVa.

Using the pyridinium ion as an example, an initial step in the over-all reaction may be envisioned as an equilibrium partition of a proton between generalized bases.



I V

The ion (V)[7] could then react directly with the base present to form salts of types III and IV, or, V could react with the anion present to form compounds of types VI and VII.[8] Compounds VI and VII could subsequently react with the base to form salts of type III or IV.



VI VII

In connection with this study 2-phenyl-2-iodoethanol (VI, X = I) and 1-phenyl-2-bromoethanol (VII, X = Br) were prepared and their reactions with pyridine type bases were studied. 2-Phenyl-2-iodoethanol reacted with pyridine to give IVa in essentially quantitative yield. No trace of IIIa was observed. Similarly 1-phenyl-2-bromoethanol reacted with pyridine to give IIIb in excellent yield and no IVb could be detected in the reaction mixture. With both halides the time required for complete reaction with pyridine was longer than that required for the formation of the corresponding salts by means of the reaction between styrene oxide and pyridinium salts.

In view of these observations VI and VII are of minor importance in the above reactions. Furthermore when VI or VII react with pyridine-type bases the halogen is displaced without the formation of styrene oxide as an intermediate.

Experimental

Preparation of Starting Materials.—The styrene oxide was a commercial sample; b. p. 66–67° (7 mm.).[9]

The iodide, bromide and perchlorate salts were prepared by mixing the appropriate aqueous acid with a slight excess of the base and evaporating the mixture on the steam-bath. The resulting salt was washed with ether and recrystallized from a suitable solvent. The melting points of the salts and the crystallization solvents were as follows: pyridine hydriodide, m. p. 175–190° (dec.), alcohol; pyridinium bromide, m. p. 215°,[10] alcohol; pyridinium perchlorate, m. p. 289°, water; β-picoline hydriodide, m. p. 87–88°, alcohol; β-picolinium perchlorate, m. p. 40–50°[11]; isoquinolinium perchlorate, m. p. 165–170°, acetone–water.

Pyridinium *p*-toluenesulfonate was prepared directly from pyridine and *p*-toluenesulfonic acid monohydrate. The product was recrystallized from acetone–alcohol, m. p. 117°.[12]

Examples of Styrene Oxide Reactions with Salts. (a) **Pyridine Hydriodide.**—A mixture consisting of 6.0 g.

(7) Kadesch, THIS JOURNAL, **68**, 43 (1946), has suggested that ions such as V undergo ring opening to give carbonium ions. If this should occur the resulting carbonium ions could react with the base present to give products of type III or IV.

(8) The formation of VI or VII, where X is perchlorate, may be assumed to be unimportant because of the poor nucleophilic character of the perchlorate ion. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, p. 301. However, because of some known additions of perchloric acid to 1,2-epoxide, an attack by perchlorate ion on V cannot be completely ruled out. Hoffmann, Zedwitz and Wagner, *Ber.*, **42**, 4390 (1909).

(9) We are indebted to the Dow Chemical Company for a generous sample of this substance.

(10) Dehn and Dewey, THIS JOURNAL, **33**, 1596 (1911).

(11) This substance was used without further purification.

(12) Rapoport, THIS JOURNAL, **68**, 341 (1946).

(0.05 mole) of styrene oxide, 8.0 g. (0.1 mole) of pyridine and 10.3 g. (0.05 mole) of pyridine hydriodide was heated on the steam-bath. Within two minutes, the pyridine hydriodide had dissolved and a vigorous reaction began. After the reaction subsided, the mixture was heated ten minutes more, cooled, layered with ether and rubbed with an applicator stick until the entire mass crystallized. The crude mixture of products weighed 13.2 g.

The solid material was leached three times with 75-cc. portions of boiling acetone and the 4.0 g. left was dissolved in 20 cc. of water containing a little alcohol. On cooling, 0.7 g. (4.2%) of a substance melting at 244–252° separated. After recrystallization from water, pure 1-(2-phenyl-2-hydroxyethyl)-pyridinium iodide (IIIa), melting at 252–255°, was obtained.

On cooling the acetone extracts from above, there separated out a compact crystalline product, 8.7 g. (52%),[13] m. p. 125–129°. Recrystallization from acetone gave pure 1-(1-phenyl-2-hydroxyethyl)-pyridinium iodide (IVa), m. p. 128–129°.

(b) Pyridinium Perchlorate and *p*-Toluenesulfonate.—As in the previous procedure, high melting acetone-insoluble salts were obtained. However, no crystalline material separated from the acetone extracts, even after concentration. Subsequently, each oil was treated with sodium iodide in acetone. At this point, the pyridinium perchlorate reaction started to deposit crystals. On long cooling of the acetone solution, followed by filtration, a 56% yield of IVa, melting at 128–129° was obtained. The sodium iodide treated acetone solution of the *p*-toluenesulfonate reaction immediately gave a precipitate of sodium *p*-toluenesulfonate. The mixture was heated and filtered. After long cooling, there separated from the filtrate a 52% yield of IVa, melting at 128–129°.

The Oxidation of IIIc to 1-Phenacylpyridinium Perchlorate.—According to the directions of Krohnke,[4] 0.15 g. of 1-(2-phenyl-2-hydroxyethyl)-pyridinium perchlorate (IIIc) in 1 cc. of water was heated under reflux for six hours with 0.5 cc. of 6 *N* sulfuric acid and 0.075 g. of sodium dichromate. On cooling, there separated out long yellow needles, which were filtered off and washed with ice-water. The yellow crystals weighing 0.1 g. (93%), were recrystallized from acetone–water, using norite, yielding white crystals melting at 189°. This material gave no depression in a mixed melting point with an authentic sample of 1-phenacylpyridinium perchlorate prepared in this Laboratory.[5]

Reactions Involving 1-Phenyl-2-bromoethanol.—By heating 1-phenyl-2-bromoethanol[14] with pyridine, on a steam-bath for twenty-four hours, and then washing the product with ether, an essentially quantitative yield of crude 2-phenyl-2-hydroxyethylpyridinium bromide was obtained. An aqueous solution of the bromide on treatment with 48% hydriodic acid gave the corresponding iodide (IIIa); yield 90%; m. p. 252–255°[15] after crystallization from alcohol–water. In a similar manner the following salts were prepared by action of the corresponding bases on 2-phenyl-2-bromoethanol; 1-(2-phenyl-2-hydroxyethyl)-3-picolinium iodide, m. p. 175–177°[15] crystallized from alcohol–water; and 2-(2-phenyl-2-hydroxyethyl)-isoquinolinium iodide, m. p. 173–176° crystallized from alcohol.

No compounds of type IV were observed in any of these reactions.

Reactions Involving 2-Phenyl-2-iodoethanol.—2-Phenyl-2-iodoethanol[6] was heated with pyridine, on a steam-bath for thirteen hours. The resulting reaction mixture was washed with dry ether and the crude crystalline product was recrystallized from acetone; yield, 82%, of 1-(1-phenyl-2-hydroxyethyl)-pyridinium iodide (IVa), m. p. 128–129°[15]; in a similar manner the reaction of 2-phenyl-2-iodoethanol with β-picoline and isoquinoline gave 83% of 1-(1-phenyl-2-hydroxyethyl)-3-picolinium iodide, m. p. 131–132°, and 86% of 2-(1-phenyl-2-hydroxyethyl)-isoquinolinium iodide, m. p. 146–147°.

Summary

1. The reaction of styrene oxide with pyridine hydriodide gives a mixture of salts consisting of 1-phenyl-2-hydroxyethylpyridinium iodide and 2-phenyl-2-hydroxyethylpyridinium iodide.

2. The generality of this reaction was established by allowing styrene oxide to react with a variety of strong acid salts of pyridine and by allowing it to react with salts of a number of pyridine-type bases.

(13) By reworking all mother liquors including that from which the high melting compound separated, the total yield of IVa, the low melting compound, was 75%.

(14) Read and Reid, *J. Chem. Soc.*, 1487 (1928).

(15) No depression in mixed melting point with the corresponding salt prepared from styrene oxide.

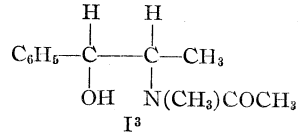
EVANSTON, ILLINOIS RECEIVED MAY 26, 1949

[CONTRIBUTION FROM THE CHEMICAL BRANCH, DIVISION OF MEDICINE, FOOD AND DRUG ADMINISTRATION, FEDERAL SECURITY AGENCY]

Mechanism and Stereochemical Course of Acyl Migrations in Derivatives of Ephedrine and ψ-Ephedrine

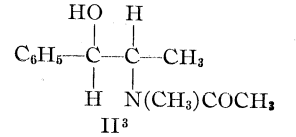
BY LLEWELLYN H. WELSH

It has been reported[1] that treatment of N-acetyl-(−)-ephedrine, I, with hot 5% hydrochloric acid quantitatively yielded a mixture of (−)-ephedrine and its diastereomer, (+)-ψ-ephedrine, in the ratio of 38:62,[2] and that inversion took place at the number one carbon atom during an N → O shift of the acetyl group prior to hydrolysis of the ester salt so formed. Under the same conditions N-acetyl-(+)-ψ-ephedrine, II, gave a product in which complete retention of configuration was evident.



I[3]

erythro configuration



II[3]

threo configuration

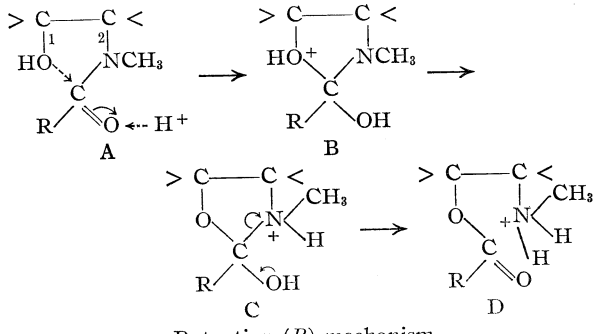
(1) Welsh, THIS JOURNAL, **69**, 128 (1947).

(2) When this reaction is carried out under temperature conditions more closely controlled than those formerly employed, a ratio of 33:67 results

(3) The projection formulas are based on the work of Leithe, *Ber.*, **65**, 660 (1932), and of Freudenberg, *et al.*, THIS JOURNAL, **54**, 234 (1932); *Ann.*, **510**, 223 (1934). Jarowski and Hartung, *J. Org. Chem.*, **8**, 565 (1943), have misinterpreted the publication of Leithe, and are in error when they state that the relative configuration of the methylamino-bearing carbon atom is unsettled.

Stereochemical results similar to these were obtained when the corresponding dry crystalline N-acetyl hydrochlorides[4] were heated at 110°. This similarity of results makes it apparent that hydrolytic cleavage of the amide linkage is not responsible for uninverted material in the product from reactions conducted in aqueous media. It was also reported that the N → O rearrangement of N-acetylephedrine in 90% acetone occurred with predominant retention of configuration.

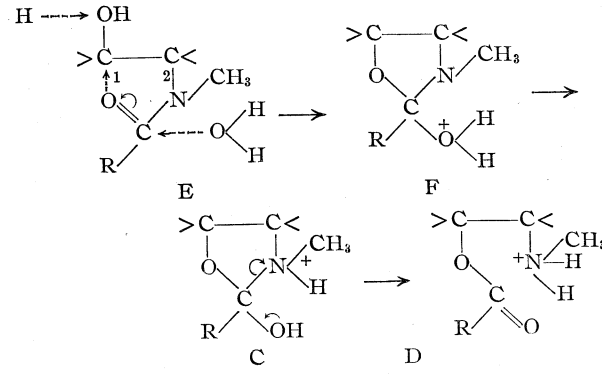
It would seem that two mechanisms are involved in the rearrangements, one leading to inversion, the other to retention of configuration.[5] A mechanism for retention is shown below.[6] Such



Retention (*R*) mechanism

a process would lead to retention of configuration since no bond of the asymmetric center is involved.[7] It is analogous to one used to represent the acid-catalyzed hydrolysis of carboxylic esters.[8] In the rearrangement, the alcoholic hydroxyl, rather than a water molecule, acts as an electron donor to the carbonyl carbon.

A suitable mechanism for inversion, given below, assumes that complete inversion at carbon one would occur as a result of a back-side approach of carbonyl oxygen while a proton attacks the hydroxyl oxygen.[9a,b]



Inversion (*I*) mechanism

TABLE I

N-AROYL DERIVATIVES OF 1-PHENYL-2-METHYLAMINO-1-PROPANOLS, $C_6H_5CHOHCH(CH_3)N(CH_3)COC_6H_4X$

X	M. p., °C. (cor.)	$[\alpha]^{20}D$ [a]	Empirical formula	Nitrogen, % Calcd.	Found [b]
		(−)-Ephedrine series			
H	110–110.5	−54.8 [c]	$C_{17}H_{19}NO_2$		[d]
o-F	127.5	−50.6	$C_{17}H_{18}FNO_2$	4.88	4.83
o-Cl	152–152.5	−30.9	$C_{17}H_{18}ClNO_2$	4.61	4.59
o-Br	159.5–160	−21.0	$C_{17}H_{18}BrNO_2$	4.02	4.00
o-CH_3	155–155.5	−39.9	$C_{18}H_{21}NO_2$	4.94	4.91
o-OCH_3	191.5–193	−66.4	$C_{18}H_{21}NO_3$	4.68	4.56
o-NO_2	117–118	−16.5	$C_{17}H_{18}N_2O_4$	8.91	8.80
		(+)-ψ-Ephedrine series			
H	137–137.5	+135.2	$C_{17}H_{19}NO_2$	5.20	5.18
o-F	134.5	+115.6	$C_{17}H_{18}FNO_2$	4.88	4.86
o-Cl	162.5–163	+102.7	$C_{17}H_{18}ClNO_2$	4.61	4.56
o-Br	153.5	+ 90.0	$C_{17}H_{18}BrNO_2$	4.02	3.99
o-CH_3	162.5–163	+121.0	$C_{18}H_{21}NO_2$	4.94	4.92
o-OCH_3	155–156	+116.2	$C_{18}H_{21}NO_3$	4.68	4.65
o-NO_2	208–208.5	+135.5 [e]	$C_{17}H_{18}N_2O_4$	8.91	8.85

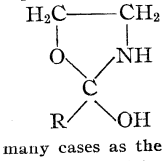
[a] Rotations are in U.S.P. chloroform, $c = 3$ (unless otherwise noted), $l = 2$. [b] Semi-micro Kjeldahl. [c] $c = 4$. [d] Chen, in a review in *J. Am. Pharm. Assoc.*, **15**, 625 (1926), has reported that this compound, m. p. 113°, has been prepared by Nagai. It does not appear to be indexed in the Western literature. [e] $c = 0.9$.

In view of the stereochemical results afforded by rearrangements of the acetylated diastereomers, one must ascribe to the ψ-ephedrine derivatives certain characteristics, inherent in the space relationships in the parent aminoalcohol, which enormously favor rearrangement with retention of configuration, while the relationships in the derivatives of ephedrine must permit rearrangement with either retention or inversion the proportion of which can be influenced relatively easily by variations in experimental conditions.

(4) In these substances the proton is probably linked to the amide oxygen: see Wheland, "The Theory of Resonance," John Wiley & Sons, Inc., New York, N. Y., 1944, p. 181.

(5) At the "Meeting in Miniature" of the Philadelphia Section of the American Chemical Society, January 23, 1948, a paper entitled "Electronic Interpretation of the *p*H-Dependent Acyl Migration in 2-Aminoethanol Systems" was presented by Dr. A. Gero to whom this writer is indebted for a copy of the manuscript. The mechanism proposed for the N → O shift in that paper will not account for rearrangement with inversion of configuration. In some respects it resembles the *R* mechanism presently proposed.

(6) Phillips and Baltzly, THIS JOURNAL, **69**, 200 (1947), have postulated the formation of a hydroxyoxazolidine, corresponding to the cyclic structures in the mechanism presented here.



(7) Retention of configuration may occur in many cases as the result of an even number of inversions as has been explained by Winstein and co-workers in a series of papers which have appeared in THIS JOURNAL since 1942 under the general title of "The Role of Neighboring Groups in Replacement Reactions." It is evident that such an explanation is not applicable to these rearrangements.

(8) Watson, "Modern Theories of Organic Chemistry," second ed., Oxford University Press, London, 1941, p. 130.

(9) (a) Frush and Isbell, *Bur. Standards J. Research*, **27**, 413 (1941), have presented a similar mechanism in explaining the formation of orthoesters, with inversion, from acetohalogen sugars in the Koenigs-Knorr reaction. (b) Fodor, Bruckner, Kiss and Óhegyi, *J. Org. Chem.*, **14**, 337 (1949), in explaining the appearance of O-benzoyl-ψ-ephedrine hydrochloride in some of their experiments on the action of ethanolic hydrogen chloride on racemic N-benzoylephedrine, have assumed that inversion results from the action of the acid on asymmetric center 1 whereby the hydroxyamide of the ψ-ephedrine configuration is formed prior to acyl migration. Such an interpretation cannot be applied to the migrations effected in this Laboratory, since the configuration of ephedrine is almost literally unaffected by the experimental conditions which effect rearrangement and inversion in its N-acyl derivatives[1]; the inversion seems clearly to be the result of a displacement reaction in which a neighboring group, in this case acylamino, participates. See Winstein, *et al.*,[7] also McCasland, Clark and Carter, THIS JOURNAL **71**, 637 (1949).

TABLE II

DATA RELATING TO REARRANGEMENTS OF COMPOUNDS OF TABLE I IN BOILING 5% HYDROCHLORIC ACID

X[a]	Total inversion, %	Time for rearr., minutes	Sample, mg.	% Hydrol.	Wt., mg.	Hydroxyamide fraction M. p., °C.	Hydroxyamide fraction $[\alpha]^{20}D$[b]	% Invers.	Total recovery, %[c]
				Ephedrine series					
H	77.2	5	651.3	3.3	629.9	.....	+ 93.6[d]	78.1	..
o-F	94.4	20	691.7	4.3	662.0	128.5–133	+106.3	94.4	98.5
o-OCH_3	94.9	60	700.0	24.6	528.0	149.5–156	+106.8	94.9	98.3
o-NO_2	97.0	35	740.4	0.9	733.4	207–207.5	+130.9[e]	97.0	99.1
o-Cl	99.3	60	732.8	4.0	703.5	162–162.5	+102.1	99.6	99.6
o-CH_3	99.9	30	681.0	1.7	669.2	162–163.5	+120.9	99.9	99.0
o-Br	98.7	90	837.7	3.6	809.2	152.5–153.5	+ 88.8	98.9	98.7
				ψ-Ephedrine series					
H	0.0	3	649.9	1.3	641.3	.....	+135.3	0.0	99.6
o-F	0.3	20	691.7	2.9	671.6	.....	+115.1	0.3	98.9
o-OCH_3	0.3	15	700.5	11.8	617.8	.....	+115.8	0.2	98.6
o-NO_2	Slight	Incomplete	...	..	...	.....	.....	..	..
o-Cl	2.6	660	730.5	23.7	557.2	160.5–162	+100.5	1.6	98.7
o-CH_3	2.4	420	682.7	10.5	611.3	.....	+118.2	1.7	99.0
o-Br	2.8	>720	841.0	12.9	732.8	151.5–153	+ 87.8	2.0	98.9

[a] As one reads down the column, the ortho substituent increases in size: the dissociation constants (K_{th}) $\times 10^5$ of the respective acids are 6.3, 54.1, 8.1, 671, 114, 12.3, 140. [b] Rotations are in U. S. P. chloroform, $c = 3$ (unless otherwise noted), $l = 2$. [c] These percentages are based on the weight of sample and the weight of the hydroxyamide fraction plus the hydroxyamide equivalent of the aminoalcohol hydrochloride fraction. [d] $c = 4$. [e] $c = 0.9$.

To obtain additional information concerning the N → O shift it was decided to investigate reactions in which migrating aroyl groups are involved. For this purpose a series of benzoyl and ortho-substituted benzoyl derivatives were prepared from the diastereomeric aminoalcohols and aroyl chlorides by the Schotten–Baumann reaction. These derivatives, along with analytical data and physical constants, are listed in Table I.

In one series of experiments, the several hydroxyamides were rearranged completely by refluxing with 5% hydrochloric acid. The aminoester salts so formed were rearranged back to hydroxyamides (a process which has not been observed to cause configurational changes[1]) by addition of alkali. Since some hydrolysis of ester salts occurs during the refluxing with acid to yield aromatic acid and parent aminoalcohol, the mixture was subjected to the separation described in the experimental part. The compositions of the hydroxyamide fractions were determined polarimetrically. The proportion of ephedrine and ψ-ephedrine in the basic fractions was determined by thermal analysis. The results of rearrangements conducted thus are summarized in Table II which also includes information on the order of size[10] of the ortho-substituents and dissociation constants[11] of the aromatic acids corresponding to the *o*-substituents.

Consideration of the results in the ephedrine series shows that the presence of an ortho-substituent on the migrating group results in a decided increase in the proportion of molecules rearranging with inversion. In addition, it is evident that among the ortho-derivatives there is no correlation between the electron displacement characteristics of the migrating groups (as measured by the K_{th} of the parent acids) and the per cent. of inversion. On the other hand, although there is a small spread (*ca.* 6%) between the maximum and minimum inversion produced, there is apparently a rough direct relationship between the size of the ortho-substituent and the extent of inversion. The effect of the ortho-substituent can be attributed to its selective steric influence on the elements of the carbonyl group[12] whereby the approach of hydroxyl oxygen to carbonyl carbon in the *R* mechanism is hindered to a much greater degree than is the approach of carbonyl oxygen to carbon one in the *I* mechanism.

From the data in Table II relating to ψ-ephedrine derivatives, one might conclude that the appearance of about 2.5% inversion in rearrangements of the CH_3, Cl and Br derivatives is a result of the proposed *I* mechanism. That the major part, if not all, of this figure is due to another type of reaction is indicated by the appearance of almost 2% inversion as a result of refluxing O-*o*-chlorobenzoyl-ψ-ephedrine hydrochloride with dilute acid for a period of time comparable to that required for rearrangement. How this inversion occurred is not obvious. It is possible that the considerably longer periods of time necessary for complete rearrangement of the CH_3, Cl and Br derivatives are due to their low solubilities or slow rates of solution in the heterogeneous system.

It is evident that the properties peculiar to the ψ-ephedrine configuration which promote rear-

(10) Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 362.

(11) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 149–152.

(12) Cohen and Schneider, THIS JOURNAL, **63**, 3382 (1941).

rangement with retention are considerably greater than the ortho-effect which tends to favor rearrangement according to an inversion mechanism.

The reaction velocity of the rearrangement of N-benzoyl-ψ-ephedrine at 30° was investigated by preparing a 95% ethanolic solution approximately 0.1 molar with respect to both hydroxyamide and hydrogen chloride, and following the progress of the reaction by measuring titrimetrically the consumption of acid after various intervals of time. By graphic means (Fig. 1) it was determined that rearrangement proceeds according to second order kinetics over the range studied (0–75%) with a velocity constant of *ca.* 8.2×10^{-1}. The velocity of

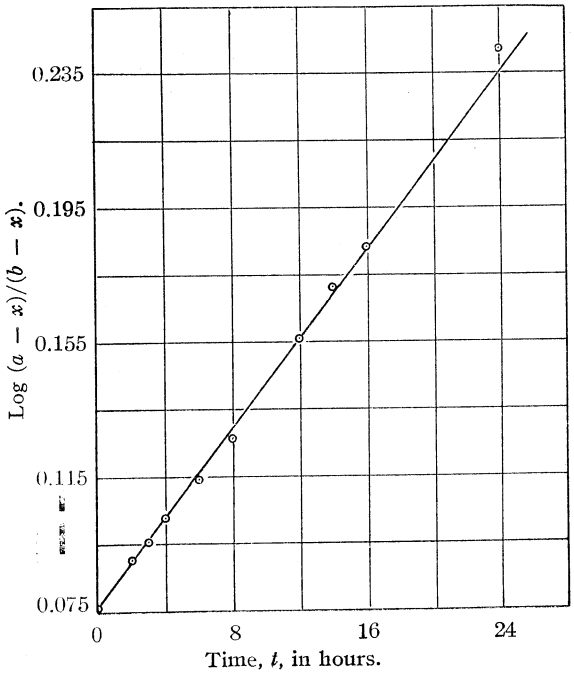


Fig. 1.—Graph showing second order reaction rate for rearrangement of N-benzoyl-(+)-ψ-ephedrine in hydrochloric acid–ethanol: *a* is initial concn. of hydrogen chloride, *b* is initial concn. of hydroxyamide, *x* is concn. of rearrangement product (all in moles per liter).

rearrangement of benzoylephedrine was followed in a similar manner. Although no attempt was made to carry out the rearrangement under controlled temperature conditions (room temperature *ca.* 30–35°) the data are suitable for a rough comparison with those afforded by the ψ-isomer at 30°. Figure 2 graphically illustrates the great difference in speeds of rearrangement of the diastereomers.[13] It was determined that rearrangement proceeds under these conditions with predominant retention of configuration (8–23% inversion).

(13) It is noted that Bruckner, Fodor, Kiss and Kovács, *J. Chem. Soc.*, 885 (1948), report that in the diastereomeric derivatives prepared by them the N → O migration of the acyl group is instantaneous in the nor-ψ-ephedrine compound and does not occur at all in the norephedrine derivative under the same conditions.

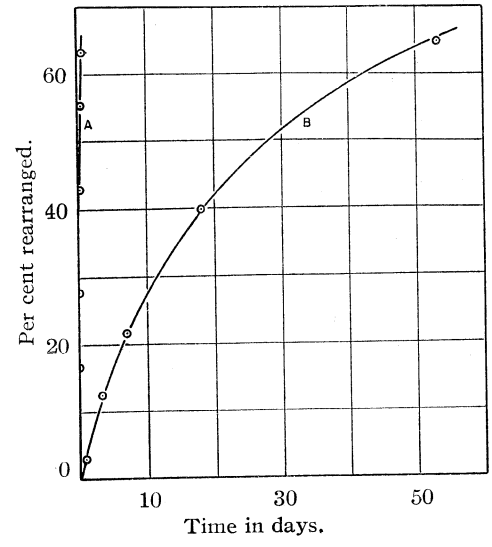


Fig. 2.—Comparison of rearrangement rates of diastereomers in 0.115 *N* ethanolic hydrochloric acid: A, benzoyl-ψ-ephedrine at 30°; B, benzoylephedrine at *ca.* 32°.

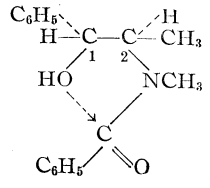
It is not a simple matter to explain the great[14] difference in the velocities of rearrangement of the diastereomers according to a retention mechanism. One would naturally expect the diastereomer having the more basic amide group to show the more rapid reaction rate; if, as has been reported,[15] ψ-ephedrine has about twice the base strength of ephedrine, and this ratio is retained in the amides, then benzoyl-ψ-ephedrine should rearrange at a greater rate than does its diastereomer.

This consideration is believed to be of secondary importance. The major factor responsible for the great difference in rates is attributed to differences in the spatial arrangements of the groups in the diastereomers.[16] Projection formula III, corresponding to structure A of the *R* mechanism, depicts a molecule of benzoyl-ψ-ephedrine at the instant the hydroxyl oxygen and carbonyl carbon atoms are closest to each other prior to actual migration. Formula IV illustrates the same situation in the diastereomer. The two embryonic ring systems are in the plane of the paper and the substituents on carbons 1 and 2 and not in the ring are above this plane where connected to solid lines and below the plane where joined to broken lines. It may be seen that a *trans* relationship exists in

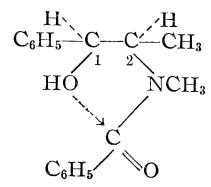
(14) The ratio is of the order of 70:1 if one compares the time required for 50% rearrangement.

(15) Abildgaard and Baggesgaard-Rasmussen, *Dansk. Tids. Farm*, **4**, 30 (1930).

(16) Fodor, *et al.*,[9b] have assumed that for an N → O rearrangement to occur the hydroxyl and methylamido groups must have a *cis* relationship, and that as a result of restricted rotation about the bond between carbons 1 and 2 such a relationship exists in compounds having the ψ-ephedrine configuration, whereas a *trans* relationship of these two groups exists in substances having the configuration of ephedrine. Their conception of restricted rotation obviously is not related to observations on molecular models which correspond to the projection formulas of Leithe and of Freudenberg, *et al.*[3] See also Fodor and Kiss, *Nature*, **163**, 287 (1949).



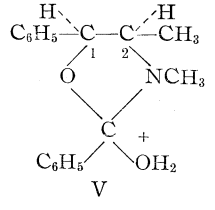
III



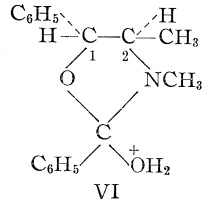
IV

the ψ-ephedrine derivative and a *cis* relationship in the diastereomer. Since a *trans* configuration should be the more equable arrangement of groups under these conditions the ψ-ephedrine configuration might be expected to augment the efforts of the hydroxyl oxygen to approach the carbon atom of the protonated amide group and thus facilitate rearrangement with retention, whereas in the ephedrine series the opposite situation would exist.

In the ψ-ephedrine series, the *R* mechanism would compete with an inversion mechanism in which, by virtue of the displacement occurring at carbon 1, the hydrogen atom and phenyl group must be forced into an orientation which establishes the *cis* relationship shown in formula V which corresponds to cyclic intermediate F in the representation of the *I* mechanism. The virtual absence of inversion in the ψ-ephedrine series may



V

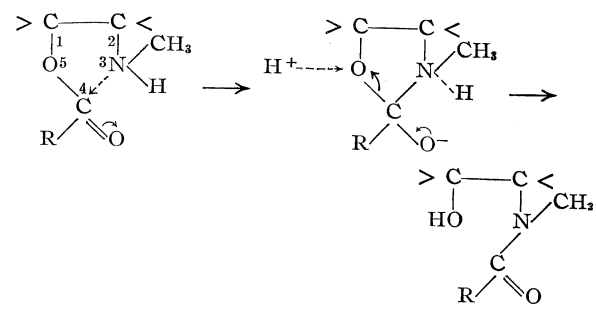


VI

be attributed to the circumstance that the energy required for this phase of the *I* mechanism is relatively high, and that the process must compete with a retention mechanism which is highly favored for reasons previously discussed.

In the ephedrine series, the inversion mechanism requires that a *trans* relationship be established in the intermediate represented by VI and corresponding to F. The displacement leading to this intermediate should be more readily achieved than that which would occur in the ψ-ephedrine series and lead to a *cis* configuration. In the ephedrine series the *I* process is competing with a retention mechanism which is not highly favored according to conclusions which have been presented. If, on this basis, it may be assumed that the two processes do not have widely differing over-all energy requirements, the observed ability of ephedrine derivatives to rearrange with either retention or inversion appears rational.

No additional study has been made in this Laboratory on the influence of various factors on the O → N shift, and no attempt will be made here to correlate the behavior of the numerous esters of aminoalcohols which have been described in the literature and which contain primary or secondary amino groups. This shift, which is not associated with inversion, could occur by the mechanism



The donation of a proton to atom 5 might take place from atom 3 of the same molecule or an adjacent rearranging molecule. In aqueous solution the donation might result from a solvent molecule. The fact that O-acetyl-ψ-ephedrine rearranges at a considerably greater speed than does its diastereomer[1] is attributed to the same factors which have been discussed in connection with the reverse migration.

Investigation of the N → O rearrangement is being continued.

Experimental

Melting points are corrected.

Sources of Aroyl Chlorides.—Benzoyl and *o*-chlorobenzoyl chlorides were obtained from Eastman Kodak Co. The five other halides were prepared from the corresponding ortho-substituted acids and thionyl chloride, and, with the exception of the nitro compound,[17] were purified by vacuum distillation.

o-Fluorobenzoic acid was prepared in 66% yield by substituting the stoichiometric amount of Eastman Kodak Co. *o*-fluorotoluene for *o*-chlorotoluene in the method of preparation of *o*-chlorobenzoic acid described by Clark and Taylor.[18] The *o*-nitrobenzoic acid[19] was Kahlbaum material, and the remainder of the acids were products of the Eastman Kodak Co.

Preparation of the Hydroxyamides.—The aminoalcohol (1.65 g., 10.0 millimoles) was dissolved in 10 cc. of chloroform and acylated by the Schotten–Baumann method with 4 cc. of 20% sodium hydroxide and a solution of 10.0–10.5 millimoles of aroyl halide in 4 cc. of chloroform. The products obtained on removing the solvent were triturated with petroleum ether and filtered off; yields of crude were practically quantitative; twice-recrystallized material averaged 82% of the theoretical. Chlorobenzoyl-ψ-ephedrine was recrystallized from ethylene dichloride. The nitrobenzoyl derivative of the same configuration was dissolved in hot pyridine and precipitated by adding propanol-2. Crude nitrobenzoylephedrine was purified best by dissolving in 10 cc. of hot trichloroethylene and adding 5 cc. of petroleum ether. The rest of the derivatives were first recrystallized by dissolving in hot 95% ethanol (10 cc. was usually used), slowly adding an equal volume of water, and finally chilling the mixture. The derivatives in this group, with the exception of methoxybenzoylephedrine, were given a second recrystallization in which benzene (10–35 cc.) and an equal volume of petroleum ether was used. Methoxybenzoylephedrine is but slightly soluble in benzene, and was therefore recrystallized a second time from ethanol–water.

Rearrangement of Hydroxyamides by Refluxing with Dilute Hydrochloric Acid (Table II).—A sample of the hydroxyamide (2.338–2.415 millimoles) was placed in a 50-cc. standard taper round-bottom flask containing a few

(17) Böetius and Römisch, *Ber.*, **68**, 1924 (1935).

(18) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 135.

(19) Kindly supplied by Mr. Theodore Perrine of the National Institute of Health.

small pieces of carborundum and 5 cc. of water. The mixture was heated under reflux until it gently boiled, then through the condenser 5 cc. of 10% hydrochloric acid (13.7 millimoles) was added from a pipet at such a speed that boiling was not interrupted.[20] The mixture was refluxed until all insoluble matter had disappeared. The time required varied with the hydroxyamide; those which required only a few minutes to form a homogeneous system were refluxed an additional five minutes to ensure complete reaction, whereas the more refractory compounds were refluxed from ten to twenty minutes after solution was complete. Occasionally the ester hydrochlorides crystallized out when rearrangement mixtures were allowed to stand overnight. The condenser and its tip were rinsed with a small amount of water, as was the neck of the flask, and the reaction mixture plus rinsings was made alkaline by adding 3.5 cc. of 20% sodium hydroxide. The heavy oil which precipitated was induced to solidify, and the solid masses were reduced to a coarse powder. The alkaline mixture was allowed to stand at least one hour to ensure that the O → N shift was complete, and was then quantitatively transferred to a separatory funnel by the use of water and U. S. P. chloroform. The system was acidified by the addition of 1.5 cc. of sulfuric acid (50% by weight) and immediately shaken. The separated chloroform layer was washed by shaking with 3 cc. of water in a second separator, and aromatic acid was extracted from the solvent by a subsequent shake-out with 10 cc. of 5% sodium hydroxide in a third funnel. The extract was then filtered through a pledget of cotton wool into a beaker, and the aqueous phases in the three funnels were extracted with an additional five 15- to 20-cc. portions of chloroform which were passed through the train of separators. The combined, filtered chloroform extracts were concentrated to a small volume, transferred to a tared 50-cc. beaker, and evaporated to dryness on the steam-bath in a current of air. Addition of a small quantity of ether to the hydroxyamide residue facilitated the crystallization of any amorphous areas present, and, after removal of this solvent, the vessel was heated one-half hour at 110°, cooled in a desiccator, and weighed. The difference between the weights of sample and recovered hydroxyamide represented the amount of material hydrolyzed. The melting point and specific rotation of the residue were determined.

The aminoalcohol fraction was isolated as the hydrochloride from the aqueous phases in the first and second funnels by a method described elsewhere.[21] After purification by treatment with small amounts of ethylene dichloride–ether, the melting range of the mixture of salts was determined, and the composition was estimated by referring to a temperature–composition diagram. As may be seen in Table II, it was necessary to apply but a slight correction to the inversion found in the hydroxyamide fraction in order to obtain the value for total inversion.

It was not practicable to completely rearrange N-*o*-nitrobenzoyl-ψ-ephedrine under conditions similar to those used on the other compounds probably because of its solubility characteristics. A 370-mg. (1.18 millimoles) sample was refluxed for six hours with about 20 cc. of 5% hydrochloric acid. The unrearranged material was filtered off, and the filtrate was worked up as in the other rearrangements. A hydroxyamide fraction of 43 mg., corresponding to 12% of the sample, was obtained. The melting point (204–205.5°) indicated the presence of a small amount of inverted material.

Originally it was planned to evaluate the stereochemical results of these rearrangements by the procedure used on the acetyl compounds,[1] *i. e.*, after completion of the N → O shift, to effect complete acid hydrolysis of the products by continued refluxing, and determine the composition of the aminoalcohol mixture so obtained. Acid hydrolysis of the mixture of benzoyl ester salts was found to proceed very slowly, however. It was practicable to convert the mixed benzoyl ester salts to hydroxyamides, quantitatively hydrolyze the latter in a 10% solution of sodium hydroxide in 50% ethanol, extract out the mixed aminoalcohols, and ascertain the proportion of inverted material in the mixture of hydrochlorides ultimately obtained. The total inversion figure corresponding to benzoylephedrine in Table II was thus determined; the mixture of hydrochlorides of ephedrine and ψ-ephedrine amounted to 99.1%. Efforts to use alkaline hydrolysis on the *o*-chlorobenzoyl derivatives showed that the substances are resistant to cleavage under these conditions, and no attempts were made to apply the procedure to other ortho-compounds.

Kinetics of Rearrangement of N-Benzoyl-ψ-ephedrine (Fig. 1).—In a 100-cc. volumetric flask was placed 2.598 g. (0.00965 mole) of N-benzoyl-(+)-ψ-ephedrine and 47 cc. of 95% ethanol. After the solid had dissolved, the flask was placed in a constant temperature bath maintained at 29.9 ± 0.2°. After equilibration, 50 cc. of a solution of concentrated hydrochloric acid in 95% ethanol (0.2301 *N* at 30° with respect to hydrogen chloride) was quickly transferred to the flask from another vessel in the bath by means of a pipet; timing of the reaction was started at the beginning of the addition. The mixture was brought up to volume by adding the necessary small amount of ethanol, and was made homogeneous by thorough agitation. As the reaction progressed, 10-cc. aliquots of the solution were pipetted out and transferred to a beaker containing 100 cc. of water which was agitated by a motor-driven stirrer. The time of beginning of addition of the aliquot to the water was taken as the end of a given reaction period. The unconsumed acid in the aqueous dilution was determined by adding standardized 0.1 *N* sodium hydroxide, dropwise and with vigorous stirring, to a methyl red end-point. From these data the concentration of rearrangement product, x, present after each reaction period was calculated. From the figures so obtained for x, and the initial concentration of acid (a, 0.1151 *M*) and of hydroxyamide (b, 0.0965 *M*), the values of the various expressions, $\log a - x/b - x$, were obtained and plotted against the appropriate reaction periods, t (Fig. 1). The best straight line based on the plot corresponded to the equation, $\log (a - x)/(b - x) = 0.006593\ t + 0.0766$, and an average reaction velocity constant of 8.16×10^{-1}. The volume of 0.1 *N* acid theoretically consumed after each reaction period was calculated by use of the equation and may be compared with the experimentally determined consumption in the following sequence in which the first figure is the reaction period in hours and the parenthetical figure is the calculated consumption of acid in cc.: 2, 1.62 (1.55); 3, 2.13 (2.16); 4, 2.68 (2.70); 6, 3.49 (3.58); 8, 4.14 (4.29); 12, 5.34 (5.34); 14, 5.81 (5.74); 16, 6.11 (6.08); 24, 7.16 (7.06). All of the deviations, with the possible exception of that corresponding to the eight-hour period (0.15 cc.), are considered to be within the experimental error of the titrations. The sum of the deviations in the nine determinations equals −0.02 cc.

(20) These are the reaction conditions referred to in footnote (2).

(21) Welsh, *J. Assoc. Official Agric. Chem.*, **30**, 467 (1947); **31**, 528 (1948).

Velocity of Rearrangement of N-Benzoylephedrine.—The progress of the rearrangement of N-benzoyl-(−)-ephedrine was experimentally followed as described above except as regards control of temperature. Facilities were not available for maintaining a regulated temperature over extended periods of time, and the reaction was allowed to proceed at the prevailing temperature of summer heat (within the approximate range of 30–35° and an average of *ca.* 32°). The consumption of acid was calculated in terms of percentage of rearrangement and the results are plotted against time in curve B, Fig. 2. Progress of the rearrangement of N-benzoyl-(+)-ψ-ephedrine is similarly plotted in curve A, Fig. 2.

A 10-cc. aliquot, representing a reaction period of fifty-three and one-third days, was used to determine the stereochemical course of rearrangement of the ephedrine derivative. Titration showed that 168 mg. (64.8%) had rearranged. The titrated solution was taken to dryness at room temperature and dried in a desiccator. The bulk of the residue was transferred to a test-tube, and the remainder was removed by the use of water and a rubber policeman. The rinsings, totaling about 15 cc., were added to the dry material, and the mixture was allowed to stand, with frequent stirring, for one-half hour. It was then filtered, and the undissolved hydroxyamide was washed with an additional 7–8 cc. of water. This fraction of unrearranged material weighed 66 mg., or 25.4% of the sample. The filtrate and washings were acidified with a few drops of hydrochloric acid, and the dissolved unrearranged hydroxyamide was extracted with small portions of ethylene dichloride. The residue of unrearranged benzoylephedrine obtained from the filtered extracts weighed 32.1 mg. (12.3% of the sample). The acidic solution containing aminoester salts was basified with 20% sodium hydroxide (to bring about the O → N shift), allowed to stand one hour, acidified with 50% sulfuric acid, and extracted with chloroform. Each extract was washed with alkali before filtering. The residue of hydroxyamides, representing material which had originally undergone the N → O shift, weighed 143.4 mg., equivalent to 55.2% of the sample or 85.2% of the weight calculated from the titration. It showed $[\alpha]^{20}D$ −31.1° (U. S. P. chloroform, c = 1.2, l = 2) which corresponds to a mixture of diastereomers containing 9.3% of the ψ-ephedrine derivative. The difference between the rearranged material isolated and that calculated from the titration is 24.9 mg., and represents substance lost in one way or another during the various operations. If it represents uninverted hydroxyamide, the minimum inversion produced corresponds to 8% of the rearranged material. If it represents inverted material, the maximum inversion produced is 23%.

O-*o*-Chlorobenzoyl-(+)-ψ-ephedrine Hydrochloride.—This substance was prepared by refluxing *o*-chlorobenzoyl-(−)-ephedrine with 5% hydrochloric acid. The crude product from the chilled reaction mixture was recrystallized from ethyl acetate; the yield of rectangular plates was 83%. The substance is a monohydrate: m. p. (hot stage) 80–85° followed by resolidification and remelting at 131–132°; $[\alpha]^{20}D$ +57.1° (water, c = 3, l = 2).

Anal. Calcd. for $C_{17}H_{18}ClNO_2 \cdot HCl \cdot H_2O$: Cl (ionic), 9.90. Found: Cl (ionic), 9.79.

On undergoing the O → N shift the salt quantitatively yielded the related hydroxyamide, m. p. 162–163°.

A sample was refluxed for six hours with 4.5% hydrochloric acid. Processing the mixture gave a hydroxyamide fraction of 76.9% of the sample weight; $[\alpha]^{20}D$ +101.0° (U. S. P. chloroform, c = 3, l = 2) corresponding to 1.3% inversion in the fraction. The fraction of aminoalcohol hydrochlorides, m. p. 178–182°, was equivalent to 21.3% of the sample; $[\alpha]^{20}D$ + 57.8° (water, c = 0.9, l = 2) representing 4.1% inversion in the fraction. The maximum inversion effected by the hot acid on the ester salt therefore totaled 1.9%.

Acknowledgment.—The author wishes to express his thanks to Dr. G. Forrest Woods of the University of Maryland for his encouraging interest in this work. Helpful discussion with Dr. H. S. Isbell of the National Bureau of Standards also is gratefully acknowledged.

Summary

1. Reaction mechanisms have been proposed to account for the inversion and retention of configuration observed during acyl migrations between nitrogen and oxygen in derivatives of ephedrine and ψ-ephedrine.

2. A series of benzoyl and *o*-substituted benzoyl derivatives of these aminoalcohols has been prepared and subjected to the N → O rearrangement under different conditions. The stereochemical results of the rearrangements have been discussed in terms of the properties of the migrating radicals and the proposed mechanisms.

3. The consistent retention of configuration observed in rearrangements in the ψ-ephedrine series and the ability of ephedrine derivatives to rearrange with either retention or inversion have been interpreted in the light of the different space relationships existing in the diastereomers and on the basis of the proposed mechanisms.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Trifluoromethylated Quinolines

BY ARAM MOORADIAN AND C. M. SUTER

In connection with the study of the antimalarial activity of 7-halo-4-aminoquinolines it seemed of interest to prepare a number of 7-trifluoromethyl-4-dialkylaminoalkylaminoquinolines to determine the effect of replacing the 7-halogen with a trifluoromethyl group. Similar work is described in the patent literature[1] and in a more recent paper[2] wherein 4-(4-diethylamino-1-methylbutylamino)-7-trifluoromethylquinoline and its intermediates are prepared. The present communication describes the preparation and proof of structure for a group of 3-methylquinolines having the trifluoromethyl substituent in the 5- or 7-position and in addition the preparation of 4-(3-diethylamino-2-hydroxypropylamino) - 7 - trifluoromethylquinoline. Furthermore it was confirmed by oxidation of the 4-hydroxy-3-carboxy intermediate to 2-amino-4-trifluoromethylbenzoic acid which was then deaminated to 4-trifluoromethylbenzoic acid, that the trifluoromethyl group is in the 7-position in the compound previously described (I).[1,2] This end-product is a new compound; but since it must be either the 2- or 4-trifluoromethylbenzoic acid, it has been assigned the latter structure, not being similar to the ortho derivative, a previously well characterized compound.[3] Finally the 3-methyl substituted derivatives were prepared by condensing *m*-trifluoromethylaniline with diethyl oxalpropionate and cyclizing the anil to a mixture of 5 and 7-trifluoromethyl-3-methyl substituted quinolines. The compound formed predominantly was the 7-trifluoroquinoline; this was proved by permanganate oxidation to give the 2-amino-4-trifluoromethylbenzoic acid also obtained by oxidation of (I). The structure of the 5-trifluoromethyl derivatives were inferred.

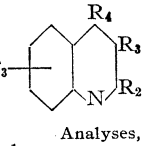
Experimental

4-(4-Diethylamino-1-methylbutylamino)-7-trifluoromethylquinoline (I).—The intermediates used were prepared essentially as described by Snyder.[1] Our poorer yield in the cyclization reaction may be ascribed to the use of mineral oil as a cyclization medium. A mixture of 22.5 g. (1.0 mol) of 4-chloro-7-trifluoromethylquinoline and 31 g. (2.0 mols) of 1-diethylamino-4-aminopentane was heated with stirring for sixteen hours at 150–160°. The reaction mixture was then diluted with four times the theoretically necessary amount of 50% acetic acid. Finally 35% sodium hydroxide solution was added with cooling till the reaction mixture was basic to litmus. The product was extracted thoroughly with a large amount of ether. The ether was evaporated and the residue distilled under high vacuum. Yield was 27.9 g., b. p. 148–154° at 0.01 micron. This sirup soon crystallized to give a non-hygroscopic solid, m. p. 81–83° after trituration with cold Skellysolve A (b. p. 28–38°).

4-(3-Diethylamino-2-hydroxypropylamino)-7-trifluoromethylquinoline (II).—A mixture of 27.4 g. (2 mols) of 3-diethylamino-2-hydroxypropylamine and 21.7 g. (1 mol) of 4-chloro-7-trifluoromethylquinoline was heated on an oil-bath to 140°. At this point heating was stopped but the temperature rose rapidly to 175°. After the temperature had dropped back to 150°, the reaction mixture was kept here for one hour more. The work up was similar to that described with (I). The product distilled at 150° under a pressure of 0.05 micron. The distillate crystallized. It was triturated under Skellysolve A and dried; yield 28.2 g., m. p. 128–129°.

TABLE I

5/7 SUBSTITUTED TRIFLUOROMETHYLQUINOLINE DERIVATIVES



R_2	R_3	R_4	Position of CF_3	Yield, %	M. p., °C.	Molecular formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	$COOC_2H_5$	OH	7	54	>300	$C_{13}H_{10}F_3NO_3$			4.91			4.69
H	COOH	OH	7	100	250–251	$C_{11}H_6F_3NO_3$			5.45			5.27
H	H	OH	7	88	266–268	$C_{10}H_6F_3NO$			6.57			6.46
H	H	Cl	7	93	70–71	$C_{10}H_5ClF_3N$			6.05			5.89
H	H	[a]	7	86	128–129	$C_{17}H_{22}F_3N_3O$	59.81	6.48	12.31	59.79	6.41	12.13
H	H	[b]	7	91	81–83	$C_{19}H_{26}F_3N_3$	64.57	7.43	11.89	64.90	7.31	11.82
$COOC_2H_5$	CH_3	OH	7	46	216–217	$C_{14}H_{12}F_3NO_3$			4.70			4.67
COOH	CH_3	OH	7	100	238–240	$C_{12}H_8F_3NO_3$			5.17			4.95
H	CH_3	OH	7	98	>300	$C_{11}H_8F_3NO$			6.16			6.17
H	CH_3	Cl	7	92	64.5–66.5	$C_{11}H_7ClF_3N$			5.70			5.54
H	CH_3	[a]	7	62	103.5–105.5	$C_{18}H_{24}F_3N_3O$	60.83	6.81	11.82	60.83	6.67	11.78
H	CH_3	[b]	7	24	Oil[c]	$C_{20}H_{28}F_3N_3$	65.36	7.70	11.43	65.10	7.65	11.23
$COOC_2H_5$	CH_3	OH	5	11	207–209	$C_{14}H_{12}F_3NO_3$			4.70			4.63
COOH	CH	OH	5	100	>300	$C_{12}H_8F_3NO_3$			5.17			5.26
H	CH_3	OH	5	97	>300	$C_{11}H_8F_3NO$			6.16			6.08
H	CH_3	Cl	5	92	102–102.5	$C_{11}H_7ClF_3N$	Cl 14.45		5.70	Cl 14.05		6.00
H	CH_3	[a]	5	42	Oil[d]	$C_{18}H_{24}F_3N_3O$	60.83	6.81	11.82	60.45	6.34	11.72

[a] 3-Diethylamino-2-hydroxypropylamino. [b] 4-Diethylamino-1-methylbutylamino. [c] $n^{25}D$ 1.5328. [d] $n^{25}D$ 1.5522.

(1) Andersag, Breitner and Jung, German Patent 683,692 (1939); *C. A.*, **36**, 4973 (1942).

(2) Snyder, Freier, Kovacic and Van Heyningen, THIS JOURNAL, **69**, 371 (1947).

(3) de Brouwer, *Bull. soc. chim. Belg.*, **39**, 298 (1930).

Ethyl 7- and 5-Trifluoromethyl-4-hydroxy-3-methyl-2-quinoline Carboxylates.—To 100 g. (1 mol) of *m*-aminobenzotrifluoride was added 138 g. (1 mol) of diethyloxalpropionate at room temperature. Some heat was evolved. The reaction mixture was kept three days at 40°. It was then washed with 0.5 *N* hydrochloric acid, 0.5 *N* sodium hydroxide solution and finally with water. A yield of 160 g. of red oil which showed some signs of crystallizing resulted. This oil was added over a period of about twenty minutes to 550 cc. of diphenyl ether kept at 260–265° and heating was continued with stirring till no more alcohol was evolved. The reaction mixture was then allowed to cool and the product was filtered off, washed with Skellysolve A and dried; yield 109.5 g., m. p. 172–184°.

The mixture was dissolved in 600 cc. of hot 95% ethanol and cooled. From the alcohol there resulted 87 g., m. p. 199–206°, which upon recrystallization gave 63 g., m. p. 216–217°. Another crystallization did not affect this melting point. This was pure ethyl 4-hydroxy-3-methyl-7-trifluoromethyl-2-quinoline carboxylate.

The alcoholic liquors were diluted with water and the precipitated product filtered and dried. The product was dissolved in 200 cc. of glacial acetic acid and the solution saturated with hydrogen chloride and cooled. This precipitated 16.5 g. of impure 7-isomer. The acetic acid solution was diluted with water and the precipitate filtered and dried to give 23.1 g. of material, melting point 197–201°. After repeated crystallization from toluene 13.3 g. of ethyl 4-hydroxy-3-methyl-5-trifluoromethyl-2-quinoline carboxylate, m. p. 207–209° resulted. A mixed melting point with the 7-isomer gave a 30° depression.

4-(3-Diethylamino-2-hydroxypropylamino)-3-methyl-7-trifluoromethylquinoline (III).—Using the standard procedures of hydrolysis, decarboxylation and chlorination, 4-chloro-3-methyl-7-trifluoromethylquinoline was prepared, and heated with two moles of 3-diethylamino-2-hydroxypropylamine at 150–170° for five hours. The reaction mixture was taken up in 40% acetic acid and brought to a *p*H of 8 with sodium hydroxide. Extraction of this solution with ether gave 28 g. of a solid, m. p. 98–150° after evaporation of the ether. This solid was distilled under a high vacuum and then crystallized from dilute dioxane giving 22.2 g. of product, m. p. 103.5–105.5°.

4-(4-Diethylamino-1-methylbutylamino)-3-methyl-7-trifluoromethylquinoline.—A mixture of 24.5 g. (1 mol) of 4-chloro-3-methyl-7-trifluoromethylquinoline and 31.6 g. (2 mols) of 4-diethylamino-1-methylbutylamine was heated to 160–170° and kept at this temperature for forty-five hours. The reaction mixture was then made alkaline with sodium hydroxide and extracted with ether. Distillation of the ether extract gave 11.0 g. of unreacted chloride and 8.7 g. of product, b. p. 135–140° at two microns, $n^{25}D$ 1.5328.

4-(3-Diethylamino-2-hydroxypropylamino)-3-methyl-5-trifluoromethylquinoline.—The 5-isomer was worked through in a similar manner and the 5-analog of III was prepared. This time the chloride and the base had to be heated together for twenty hours. From 18.3 g. of 4-chloro-3-methyl-5-trifluoromethylquinoline, 11.3 g. of 4-(3-diethylamino-2-hydroxypropylamino)-3-methyl-5-trifluoromethylquinoline resulted as an oil, b. p. 130–135° at 0.1 micron, $n^{25}D$ 1.5522.

2-Amino-4-trifluoromethylbenzoic Acid.—Eleven and four-tenths grams (1 mol) of 4-hydroxy-3-methyl-7-trifluoromethylquinoline was dissolved in 600 cc. of water containing 5 g. of potassium hydroxide at 80°. To this was added a solution of 31.6 g. (4 mols) of potassium permanganate in 800 cc. of water at 65°. The solution was stirred for thirty minutes and then decolorizing charcoal was added and stirring continued for five minutes more. The reaction mixture was filtered through filter-cel and evaporated to 200 cc. This was then made acid to congo with hydrochloric acid to give a product which was filtered off. This product was refluxed with 20 cc. of concentrated hydrochloric acid and 60 cc. of water for three hours and again filtered. The filtrate was acidified with acetic acid and the precipitated product filtered and dried in a desiccator. Recrystallization from benzene gave a product, m. p. 172–174°.

Anal. Calcd. for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.83; H, 3.40; N, 6.78.

Similarly in the series where the 3-methyl group was lacking 3-carboxy-2-hydroxy-7-trifluoromethylquinoline was oxidized to an acid, m. p. 172–174°, mixed m. p. 172–174°.

4-Trifluoromethylbenzoic Acid.—To a solution of 0.35 g. (1 mol) of sodium nitrite and 0.6 cc. of 35% sodium hydroxide in 10 cc. of water was added 1.06 g. (1 mol) of 2-amino-4-trifluoromethylbenzoic acid. The resulting solution was then added to 2.5 cc. of concentrated hydrochloric acid and 5 g. of ice. This diazo solution was allowed to stand ten minutes and then poured slowly into 7.5 cc. of 95% alcohol containing a small amount of copper sulfate. Soon the reaction mixture became cloudy and crystals were deposited. These were filtered off, dissolved in sodium hydroxide solution, treated with charcoal, and the filtered solution acidified, to precipitate the product which was filtered and dried in vacuum desiccator, m. p. 219–220°.

Anal. Calcd. for $C_8H_5F_3O_2$: C, 50.84; H, 2.65. Found: C, 50.63; H, 2.68.

Summary

A series of 5- and 7-trifluoromethylquinolines have been prepared and their structures proved.

RENSSELAER, NEW YORK RECEIVED MAY 27, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

2-Methylcellulose[1]

BY J. M. SUGIHARA[2] AND M. L. WOLFROM

The selective substitution of the hydroxyl group on carbon-2 of carbohydrates has been accomplished by the preparation of 2-methyl-starch by Gaver,[3] of 2-methyl-D-glucose diethyl mercaptal by Lieser,[4] and of 2-methyl-D-glucose and 3-methyl-D-glucose, as derivatives, from a partially methylated cellulose by Heddle and Percival.[5] Lieser[6] has described a methylated cellulose, containing approximately one methoxyl group per two anhydro-D-glucose units, that on hydrolysis yielded 2-methyl-D-glucose, isolated as its phenylhydrazone. Since certain cellulose derivatives of known structure were desired in this Laboratory, the general method described by Gaver[3] was applied to the preparation of a 2-methylcellulose.

It is a commonly accepted fact that hydroxyl groups on carbon atoms α to carbonyl groups are acidic. In the cellulose molecule the hydroxyl group on carbon-2 might be expected to be a stronger acid than the other hydroxyl groups. The reaction of cellulose in an activated form with sodium hydroxide in a near anhydrous medium appeared to justify this assumption. One to 1.2 equivalents of base could be introduced for each anhydro-D-glucose unit. The amount in excess of one was undoubtedly base, not removed by washing and still adsorbed on the cellulose. This appeared probable since the alkali content of those preparations containing more than one equivalent of base per anhydro-D-glucose unit could be reduced to one by suspending at room temperature, the alkali cellulose in anhydrous acetone containing acetyl chloride.

The reaction of the alkali cellulose with methyl iodide occurred with no difficulty. The color of the former, which varied from a light buff to a yellow brown, was in every case removed upon methylation to form colorless, fibrous 2-methylcellulose. The latter had considerable water solubility. This product followed the trend of other methylcelluloses in being less water-soluble at a higher temperature with solubility increasing as the solution was cooled.[7]

To determine the degree of degradation which occurred in the formation of 2-methylcellulose, the cotton linters, the activated cellulose and 2-methylcellulose were nitrated and viscosities were determined by the method of Berl.[8] The calculated degrees of polymerization for the cotton linters, activated cellulose and 2-methylcellulose were 1680, 570 and 88, respectively. The figures are primarily of comparative significance. The nitrate exhibited good film-forming properties.

The structure of 2-methylcellulose was clarified using a degradative procedure. The polymer was methanolyzed in the usual fashion. The methyl D-glucoside mixture obtained was hydrolyzed by acid, and the resultant sugar was converted into the diethyl thioacetal. Crystalline 2-methyl-D-glucose diethyl thioacetal was isolated by a chromatographic technique. No other crystalline compounds were isolable. Control experiments demonstrated that it was possible to detect and to separate small quantities of D-glucose diethyl thioacetal had such been present. Since the methoxyl content of the methylcellulose was 1.03 groups per anhydro-D-glucose unit and since no D-glucose diethyl thioacetal was obtained, the contribution of dimethyl derivatives would not be significant. Therefore, we believe that the cellulose was in all probability uniformly methylated with the methyl group located mainly on C-2 of each anhydro-D-glucose unit.

Experimental

Sodium 2-Cellulosate.—Twenty grams of cotton linters (defatted and bleached) was dissolved in 600 ml. of cuprammonium hydroxide[9] and was regenerated by pouring the viscous solution into 1.5 liters of 6 *N* sulfuric acid. The activated cellulose was filtered and was washed thoroughly with water; yield 192 g. (wet). The water in 96 g. of the wet fibers was replaced by butanol-1. This was accomplished by vigorously stirring the heated suspension while distilling the water–butanol-1 azeotrope, at atmospheric pressure, through a 30-cm. Vigreux column. A solution of 20 g. (8 equivs. per anhydro-D-glucose unit) of sodium hydroxide in 30 ml. of water was added and distillation was continued to remove the additional water. When the temperature at the top of the column reached 100°, distillation was continued for three hours at a rate sufficient to remove any additional water present or formed in the reaction. The alkali cellulose formed was filtered and washed thoroughly with absolute ethanol; yield 10.9 g. (dried in vacuum desiccator over anhydrous calcium chloride).

Anal. Na, 1.08 equivs. per anhydro-D-glucose unit (detd. by suspension in excess standard acid followed by titration with standard base to phenolphthalein endpoint).

2-Methylcellulose.—A suspension of 9.82 g. of the alkali cellulose and 20 ml. of methyl iodide was placed in a bomb tube and heated at 100° for two and one-half hours. The methylated product was treated with sodium hydroxide again as previously described; yield 7.30 g. (dried in vacuum desiccator over anhydrous calcium chloride).

Anal. Na, 0.31 equiv. per anhydro-D-glucose unit (by titer).

An amount of 7.00 g. of the above material was remethylated in a bomb tube with 20 ml. of methyl iodide at 100° for two and one-half hours. The product was

(1) A preliminary communication on this work has appeared in *Abstracts Papers Am. Chem. Soc.*, **115**, 23Q (1949).

(2) Research Associate of The Ohio State University Research Foundation (Project 313).

(3) K. M. Gaver, U. S. Patent 2,397,732 (Apr. 2, 1946); Ph.D. Dissertation, The Ohio State University, 1945.

(4) T. Lieser and E. Leckzyck, *Ann.*, **511**, 137 (1934).

(5) W. J. Heddle and E. G. V. Percival, *J. Chem. Soc.*, 249 (1939).

(6) T. Lieser, *Ann.*, **470**, 104 (1929).

(7) J. F. Haskins, *Advances in Carbohydrate Chem.*, **2**, 291 (1946).

(8) E. Berl, *Ind. Eng. Chem., Anal. Ed.*, **13**, 322 (1941).

(9) R. A. Joyner, *J. Chem. Soc.*, **121**, 1912 (1922).

thoroughly washed with acetone and dried (over phosphoric anhydride at 78° *in vacuo*); yield 6.31 g. The fibrous substance showed a significant and reverse solubility in water; it was insoluble in methanol, acetone and chloroform but exhibited some solubility in pyridine.

Anal. Calcd. for $(C_6H_9O_4\text{-}OCH_3)_x$: OCH_3, 17.61. Found: OCH_3, 18.13; Na, 0.04 equiv. per anhydro-D-glucose unit (by titer).

Hydrolysis of 2-Methylcellulose to 2-Methyl-D-glucose Diethyl Thioacetal.—Following the general methanolysis procedure of Irvine and Hirst,[10] 2.3 g. of 2-methylcellulose was methanolyzed for sixty hours at 130° with 50 ml. of methanol containing 0.85% of dry hydrogen chloride. The resultant cooled solution was treated with silver carbonate and activated charcoal and concentrated to dryness under reduced pressure; yield 2.2 g. (85%).

Following the procedure of Haworth, Hirst and Teece,[11] the above glycoside (2.2 g.) was heated in 25 ml. of 2 *N* hydrochloric acid at 85–95° for fourteen hours. The cooled solution was neutralized with silver carbonate, residual silver was removed with hydrogen sulfide and the solution was concentrated to dryness under reduced pressure; yield 1.8 g. (88%).

The above product (1.8 g.) was dissolved at 0° in 2 ml. of concentrated hydrochloric acid (*ca.* 12 *N*) and treated with 2 ml. of ethanethiol. The resultant mixture was maintained at 0° for two hours with stirring. Cold, concentrated ammonium hydroxide (*ca.* 15 *N*) was added at 0° to neutrality and the precipitated solid was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. The residue was repeatedly extracted with chloroform. Solvent removal left a semi-solid product which was combined with the initially precipitated material and treated with activated charcoal in methanol solution; yield 2.1 g. (76%). The ammonium chloride residue contained a negligible amount of organic material as determined by acetylation and extraction of the acetates formed.

An amount of 180 mg. of the above crude thioacetal was dissolved in 25 ml. of warm chloroform (containing 0.5% ethanol), and placed at the top of a column (200 mm. × 35 mm. diam.[12]) of acid-washed Magnesol–Celite.[13]

A mixture of 5 parts (by wt.) of Magnesol and 1 part of Celite was suspended with efficient stirring in a solution composed of 1 part (by vol.) of concentrated hydrochloric acid and 3 parts of water. The amount of Magnesol–Celite added to the diluted acid was regulated so that a very thin paste resulted. After stirring for sixty minutes, the slurry was filtered and washed free of chloride ion (to silver nitrate) with water and the water was displaced with acetone. The material was dried at room temperature overnight and then for two hours at 110°. The adsorbent was cooled, and only that portion which passed a 200-mesh (per linear inch) sieve was used in the chromatography as described. The chromatogram was developed with 350 ml. (5 column lengths) of 30:1 (by vol.) chloroform (containing 0.5% by vol. ethanol)–*t*-butyl alcohol and streaked with alkaline permanganate indicator.[14] The material in the main zone, located about one-third of a column length from the top, was eluted with 50 ml. of methanol; yield 93 mg. (52%), m. p. 115–125°, $[\alpha]^{25}D$ −18° (*c* 1.82, pyridine). This was recrystallized from methanol; yield 69 mg., m. p. 155–156° (unchanged on admixture with an authentic specimen of 2-methyl-D-glucose diethyl thioacetal of m. p. 154.5–155.5°), $[\alpha]^{23}D$ −25° (*c* 1.51, pyridine). The accepted constants[15] for this substance are: m. p. 156–157°, $[\alpha]^{20}D$ −25° (*c* 1.49, pyridine).

A zone appearing at the top of the column was eluted to yield a sirup; yield 24 mg. The effluent also gave a sirup; yield 4.9 mg. Both of the sirups failed to crystallize even when rechromatographed.

In a model experiment, 100 mg. of an equal mixture of D-glucose diethyl thioacetal and 2-methyl-D-glucose diethyl thioacetal was chromatographed as described above. Two zones formed, separated by a distinct though narrow interzone. The upper zone, located about one fourth of a column length from the top, contained the D-glucose diethyl thioacetal.

Action of Acidic Reagents on 2-Sodium Cellulosate.—An amount of 1.023 g. of alkali cellulose (Na, 1.24 equivs. per anhydro-D-glucose unit) was suspended in 4 ml. of acetyl chloride and 50 ml. of anhydrous acetone at 25° for three hours. The fibers were filtered and thoroughly washed with absolute ethanol; yield 1.013 g.

Anal. Na, 1.01 equivs. per anhydro-D-glucose unit (by titer).

An amount of 1.460 g. of alkali cellulose (Na, 1.25 equivs. per anhydro-D-glucose unit) was suspended in 7 ml. of acetic anhydride and 50 ml. of anhydrous acetone under reflux for five hours; yield 1.445 g.

Anal. Na, 1.09 equivs. per anhydro-D-glucose unit (by titer).

Viscosity Determinations.—Cotton linters, the cuprammonium activated cellulose and 2-methylcellulose were nitrated using the method described by Berl.[8] The nitrates were dissolved in *n*-butyl acetate, and the viscosities were measured in an Ostwald viscometer. The nitrate of the 2-methylcellulose could be cast into films. The times of flow in minutes at 25° were as follows: nitrated linters (12.9% N; *c*, 0.025; d^{25}_4, 0.871), 2.923; nitrated activated linters (12.4% N; *c*, 0.250; d^{25}_4, 0.873), 5.130; nitrated 2-methylcellulose (8.4% N; *c*, 0.224; d^{25}_4, 0.872), 2.432; solvent (d^{25}_4, 0.871), 2.001. Employing the formula of Staudinger and Mohr,[16] $K_m = 11 \times 10^{-4}$, the degrees of polymerization found were 1680, 570 and 88, respectively.

Acknowledgment.—This work was supported by the Ordnance Department under contract (W-33-019ord-6279; supervising agency, Ballistic Research Laboratories, Aberdeen Proving Ground, Maryland) with The Ohio State University Research Foundation. We wish to acknowledge the assistance of Mr. E. E. Dickey and Mr. H. C. Prosser.

Summary

Activated cotton linters reacted with sodium hydroxide in a nearly anhydrous medium to form an alkali cellulose, which reacted with methyl iodide to yield a methylcellulose (D. P. *ca.* 100 by nitrate viscosity) containing 1.03 methoxyl groups per anhydro-D-glucose unit. That the methylation was effected largely on C-2 results from the fact that methanolysis of the polymer followed by hydrolysis and mercaptalation yielded 2-methyl-D-glucose diethyl mercaptal as the only chromatographically isolable crystalline product.

COLUMBUS, OHIO RECEIVED MAY 12, 1949

(10) J. C. Irvine and E. L. Hirst, *ibid.*, **121**, 1585 (1922).

(11) W. N. Haworth, E. L. Hirst and Ethel G. Teece, *ibid.*, 2858 (1931).

(12) Adsorbent dimensions.

(13) Magnesol, a product of Westvaco Chlorine Products Co., South Charleston, West Virginia. Celite 535, a product of Johns-Manville Co., New York, N. Y.

(14) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, THIS JOURNAL, **67**, 527 (1945).

(15) P. E. Papadakis, *ibid.*, **52**, 2148, 3465 (1930); P. Brigl and R. Schinle, *Ber.*, **63**, 2884 (1930); Tollens–Elsner, "Kurzes Handbuch der Kohlenhydrate," J. A. Barth, Leipzig, 1935, p. 208, footnote 6.

(16) H. Staudinger and R. Mohr, *Ber.*, **70**, 2296 (1937).

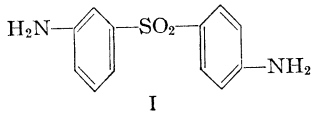
[CONTRIBUTION FROM THE CHEMICAL LABORATORY, NORTH TEXAS STATE COLLEGE]

α-(4-Aminophenylsulfonyl)-acetophenone Derivatives[1]

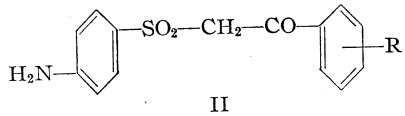
BY PRICE TRUITT, RICHARD STEAD,[2] LOREN M. LONG[3] AND WILLIAM J. MIDDLETON[4]

Numerous attempts have been made to decrease the toxicity of the tuberculostatic compound, 4,4′-diaminodiphenyl sulfone, I.[5-10]

Markees and Burger[11] have reported that the replacement of the sulfone linkage of Promizole with the cyclopropyl group led to a compound active against *M. tuberculosis* in Dubos' medium. Thus, it appears that the $-SO_2-$ linkage in some of the antitubercular sulfones can be replaced by other groups without destroying its activity. However, little work has been carried out to find the effect on the physiological activity that would be produced by replacing this sulfone linkage by other sulfone bearing groups. The present paper is a report of the synthesis of a group of compounds differing from the diaminodiphenyl sulfones in that the $-SO_2-$ group has been replaced by $-SO_2-CH_2-CO-$ as shown by comparing formula I with II.



I



II

Alkaline cleavage of these phenacyl phenyl sulfones has also been studied. It is noted that these keto sulfones could theoretically be hydrolyzed to yield a benzoic acid and a methyl sulfone or an acetophenone and a sulfonic acid. α-Phenylsulfonylacetophenone, gave a 97% yield of benzoic acid; however, only 75% of the methyl phenyl sulfone could be isolated. α-Phenylsulfonyl-4-chloro-acetophenone gave a 90% yield of *p*-chlorobenzoic acid; α-(4-nitrophenylsulfonyl)-acetophenone gave only a 64% yield of benzoic acid; α-phenylsulfonyl-2-acetonaphthone gave 65% yield of 2-naphthoic acid. The kinetics of these hydrolyses are now under investigation in this Laboratory.

(1) This work was aided by a grant from Parke, Davis and Company, Detroit, Michigan.

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(3) Research Chemist, Parke, Davis and Company, Detroit, Michigan.

(4) Parke, Davis Fellow, 1948-1949. Present address: University of Illinois, Urbana, Ill.

(5) Bauer, THIS JOURNAL, **61**, 617 (1939).

(6) Raiziss, Clemence and Freifelder, *J. Am. Pharm. Assoc.*, **33**, 43 (1944).

(7) Bambas, THIS JOURNAL, **67**, 671 (1945).

(8) Feldman and Hinshow, *Proc. Staff Meeting, Mayo Clinic*, **19**, 25 (1944).

(9) Amstutz and Neumoyer, THIS JOURNAL, **69**, 1925 (1947).

(10) Gilman and Broadbent, *ibid.*, 2053.

(11) Markees and Burger, *ibid.*, **70**, 3329 (1948).

Five of the sulfones reported in this paper have been tested for activity against tuberculosis but none showed appreciable activity, as compared to 4,4′-diaminodiphenyl sulfone.

Experimental

4-Nitroacetophenone.—A solution of 3.6 g. (0.087 mole) of diazomethane and 5 g. (0.027 mole) of 4-nitrobenzoyl chloride in dry ether at 0°. The reaction of this diazo ketone with hydriodic acid gave 2.1 g. of product, m. p. 80°. Barkenbus and Clements[12] prepared this compound by another method and reported it to melt at 80–81°.

4-Nitrophenacyl Chloride.—This compound was prepared by the action of concentrated hydrochloric acid on 4-nitrophenyl diazomethyl ketone. The same quantities of reagents as in the previous preparation gave 1.8 g. of 4-nitrophenacyl chloride, m. p. 107°.[13]

α-(4-Nitrophenylmercapto)-acetophenone, Table I. Procedure A.[14]—A solution of 40.1 g. (0.334 mole) of acetophenone in 100 cc. of carbon tetrachloride was added to a solution of 4-nitrophenylsulfenyl chloride,[15] m. p. 94–95°, obtained from 50 g. of 4,4′-dinitrodiphenyl disulfide. After refluxing four hours, a yellow granular solid separated and was filtered. Recrystallization gave the desired mercapto compound.

Procedure B.[16]—A suspension of 0.25 mole of sodium 4-nitrothiophenolate in 300 cc. of dry benzene was cooled to 0° and 38.6 g. (0.25 mole) of phenacyl chloride in dry ether was added dropwise. The temperature was kept below 10° during the addition. After removal of the sodium chloride, concentration of the filtrate gave yellow crystals.

The remaining compounds of this type, were prepared by one of these methods and the pertinent data recorded in Table I.

α-(4-Nitrophenylsulfonyl)-acetophenone, Table II.—To a suspension of 20 g. of α-(4-nitrophenylmercapto)-acetophenone, in 200 cc. of glacial acetic acid and 50 cc. of acetic anhydride at 80° was added dropwise 50 cc. of 30% hydrogen peroxide. The light yellow solid which separated on dilution with water was filtered and recrystallized from a chloroform–hexane solution.

The oxidations of the various sulfides were carried out in the same manner and the data recorded in Table II.

α-(4-Aminophenylsulfonyl)-acetophenone, Table III.—To a suspension of 6.1 g. (0.2 mole) of α-(4-nitrophenylsulfonyl)-acetophenone, in 100 cc. of water was added 15 g. of iron powder and 0.1 cc. of glacial acetic acid and the mixture stirred at 85–90° for ten hours. The product was extracted from the insoluble filter cake by means of hot alcohol or acetone. Recrystallization from ethanol gave very light tan flakes.

The reduction of the other nitro sulfones was fashioned in the same manner, except in one instance (see note *b*, Table III) catalytic reduction was used instead of the iron reduction and the yield from this reduction with hydrogen and Raney Ni catalyst gave almost twice as good a yield and the product had a better appearance. However, the amino compound from each procedure had the same melting point.

The data for all the corresponding compounds are recorded in Table III.

Hydrolysis of α-Phenylsulfonylacetophenone.—A mixture of 2.63 g. (0.01 mole) of α-phenylsulfonylacetophe-

(12) Barkenbus and Clements, *ibid.*, **56**, 1369 (1934).

(13) Dale and Nierenstein, *Ber.*, **60**, 1027 (1927).

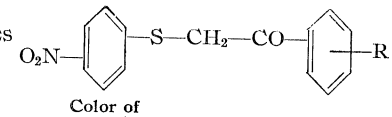
(14) Zincke, *Ann.*, **406**, 126 (1914).

(15) "Organic Syntheses," Coll. Vol. II, sec. ed., p. 455.

(16) Waldron and Reid, THIS JOURNAL, **45**, 2399 (1923).

TABLE I

α-(4-NITROPHENYLMERCAPTO)-ACETOPHENONES

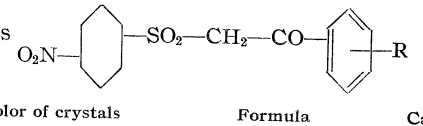


R	Method of prepn.	Yield, % A	Yield, % B	M. p.,[a] °C.	Recryst. from	Color of crystals	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Hydrogen	A, B	96	91	139	Acetone–H_2O	Yel. gr. plates	$C_{14}H_{11}NO_3S$	5.12	5.19
p-Methyl	A	85		123	Ace.–H_2O	Yel. flakes	$C_{15}H_{13}NO_3S$	4.88	4.79
p-Methoxy	A	88		158	Alcohol	Wh. ndls.	$C_{15}H_{13}NO_4S$	4.62	4.69
p-Bromo	A	90		132	Alc. ace.–H_2O	Yel. ndls.	$C_{14}H_{10}BrNO_3S$	3.87	3.83
p-Chloro	A, B	35	58	121	Alcohol	Lt. yel. ndls.	$C_{14}H_{10}ClNO_3S$	4.55	4.57
p-Nitro	A, B	80	83	160	Alc.–H_2O	Lt. cream ndls.	$C_{14}H_{10}N_2O_5S$	8.81	8.91
m-Nitro	A	92		134	Acetone	Lt. yel. matted nd.	$C_{14}H_{10}N_2O_5S$	8.81	8.82
[b]	A	70		153	Alcohol	Yel. flakes	$C_{18}H_{13}NO_3S$	4.33	4.45

[a] All melting points with the Fisher–Johns melting point apparatus. [b] The phenyl radical to which the R group is attached is replaced by the 2-naphthyl radical.

TABLE II

α-(4-NITROPHENYLSULFONYL)-ACETOPHENONES

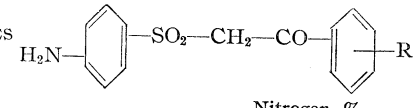


R	Yield, %	M. p., °C.	Recryst. from	Color of crystals	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Hydrogen	90	129	$CHCl_3C_6H_{14}$	Lt. cream rods	$C_{14}H_{11}NO_5S$	4.59	4.67
p-Methyl	95	155	Alc. H_2O	Wh. ndls.	$C_{15}H_{13}NO_5S$	4.39	4.57
p-Methoxy	93	258	Alcohol	Wh. ndls.	$C_{15}H_{13}NO_6S$	4.17	4.19
p-Bromo	80	161	Alc. H_2O	Lt. yel. ndls.	$C_{14}H_{10}BrNO_5S$	3.65	4.14
p-Chloro	94	146	Acetone	Lt. yel. ndls.	$C_{14}H_{10}ClNO_5S$	4.12	4.15
p-Nitro	92	257	Alcohol	V. long yel. ndls.	$C_{14}H_{10}N_2O_7S$	8.00	8.22
m-Nitro	87	145	Acetone	Wh. rods	$C_{14}H_{10}N_2O_7S$	8.00	8.17
[a]	99	171	Ace.–H_2O	Cream[b] ndls.	$C_{18}H_{13}NO_5S$	3.94	4.06

[a] 2-Naphthyl group replaces the phenyl group to which R is attached and R is hydrogen. [b] Light burnt-orange color from alcohol.

TABLE III

α-(4-AMINOPHENYLSULFONYL)-ACETOPHENONES



R	Yield, %	M. p., °C.	Recryst. from	Color of crystals	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Hydrogen	60	165	Ace. H_2O	Lt. tan flakes	$C_{14}H_{13}NO_3S$	5.09	5.09	11.64	11.34
p-Methyl	55	157	Alcohol	White flakes	$C_{15}H_{15}NO_3S$	4.84	4.78	11.09	11.24
p-Methoxy	45	123	Acetone	Gray flakes	$C_{15}H_{15}NO_4S$	4.59	4.50		
p-Bromo	50	197	*i*-Pr. alc.	White flakes	$C_{14}H_{12}BrNO_3S$	3.95	3.98	9.03	8.63
p-Chloro	27	179	Acetone	Cream flakes	$C_{14}H_{12}ClNO_3S$	4.52	4.70	10.33	10.09
p-Amino[a]	44	230	Alcohol	Lt. cream ndls.	$C_{14}H_{14}N_2O_3S$	9.66	9.89	11.03	10.92
m-Amino	35	240	Alcohol	Yel. ndls.	$C_{14}H_{14}N_2O_3S$	9.66	9.85	11.03	10.87
[b]	84[c]	158	Alcohol	Gray cream plates	$C_{18}H_{15}NO_3S$	4.31	4.28	9.84	9.67

[a] The preparation of this compound was described in a recent patent by F. Bergel, A. Morrison, A. R. Moss and H. Rinderknecht, British Patent 601,329, May 4, 1948. These workers prepared this compound by the method described by Troeger and Beck, *J. prakt. Chem.*, [2] **87**, 299 (1913). The reaction involves the interaction of substituted phenacyl chlorides with substituted sodium benzenesulfenates. This patent states that the above compound melted at 227°. We found that this substance melted at 230° [b] The phenyl ring with the R group is replaced by 2-naphthyl and R is hydrogen. [c] Catalytic reduction with Raney nickel and hydrogen at 40 pounds pressure. Iron reduction gave only 44% yield and the product was slightly reddish and this color could not be removed.

none and 11.51 cc. of 0.877 molar potassium hydroxide (0.01 mole) was refluxed for 100 minutes. The reaction solution was diluted to 200 cc. with water, cooled and extracted four times with 50-cc. portions of ether. Evaporation of this ether extract gave 1.207 g. of ether soluble product, m. p. 85°. Recrystallization raised the melting point to 87°. Acetophenone melts at 88°. This yield represented 74% of the theoretical.

The aqueous solution obtained after ether extraction was acidified and the insoluble precipitate weighed 1.19 g. and melted at 121.5° without recrystallization. Benzoic acid melts at 122°. This represents a yield of 97% of the theoretical of benzoic acid.

Hydrolysis of α-(4-Nitrophenylsulfonyl)-acetophenone.—Hydrolysis of 3.00 g. (0.0098 mole) of α-(4-nitrophenylsulfonyl)-acetophenone gave 0.50 g. of benzoic acid, 62% of theoretical, m. p. 119°.

Hydrolysis of α-(4-Nitrophenylsulfonyl)-2-acetonaphthone.—Hydrolysis of 2.1 g. (0.006 mole) of α-(4-nitrophenylsulfonyl)-2-acetonaphthone according to the pre-

vious procedure gave 0.66 g., 65%, of 2-naphthoic acid, m. p. 183°. 2-Naphthoic acid is recorded as melting at 185°.

Hydrolysis of α-(4-Nitrophenylsulfonyl)-4-chloro-acetophenone.—Hydrolysis of 2.34 g. (0.007 mole) of this compound gave 0.97% g., 90% of 4-chlorobenzoic acid, m. p. 238. The literature gives the melting point of this compound as 243°.

Summary

The synthesis of eight α-(4-nitrophenylmercapto)-acetophenones has been accomplished by one of two procedures and in some instances by both procedures. Each of the mercapto compounds was subsequently oxidized to the sulfone, then followed by reduction to the corresponding α-(4-aminophenylsulfonyl)-acetophenone.

None of the compounds tested were found to be active against tuberculosis.

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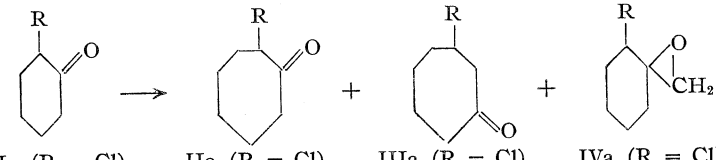
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Ring Enlargements. I. The Ring Enlargement of 2-Chlorocyclohexanone and 2-Phenylcyclohexanone

BY C. DAVID GUTSCHE

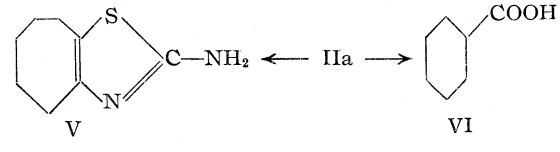
The ring enlargement of carbocyclic ketones by means of diazomethane has received occasional attention in the two decades since Mosettig and Burger[1] found that cyclohexanone could be smoothly converted to cycloheptanone through the action of this reagent. The synthetic value of these reactions, however, has been largely confined to the ring enlargement of symmetrical ketones, for unsymmetrically substituted ketones often yield mixtures of products.[2] The ratio of isomers present in such mixtures has in no case been accurately ascertained, as a consequence of which considerable confusion exists concerning the course of certain ring enlargements. The present communication discusses the ring enlargement of two 2-substituted cyclohexanones, (Ia) and (Ib), for which the ratio of isomers produced has been determined with fair accuracy.



Ia (R = Cl) IIa (R = Cl) IIIa (R = Cl) IVa (R = Cl)
Ib (R = C_6H_5) IIb (R = C_6H_5) IIIb (R = C_6H_5) IVb (R = C_6H_5)

Ring Enlargement of 2-Chlorocyclohexanone (Ia).—The reaction of Ia with ethereal diazomethane was reported by Giraitis and Bullock[3] in a Communication to the Editor which has not been followed by a fuller exposition of their work. These experimenters claimed that the product from this reaction was pure 2-chlorocycloheptanone (IIa) and that it was obtained in practically quantitative yield. Steadman,[4] using Meerwein's[5] procedure for conducting diazomethane ring enlargements, later showed that chlorocycloheptanone was produced in only 50–60% yield and that the isomeric oxide (IVa) accounted for at least 16% of the product. Steadman sought to prove the structure of the former by the base-catalyzed conversion to cyclohexanecarboxylic acid (VI), a reaction characteristic of cyclic 2-chloroketones.[6] From the chlorocycloheptanone fraction he obtained, upon treatment with alcoholic sodium hydroxide, a 36% yield of "somewhat impure" VI which was identified by conversion to the known amide. The relatively low yield of VI was not rationalized and, as will be shown below, was actually due to the fact that the chlorocycloheptanone fraction consisted of a mixture of the 2- and 3-chloro compounds.

2-Chlorocyclohexanone was treated with nitrosomethylurethan according to the directions of Steadman[4] and his reported yields were duplicated. Two reactions characteristic of the 2-chloroketo grouping were carried out with the chlorocycloheptanone fraction, and the results were compared with the same reactions in which authentic IIa was used as the starting material. In both reactions the material from the ring enlargement resembled the authentic 2-chloroketone qualitatively but not quantitatively. Authentic IIa could be converted by treatment with thiourea to 2-amino-4,5,6,7-tetrahydro-4-cycloheptathiazole, V, in 72% yield whereas the product of ring enlargement produced V in only 17.5% yield. Thus, on the basis of these data, the product of ring enlargement is indicated to consist of 24% of IIa and 76% of IIIa. This ratio of isomers was closely substantiated in the base-catalyzed conversion of the chloroketone to cyclohex-



V VI

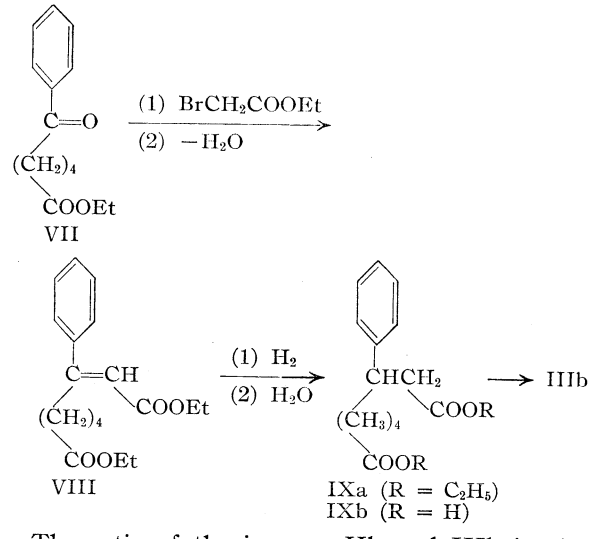
(1) Mosettig and Burger, THIS JOURNAL, **52**, 3456 (1930).
(2) Adamson and Kenner, *J. Chem. Soc.*, 181 (1939).
(3) Giraitis and Bullock, THIS JOURNAL, **59**, 951 (1937).
(4) Steadman, *ibid.*, **62**, 1606 (1940).
(5) Meerwein, German Patent 579,309 [*C. A.*, **27**, 4546 (1933)].
(6) Favorskii and Boshowski, *J. Russ. Phys.-Chem. Soc.*, **50**, 582 (1917) [*C. A.*, **18**, 1476 (1924)].

anecarboxylic acid (VI). The authentic material yielded VI in 69% yield whereas the ring enlargement product formed VI in only 15% yield. From these data the product of ring enlargement is indicated to consist of 22% of IIa and 78% of IIIa. That the product resulting from the treatment of IIa with potassium carbonate was indeed VI instead of 2-hydroxycycloheptanone, as previously reported by Kötz and his co-workers,[7] was proved by conversion to the known amide of VI. Meerwein[8] has also cited this inconsistency in Kötz' data.

Steadman[4] subjected the chlorocycloheptanone obtained by ring enlargement of Ia to further reaction with nitrosomethylurethan and obtained a product to which the structure of 2-chlorocyclooctanone was assigned, the proof again depending upon a ring contraction to cycloheptanecarboxylic acid for which no yields were given. In view of the results of the present work it is quite probable that this chlorocycloöctanone was a mixture of the 2-, 3- and 4-chloro isomers containing very little of the 2-chloro isomer.

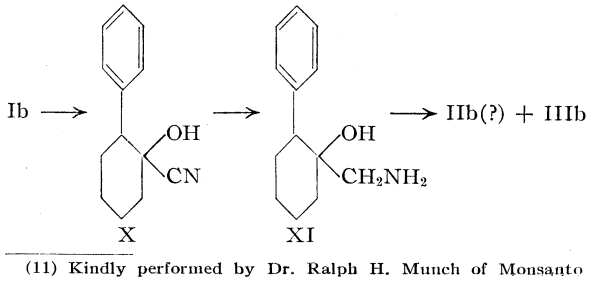
Ring Enlargement of 2-Phenylcyclohexanone (Ib).—The ring enlargement of Ib, which has not been previously carried out, was effected by two methods but only the diazomethane method was carefully investigated. A smooth reaction took place between Ib and nitrosomethylurethan in the presence of methanol and potassium carbonate, and fractional distillation of the product yielded two main fractions. The lower boiling material, obtained in 21.5% yield, was identified as 4-phenyl-1-oxaspiro[2,5]octane[9] (IVb) from its failure to react with semicarbazide and from its reaction with piperidine to form an amino alcohol. The higher boiling fraction, representing a 49.5% yield, had an analysis compatible with phenylcycloheptanone and formed a semicarbazone in quantitative yield. The semicarbazone, however, melted over a wide range and consisted of a methanol-soluble and a methanol-insoluble component. From the latter there was obtained a pure semicarbazone which was shown to be identical with that of IIIb. The methanol-soluble fraction was difficult to purify but finally yielded a semicarbazone identical with that of IIb. The presence of IIb was also demonstrated by the isolation from the higher boiling fraction of a 2,4-dinitrophenylhydrazone identical with that from IIb.

The most apparent method for the determination of the isomer ratio in the phenylcycloheptanone series depended upon a comparison of the physical characteristics of the mixture with pure IIb and IIIb. 2-Phenylcycloheptanone (IIb) had previously been prepared by Tiffeneau and his co-workers[10] by the isomerization of 1-phenyl-1,2-epoxycycloheptane. However, a less equivocal method, previously employed for the preparation of other 2-substituted cycloheptanones[2,3] appeared to be the ring enlargement of cyclohexanone by means of phenyldiazomethane. Thus, when a mixture of cyclohexanone, methanol and potassium carbonate was treated with nitrosobenzylurethan a smooth reaction took place to yield 26% of IIb. 3-Phenylcycloheptanone, IIIb, hitherto unknown, was synthesized from ethyl δ-benzoylvalerate (VII) in 23% over-all yield according to the method indicated below.



The ratio of the isomers IIb and IIIb in the mixture produced by diazomethane ring enlargement of Ib was most satisfactorily ascertained by infrared analysis.[11] By a quantitative comparison at several wave lengths of the absorptions of IIb, IIIb, and the mixture an average value was obtained (maximum deviation ±3%) which indicated the mixture to contain 81% of IIb and 19% of IIIb. The refractive indices also reflected this isomer ratio. That of the mixture (1.5387) indicated about 75% of IIb (1.5389) and 25% of IIIb (1.5380).

A second method of ring enlargement of Ib was investigated and found to produce a mixture from which the semicarbazone of IIIb could be isolated. 2-Phenylcyclohexanone (Ib) was converted with hydrogen cyanide to 1-cyano-1-hydroxy-2-phenylcyclohexane (X). Hydrogenation to the amino alcohol (XI) followed by treatment



(7) Kötz, Blendermann, Rosenbusch and Sirringhaus, *Ann.*, **400**, 55 (1913).

(8) Meerwein, *Ann.*, **417**, 259 (1917).

(9) Nomenclature based on Patterson-Capell Ring Index Compound No. 474.

(10) Tiffeneau, Weill, Gutmann and Tchoubar, *Compt. rend.*, **201** 277 (1935).

(11) Kindly performed by Dr. Ralph H. Munch of Monsanto Chemical Company, St. Louis.

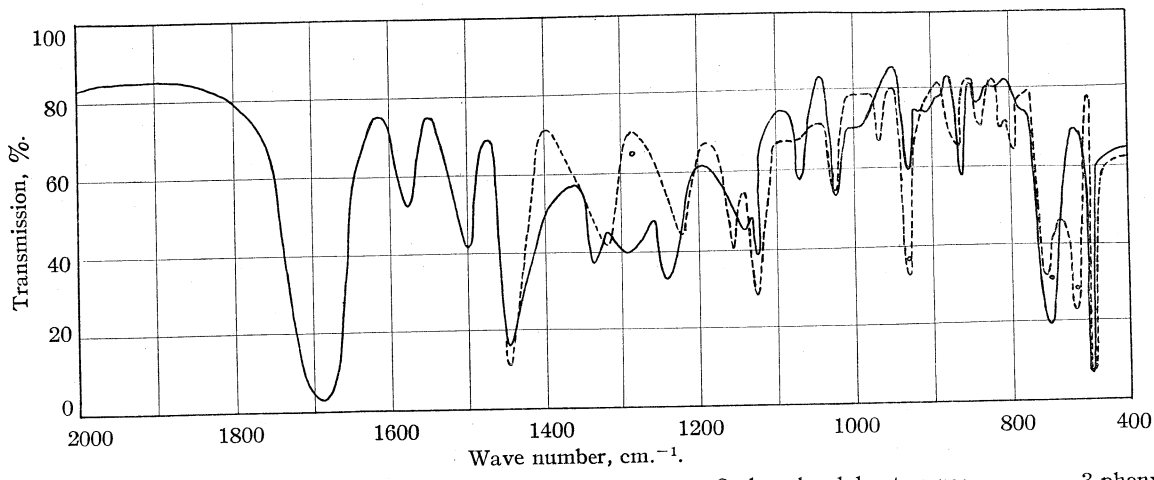


Fig. 1.—Infrared absorption spectra of phenylcycloheptanones: – – – – –, 2-phenylcycloheptanone; ————, 3-phenylcycloheptanone; o o o, points on the absorption curve of the mixture at which quantitative comparisons were made.

with nitrous acid gave a product containing approximately 84% of ketonic material which was a mixture probably containing IIb and IIIb. The semicarbazone of IIIb was isolated in a pure form but the residual semicarbazone could not be purified.

Acknowledgment.—We gratefully acknowledge a generous Research Corporation grant which has made possible the purchase of certain equipment necessary for this work. We are indebted to Dr. Ralph H. Munch for performing the infrared measurements and quantitatively interpreting the infrared data and to Dorothy Kuenne for performing the micro-analyses.

Experimental[12]

Diazomethane Ring Enlargement of 2-Chlorocyclohexanone (Ia).—The directions of Steadman[4] were precisely followed. From 76.0 g. of freshly distilled 2-chlorocyclohexanone, 57 cc. of methanol, 1.0 g. of finely powdered sodium carbonate and 84 g. of nitrosomethylurethan there was obtained, after fractionation through a thirty-four inch, glass helix-packed column, 12.1 g. (14%) of 4-chloro-1-oxaspiro[2,5]octane (IVa), b. p. 70–75° (14 mm.), 43.1 g. (51%) of chlorocycloheptanone, b. p. 92–95° (14 mm.), and 26.2 g. (32%) of an intermediate fraction, b. p. 75–90° (14 mm.). The major portion of the chlorocycloheptanone fraction had a b. p. of 94–95° (14 mm.), $n^{25}D$ 1.4824, and the following analysis.

Anal. Calcd. for $C_7H_{11}ClO$: C, 57.34; H, 7.56; Cl, 24.18. Found: C, 57.22; H, 7.57; Cl, 23.92.

2-Amino-4,5,6,7-tetrahydro-4-cycloheptathiazole (V). (a) **From Authentic 2-Chlorocycloheptanone.**—Cycloheptanone[13] was converted in 52% yield to 2-chlorocycloheptanone (b. p. 94–96° at 14 mm.; $n^{25}D$ 1.4836) by the method described for the chlorination of cyclohexanone.[14] When a 1.00-g. sample of this material was treated with 0.52 g. of finely powdered thiourea and the mixture heated on the steam-bath for two hours, 1.49 g. (98%) of an almost colorless solid was obtained. This was dissolved in water (completely soluble), the solution made basic with potassium hydroxide, and the thiazole extracted into benzene. Evaporation of the benzene left 0.82 g. (72%) of orange colored material; m. p. 65–70° (previous softening). Sublimation at 95° (0.05 mm.) followed by two recrystallizations from hexane containing a few drops of benzene yielded colorless, glistening prisms; m. p. 76.5–77.5°. Erlenmeyer and Schoenauer[15] prepared the hydrochloride of V but did not convert it to the free base.

Anal. Calcd. for $C_8H_{12}N_2S$: C, 57.10; H, 7.19. Found: C, 57.08; H, 6.98.

(b) **From Chlorocycloheptanone Obtained by Ring Enlargement of 2-Chlorocyclohexanone.**—A 1.00-g. sample of the chlorocycloheptanone obtained by ring enlargement of 2-chlorocyclohexanone was treated with thiourea as described above. The red-brown product failed to solidify upon cooling and was only partially soluble in water. From the water-soluble portion there was obtained 0.20 g. (17.5%) of a material which solidified when seeded with authentic thiazole (V). The water-insoluble, benzene-soluble portion amounted to 0.80 g.

Cyclohexanecarboxylic Acid (VI): (a) **From Authentic 2-Chlorocycloheptanone.**—A 5.00-g. sample of authentic 2-chlorocycloheptanone was treated with 20 cc. of water and 15 g. of potassium carbonate.[7] The mixture was stirred rapidly and heated at reflux for six hours and the product then separated into acidic and neutral fractions in the usual manner. From the acidic fraction there was obtained 3.00 g. (69%) of material melting at 22–26° from which an amide melting at 183–184° was prepared. Cyclohexanecarboxylic acid is reported to melt at 29° and its amide at 184°.[16] The neutral fraction amounted to 0.76 g.

(b) **From Chlorocycloheptanone Obtained by Ring Enlargement of 2-Chlorocyclohexanone.**—A 5.00-g. sample of the chlorocycloheptanone obtained by ring enlargement of 2-chlorocyclohexanone was treated in the same fashion as described above to yield 0.65 g. (15%) of VI and 2.91 g. of a neutral, viscous oil.

Diazomethane Ring Enlargement of 2-Phenylcyclohexanone (Ib).—In a three-necked flask fitted with a stirrer, reflux condenser and dropping funnel was placed 50 g. (0.287 mole) of 2-phenylcyclohexanone,[17] 150 cc. of methanol and 2 g. of finely powdered potassium carbonate. To the rapidly stirred suspension there was added, over a period of two hours, 43 g. (0.296 mole) of nitrosomethylurethan, the reaction temperature being held at 25–30° by means of a water-bath. After the addition of nitrosomethylurethan was completed, stirring was discontinued and the reaction mixture was allowed to stand at room temperature for ten hours. The potassium carbonate was

(12) All melting points are corrected.

(13) Kohler, Tishler, Potter and Thompson, THIS JOURNAL, **61**, 1057 (1939).

(14) Newman, Farbman and Hipsher, *Org. Syntheses*, **25**, 22 (1945).

(15) Erlenmeyer and Schoenauer, *Helv. Chim. Acta.*, **24**, 172E (1941).

(16) Lumsden, *J. Chem. Soc.*, 90 (1905).

(17) Newman and Farbman, THIS JOURNAL, **66**, 1550 (1944).

then removed by filtration, the volatile products evaporated under vacuum on the steam-bath and the residue fractionally distilled through a thirty-four inch, glass helix-packed column. The eight fractions collected were combined as follows: (a) 11.6 g. (21.5%), b. p. 114–117° (2.5 mm.), (b) 1.7 g., b. p. 117–123° (2.5 mm.), (c) 6.7 g., b. p. 123–131° (3 mm.), (d) 26.7 g. (49.5%), b. p. 131–133° (3 mm.).

4-Phenyl-1-oxaspiro[2,5]octane (IVb).—Fraction a from the diazomethane ring enlargement of 2-phenylcyclohexanone solidified after standing several hours, m. p. 53–55° after pressing on a porous plate. Two recrystallizations from petroleum ether (30–60°) gave the oxide (IVb) as colorless, large cubes, m. p. 60.5–62°.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.87; H, 8.39.

The piperidino derivative of IVb was prepared by refluxing a 1.85-g. sample from fraction a with 2.0 cc. of piperidine for two and one-half hours and then allowing the mixture to stand at room temperature for two days. When a benzene extract of this reaction mixture was shaken with dilute hydrochloric acid there precipitated 1.60 g. of a white solid. This was removed by filtration and recrystallized twice from benzene containing a few drops of methanol to yield colorless, fine needles of the hydrochloride of the piperidino derivative of IVb, m. p. 225–226° (some previous softening).

Anal. Calcd. for $C_{18}H_{28}ClNO$: C, 69.76; H, 9.11. Found: C, 69.60; H, 9.06.

The crude free base, obtained by neutralization of the hydrochloride described above, was molecularly distilled at 100° (0.02 mm.) to yield a yellow oil which solidified after standing several hours. Recrystallization from petroleum ether (30–60°) cooled in an acetone–Dry Ice-bath yielded colorless crystals; m. p. 39–40°.

Anal. Calcd. for $C_{13}H_{27}NO$: C, 79.07; H, 9.95. Found: C, 79.09; H, 9.70.

Phenylcycloheptanones (IIb and IIIb) from Diazomethane Ring Enlargement of 2-Phenylcyclohexanone.—Fraction *d* from the diazomethane ring enlargement of 2-phenylcyclohexanone crystallized when it was cooled in an acetone–Dry Ice mixture and seeded with pure, crystalline 2- or 3-phenylcycloheptanone; m. p. 0–17°, $n^{25}D$ 1.5387.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.94; H, 8.30.

A 10.1-g. portion of fraction d was converted to 13.4 g. (101%) of a white, powdery semicarbazone, m. p. approximately 120–140°. After trituration with boiling methanol, a residue of 1.70 g. (13%) remained, m. p. 212–214° (dec., previous softening), which, after several recrystallizations from absolute ethanol, gave colorless, glistening blades melting at 219–220° (dec.) and showing no depression in m. p. when admixed with the semicarbazone of 3-phenylcycloheptanone. Repeated recrystallization of the methanol-soluble fraction from methanol cooled to −5° yielded a compound melting at 155–156° (dec.) and showing no depression in m. p. when admixed with authentic semicarbazone of 2-phenylcycloheptanone.

A 0.500-g. sample of fraction d was converted to a mixture of 2,4-dinitrophenylhydrazones which solidified only after standing for several hours and which was completely soluble in ether. The ether solution, after standing at room temperature for several days, however, deposited 0.10 g. of a yellow solid; m. p. 166–169.5° (dec.). Two recrystallizations from ethanol furnished yellow, fine needles melting at 170.5–172° (dec.) which did not depress the m. p. of authentic 2,4-dinitrophenylhydrazone of 2-phenylcycloheptanone.

The infrared data for the mixture of IIb and IIIb were obtained from a sample of fraction d.

2-Phenylcycloheptanone (IIb).—A stirred mixture of 66 g. (0.675 mole) of cyclohexanone, 100 cc. of methanol, and 2 g. of finely powdered potassium carbonate was treated, over a period of seven hours, with 141 g. (0.675 mole) of nitrosobenzylurethan,[18] the reaction temperature being maintained at 25–30°. The mixture was stirred overnight at room temperature and then worked up as described above. The crude product was fractionated through a thirty-four inch, glass helix-packed column to yield 33.2 g. (26%) of material boiling at 133–137° (4 mm.) and melting at 11–19°. Two recrystallizations from petroleum ether (30–60°), the entire operation performed in a refrigerator, yielded the pure ketone as colorless, very long needles; m. p. 21–23°, $n^{25}D$ 1.5389, μ_{max}^{liquid} cm.$^{-1}$ 700, 717, 756, 795, 840, 867, 934, 967, 1027, 1125, 1154, 1223, 1317, 1450, 1500, 1576, 1688.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.79; H, 8.41.

The **semicarbazone of 2-phenylcycloheptanone**, prepared from 1.00 g. of the oil described above, consisted of 1.17 g. (90%) of slightly tacky, colorless material. Trituration with ether left 0.57 g. (44%) of a white solid, m. p. 133–136°, which, after two recrystallizations from methanol, produced colorless, glistening plates; m. p. 155–156°. Tiffeneau[10] has reported the m. p. as 156°.

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81. Found: C, 68.73; H, 7.85.

The **2,4-dinitrophenylhydrazone of 2-phenylcycloheptanone** was obtained in the usual manner and recrystallized from ethanol to yield yellow crystals, m. p. 138.5–142.5°. A second recrystallization from ethanol produced yellow needles, m. p. 171–172° (dec.).

Anal. Calcd. for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.47. Found: C, 61.94; H, 5.38.

With both the semicarbazone and the 2,4-dinitrophenylhydrazone of 2-phenylcycloheptanone it appears that a conversion to a higher melting form takes place during recrystallization. This anomalous behavior of derivatives of 2-substituted cyclic ketones has also been observed by other workers.[2]

2-Phenyl-1,6-dicarbethoxyhexene-1 (VIII).—To a three-necked flask fitted with a stirrer, a reflux condenser and a dropping funnel was added 36 g. (0.155 mole) of ethyl δ-benzoylvalerate (VII),[19] 27 g. (0.162 mole) of ethyl α-bromoacetate, 180 cc. of dry, thiophene-free benzene, 10.5 g. (0.162 mole) of granulated, activated[20] zinc and a few crystals of iodine. The reaction mixture was stirred and refluxed for two hours, 12.5 g. (0.075 mole) of ethyl α-bromoacetate and 4.9 g. (0.075 mole) of zinc then added, and stirring and refluxing continued for another hour. The mixture was cooled, treated with 80 cc. of ethanol followed by water, and the organic material was then extracted into benzene. After washing with dilute hydrochloric acid and water, the benzene solution was distilled until no more water appeared in the distillate and the dehydration of the hydroxy ester then carried out with 2.0 cc. of phosphorus oxychloride according to the method of Lipkin and Stewart.[21] The dehydration required five and one-half hours during which time 2.0 cc. (74%) of water was collected. The reaction mixture was then cooled, extracted several times with water, the benzene removed by evaporation under vacuum and the residue fractionally distilled through a ten-inch Vigreux column. The major fraction consisted of 31.7 g. (67.5%) of a yellow oil, b. p. 149–155° (0.1 mm.). A middle fraction taken for analysis had the b. p. 152–153° (0.1 mm.) and $n^{25}D$ 1.5121.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.82; H, 7.70

2-Phenyl-1,6-dicarbethoxyhexane (IXa).—A solution of 30.7 g. of 2-phenyl-1,6-dicarbethoxyhexene-1 (b. p. 149–155° at 0.1 mm.) in 100 cc. of ethyl acetate was treated with 2.00 g. of 10% palladium on charcoal (Baker Co.) and submitted to hydrogenation at room temperature and atmospheric pressure. After the required volume of hydrogen had been absorbed (five hours), the catalyst was removed by filtration, the solvent evaporated under vac-

(18) v. Pechmann, *Ber.*, **31**, 2640 (1898).

(19) Papa, Schwenk and Hankin, THIS JOURNAL, **69**, 3018 (1947).

(20) Fieser and Johnson, *ibid.*, **62**, 575 (1940).

(21) Lipkin and Stewart, *ibid.*, **61**, 3295 (1939).

uum and the residue distilled through a ten-inch Vigreux column to yield 26.4 g. (85%) of a colorless oil, b. p. 139–141° (0.08 mm.), $n^{25}D$ 1.4870.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.53; H, 8.30.

2-Phenyl-1,6-dicarboxyhexane (IXb).—A 25.4-g. sample of 2-phenyl-1,6-dicarbethoxyhexane (b. p. 139–141° at 0.08 mm.) was refluxed for seven hours with 100 cc. of ethanol and 100 cc. of 30% potassium hydroxide solution. The crude product, obtained in the usual manner, consisted of a slightly sticky, yellow solid. One recrystallization from benzene followed by drying under high vacuum yielded 19.3 g. (93%) of product; m. p. 79–82°. Three recrystallizations from benzene yielded glistening, short blades, m. p. 86–86.5°.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.07; H, 7.08.

3-Phenylcycloheptanone (IIIb).—An 18.5-g. sample of 2-phenyl-1,6-dicarboxyhexane (m. p. 79–82°) was dissolved in 100 cc. of ethanol, neutralized to phenolphthalein with 1 *N* sodium hydroxide solution and converted with thorium tetrachloride to 27.5 g. (102%) of the thorium salt.[22] Pyrolysis of the thorium salt at 400° and 0.5 to 2 mm. afforded 8.40 g. (60%) of a dark green oil which, upon fractionation through an eight-inch Vigreux column, yielded 6.10 g. (44%) of a yellow-green oil, b. p. 131–134° (2 mm.). The oil was crystallized twice from petroleum ether (30–60°) (the entire operation carried out in the refrigerator) to produce colorless, long needles, m. p. 17–18°, $n^{25}D$ 1.5380, μ_{max}^{liquid} cm.$^{-1}$ 700, 751, 840, 862, 934, 1027, 1070, 1125, 1141, 1241, 1287, 1338, 1450, 1500, 1576, 1688.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.76; H, 8.36.

The **semicarbazone of 3-phenylcycloheptanone** was prepared in the usual manner and obtained, after several recrystallizations from ethanol, as colorless, glistening blades, m. p. 220–221° (dec.).

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81. Found: C, 68.68; H, 7.61.

The **2,4-dinitrophenylhydrazone of 3-phenylcycloheptanone** was prepared in the usual manner and obtained, after three recrystallizations from ethanol, as yellow-orange needles, m. p. 145–146° (dec.).

Anal. Calcd. for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.47. Found: C, 62.12; H, 5.47.

Infrared Analysis.[11]—The infrared spectra were measured in a Perkin–Elmer model 12 C instrument on the pure materials in layers 0.02 mm. thick. The data are given in Table I.

TABLE I

μ cm.$^{-1}$	Log of ratio of % transmissions	% 2-Isomer	% 3-Isomer
717	0.412/0.492	83.5	(16.5)
751	.056/ .292	(81.0)	19.0
862	.013/ .075	(83.0)	17.0
934	.266/ .340	78.5	(21.5)
1287	.050/ .263	(81.0)	19.0

1-Cyano-1-hydroxy-2-phenylcyclohexane (X).—To a stirred, ice-cold mixture of liquid hydrogen cyanide (prepared from 20 g. of potassium cyanide[23]) containing five drops of piperidine was added, over a period of ten minutes, 10.0 g. of 2-phenylcyclohexanone. The reaction mixture was stirred for one hour at ice-bath temperature and the excess hydrogen cyanide then removed to leave 11.4 g. (99%) of a white solid melting at 87–94° (some previous softening) and probably consisting of a mixture of epimeric cyanohydrins. A 10.0-g. portion of the product was dissolved in benzene, the solution washed with dilute hydrochloric acid and water, and then concentrated by boiling. From the cooled solution there precipitated 4.50 g. of colorless cyrstals, m. p. 105–110° (previous softening). A portion of this material was sublimed at 100° (0.01 mm.) and recrystallized twice from benzene to give colorless, felted needles, m. p. 112–113°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.48; H, 7.28.

3-Phenylcycloheptanone from Ring Enlargement of 1-Cyano-1-hydroxy-2-phenylcyclohexane.—The reduction of the cyanohydrin (X) to the amino alcohol (XI) and subsequent rearrangement with nitrous acid was carried out by a method patterned after that described by Goldberg and Studer.[24] A 1.52-g. sample of sublimed cyanohydrin (m. p. 105–110° with previous softening) was dissolved in 25 cc. of glacial acetic acid, treated with 0.200 g. of Adams catalyst (Baker Co.) and subjected to hydrogenation at room temperature and atmospheric pressure. When the required amount of hydrogen had been absorbed (twelve hours) the catalyst was removed by filtration and the filtrate diluted to 250 cc. with water. This solution was then cooled to 0° and treated, over a period of ten minutes, with 20 cc. of an aqueous solution containing 1.57 g. of sodium nitrite. The reaction mixture was stirred for four hours at 0° and then allowed to stand for five hours at room temperature. Several extractions of the reaction mixture with ether–benzene yielded, after evaporation of the solvent, 1.07 g. of a yellow oil which was converted to 1.18 g. (84%) of a sticky semicarbazone. Trituration of the crude semicarbazone with ether left 0.25 g. of a white powder melting at 212–217° (dec.) which, after several recrystallizations from ethanol, produced colorless, glistening blades, m. p. 219–220° (dec.). No depression in m. p. was observed when this material was admixed with authentic semicarbazone of 3-phenylcycloheptanone.

Summary

The ratio of the 2- and 3-substituted cycloheptanones formed by diazomethane ring enlargement of 2-substituted cyclohexanones has been investigated for two series. 2-Chlorocyclohexanone yields a mixture containing approximately 23% of the 2-isomer and 77% of the 3-isomer; 2-phenylcyclohexanone yields a mixture containing approximately 81% of the 2-isomer and 19% of the 3-isomer. The ratio of isomers in the chlorocycloheptanone series was determined by chemical means and in the phenylcycloheptanone series by infrared analysis.

ST. LOUIS, MISSOURI RECEIVED MAY 5, 1949

(22) *Cf.* Ruzikca and Brugger, *Helv. Chim. Acta*, **9**, 339 (1926).

(23) Wade and Panting, *J. Chem. Soc.*, 255 (1898).

(24) Goldberg and Studer, *Helv. Chim. Acta*, **24**, 478 (1941).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Chemical Interactions of Amino Compounds and Sugars. IV.[1] Significance of Furan Derivatives in Color Formation[2]

BY M. L. WOLFROM, R. D. SCHUETZ[3] AND LIEBE F. CAVALIERI[3]

It has long been known that aqueous solutions of the reducing sugars become dark in color on heating with amino acids and that under certain conditions dark-colored, insoluble products are formed. This complex set of reactions is known as the "browning" or Maillard[4] reaction and is believed to play a role, at times beneficial and at times not, in the processing of foods. It is the purpose of this communication to study the possible contributions to these phenomena made by furan derivatives formed from the sugars. That furan derivatives may play a role in these reactions has been suggested by Roxas,[5] Beckley[6] and others.

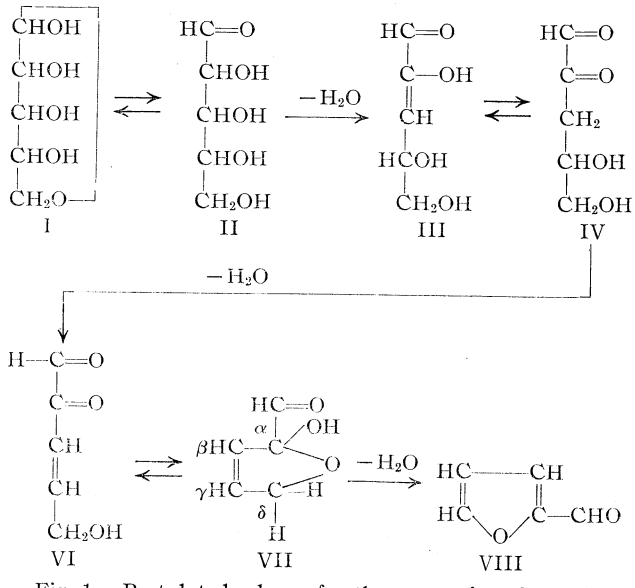


Fig. 1.—Postulated scheme for the conversion of pentoses to 2-furaldehyde.

It is well established that pentoses yield 2-furaldehyde (furfural) on heating with mineral acids. Hurd and Isenhour[7] have shown that this reaction is first order in its early stages if the 2-furaldehyde is removed by steam distillation as fast as formed. Mineral acidity is not required for this conversion, small amounts of 2-furaldehyde being formed when aqueous solutions of the pentoses are refluxed.[8,9]

We believe that the conversion of the pentoses to 2-furaldehyde follows the route outlined in Fig. 1. This scheme is analogous to that previously suggested[1] for the directly related conversion of hexoses to 5-(hydroxymethyl)-2-furaldehyde ("HMF") and is based upon similar evidence.

An aqueous solution of D-xylose was refluxed. After ninety minutes of refluxing, a distinct band with a maximum at 227 mμ (Fig. 3, curve 1) was evident. After three and one-half hours of heating (curve 2) a second band was developing in the region of 277 mμ. At the end of eight hours (curve 3) the maximum at 227 mμ had increased and that at 277 mμ was increasing at an even greater rate. On continued heating for twelve and one-half hours (curve 4) the ratio of the substance producing the band at 277 mμ to the other (producing the band at 227 mμ) became about equal. Further heating for periods of sixteen hours (curve 5) and nineteen hours (curve 6), respectively, greatly increased the ratio of the substance causing absorption at 277 mμ to that producing absorption at 227 mμ. Finally, after a period of heating of twenty-two hours (curve 7), the typical absorption spectrum of 2-furaldehyde (Fig. 4) was developing. The absorption characteristics of 2-furaldehyde as shown in Fig. 4 are in agreement with previously reported[10] data.

It is to be noted first that after one and one-half hours there is absorption only at 227 mμ. That

(1) Previous communication in this series: M. L. Wolfrom, R. D. Schuetz and L. F. Cavalieri, THIS JOURNAL, **70**, 514 (1948).

(2) The subject matter of this paper has been undertaken in cooperation with the Committee on Food Research of the Quartermaster Food and Container Institute for the Armed Forces under a contract (W-44-109Q M 1027) with The Ohio State University Research Foundation. The opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or indorsement of the War Department.

(3) Research Associate of The Ohio State University Research Foundation, Projects 278 and 238, respectively.

(4) L.-C. Maillard, *Compt. rend.*, **154**, 66 (1912); *Ann. chim.*, [9] **5**, 258 (1916).

(5) M. L. Roxas, *J. Biol. Chem.*, **27**, 71 (1916).

(6) V. A. Beckley, *J. Agr. Sci.*, **11**, 69 (1921).

(7) C. D. Hurd and L. L. Isenhour, THIS JOURNAL, **54**, 317 (1932); see also A. P. Dunlop, *Ind. Eng. Chem.*, **40**, 204 (1948).

(8) C. D. Hurd, C. D. Kelso and (Mrs.) E. Rondestvedt (Report to the Quartermaster Food and Container Institute for the Armed Forces, July to September, 1946) have isolated 2-furaldehyde, identified as the semicarbazone, in 2% yield, by steam-distilling aqueous solutions of D-xylose in the presence of glycine.

(9) R. G. Rice, Abstracts of Papers, 112th Meeting American Chemical Society, New York, N. Y., p. 3A, September, 1947, has identified 2-furaldehyde in the steam-distillate from aqueous solutions of D-xylose and L-arabinose in the presence and absence of glycine.

(10) L. Marchlewski and J. Mayer, *Bull. intern. acad. polon. sci.. Classe sci. math. nat.*, 1929A, No. 3, 169.

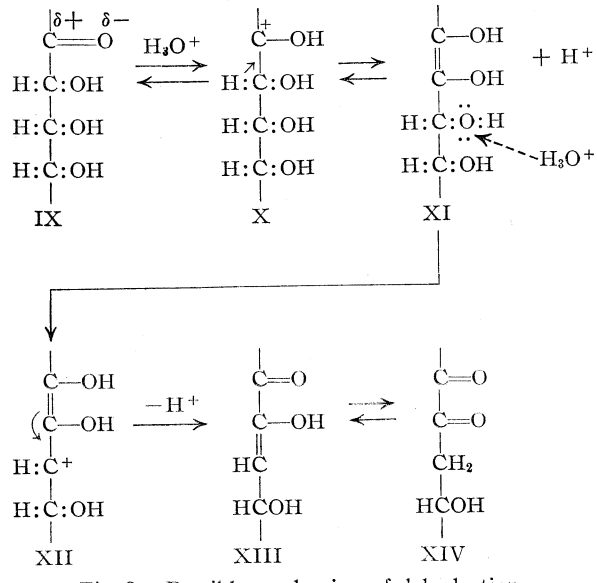


Fig. 2.—Possible mechanism of dehydration.

the substance producing this band is not 2-furaldehyde is evident from the fact that the major peak at 277 mμ is missing. The absorption band at 227 mμ is such as would be given by a conjugated acyclic diene or enal.[1]

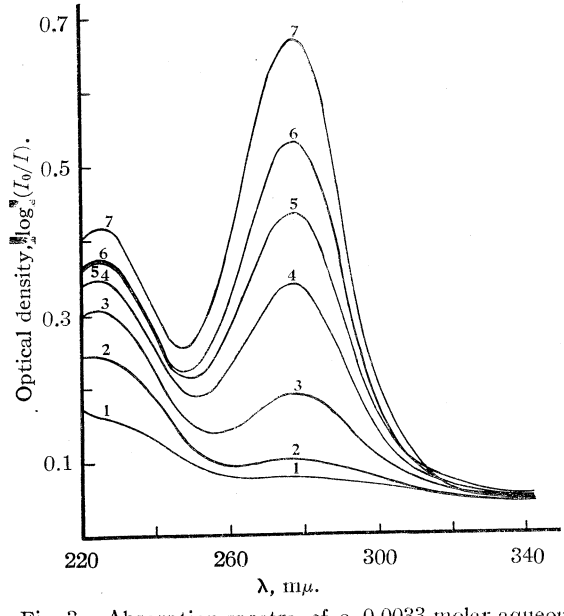


Fig. 3.—Absorption spectra of a 0.0033 molar aqueous D-xylose solution, initial *p*H 6.5, after refluxing for various time intervals. Curve 1, after one and one-half hours; curve 2, after three and one-half hours; curve 3, after eight hours; curve 4, after twelve and one-half hours; curve 5, after sixteen hours; curve 6, after nineteen hours; curve 7, after twenty-two hours. Beckman spectrophotometer (Model DU), 1-cm. cell, slit width 0.19–0.61 mm., optical densities 0.025–1.743.

To explain these absorption curves it is postulated that D-xylose, represented by I (Fig. 1) is transformed first into II or its aldehydrol.[11]

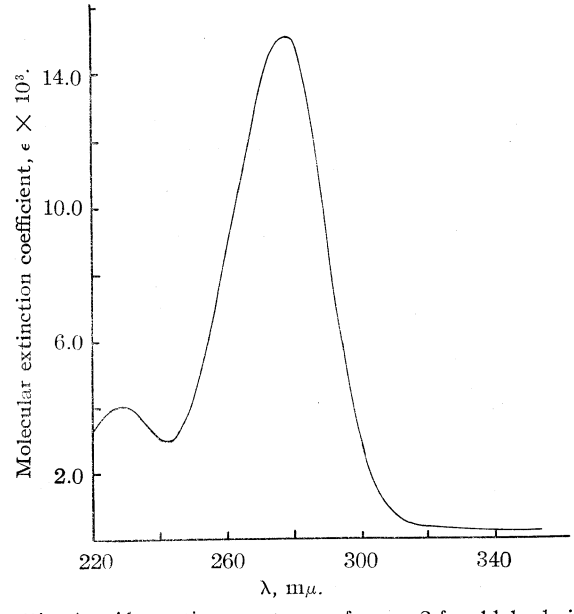


Fig. 4.—Absorption spectrum of pure 2-furaldehyde in water: concentration, 1.155×10^{-4} mole per liter; $\epsilon = 1/c \log (100/T)$ wherein c is the molar concentration and T is the percentage transmission; ϵ = 15,100, max. 277 mμ (major peak); ϵ = 4060, max. 227 mμ (minor peak); slit width 0.19–0.61 mm., optical densities 0.025–1.743; Beckman spectrophotometer (Model DU).

Substance II is a β-hydroxy carbonyl compound and undergoes dehydration to yield the conjugated enal III. The keto tautomer IV again loses water by dehydration from a β-hydroxy carbonyl system and produces VI. Both IV and VI can be in equilibrium with their ring structures V and VII, respectively. A final dehydration with bond adjustment then yields 2-furaldehyde (VIII). Such a bond adjustment may possibly involve a proton shift from the δ carbon of VII subsequent to a dehydration between its α and β carbons. Support for this reaction sequence is found in the work of Wolfrom, Wallace and Metcalf.[12] These workers isolated, in the form of its phenylosazone, the analog of VI as an intermediate in the action of mineral acid upon a hexose derivative. Isbell[13] assumes the same intermediates as involved in a series of successive electron displacements, the driving force for which is the combination of hydroxyl groups with hydrogen ions to form water.

The ease of acid dehydration of β-hydroxy carbonyl compounds may be interpreted electronically in the following fashion (Fig. 2). The polarization (IX) of the carbonyl group as enhanced by acid catalysis (X) allows the release of a proton

(11) See R. Bieber and G. Trümpler, *Helv. Chim. Acta*, **30**, 1860 (1947).

(12) M. L. Wolfrom, E. G. Wallace and E. A. Metcalf, THIS JOURNAL, **64**, 265 (1942).

(13) H. S. Isbell, *J. Research Natl. Bur. Standards*, **32**, 45 (1944); **33**, 45 (1944).

to form the enediol XI. These reactions are reversible and all of the hydroxyls present are under attack by the hydronium ions present in the solution. That hydroxyl will be released which is the most basic. Of the hydroxyl groups present, the several secondary hydroxyls are more basic than either the enolic hydroxyls or the terminal primary hydroxyl. The secondary hydroxyl which is removed, however, is that one adjacent to the enolic hydroxyl, the extra impetus for its release being provided by the electron pair of the endiolic function tending to produce the resonating system of conjugated double bonds shown in XIII (its tautomer is XIV). The essentially irreversible change from XI to XIII is represented as passing through the intermediate XII which is stabilized by the ejection of a proton and the shift of the electron pair down the carbon chain.

A dilute solution (0.05 *M*) of D-xylose was refluxed for one thousand minutes in the presence and absence of significant amounts of glycine. At the end of this period the amount of 2-furaldehyde formed was determined spectroscopically in the solution. The data are recorded in Table I and it is seen that the total conversion to furan bodies is small and is enhanced by the presence of glycine. Similar conclusions were expressed by Rice[9] on employing somewhat different experimental conditions. It is believed that the main aldehydic substance determined spectroscopically is 2-furaldehyde but it is not excluded that other carbonyl-containing compounds might have been present and caused absorption in the same band. The dilute solutions were adopted in order to yield sharp spectroscopic data. The presence of

TABLE I

Conversion of 0.0500 *M* Aqueous Solutions of D-Glucose and D-Xylose to Furan Bodies on Heating under Reflux (101°) for 1000 Minutes in the Presence and Absence of Glycine

Sugar	Glycine, *M*	pH Initial	pH Final	T,[a] %	Conversion to furan bodies,[b] %
D-Glucose	0.0	6.5	4.8	9.5	0.124
	.0	6.5	4.8	6.6	.144
	.0300	6.4	5.1	5.4	.154
	.0500	6.4	5.2	49.6[c]	.185
	.0500	6.4	5.2	50.6[c]	.179
	.0751	6.3	5.0	43.1[c]	.222
	.1000	6.2	5.0	28.2[c]	.333
	.1000	6.2	5.0	27.6[c]	.339
D-Xylose	0.0	6.7	4.4	14.7[c]	0.556
	.0	6.7	4.4	14.3[c]	.564
	.0300	6.6	5.1	11.2[c]	.633
	.0500	6.5	5.1	5.3[c]	.850

[a] Per cent. transmission at 285 mμ ($\epsilon_{max.} = 1/[HMF] \log 100/T = 16{,}500$) for D-glucose and at 277 mμ ($\epsilon_{max.} = 1/[F] \log 100/T = 15{,}000$) for D-xylose; 1 cm. cell; Beckman spectrophotometer, Model DU; all solutions made from triply distilled water. [b] Conversion to 5-(hydroxymethyl)-2-furaldehyde (HMF) for D-glucose and 2-furaldehyde (F) for D-xylose. [c] Diluted five times for absorption measurements.

2-furaldehyde in these solutions is established by its isolation in this Laboratory and in others.[8,9]

We next sought to determine whether this small amount of 2-furaldehyde, produced on heating aqueous solutions of pentoses, could be a factor in the "browning" of such solutions on heating with glycine. To this end equimolar (0.25 *M*) solutions of the pertinent substances were refluxed and the degree of coloration at various time intervals was measured at a selected wave length (490 mμ). Highly purified materials were employed and the results were reproducible to within approximately 5%. Curve F of Fig. 5 shows that 2-furaldehyde and glycine "brown" at a high rate of speed in accordance with the findings of Kertesz and coworkers.[14] No initial induction period was present. The upturn of the curve at the end, indicating a decreased rate of color formation, may be due at least in part to the formation of a colloidal solution containing suspended particles removed from the reaction sphere; particles actually separated at the last point measured. Thus 2-furaldehyde seems to be a real and powerful color precurser for glycine solutions. D-Xylose and pure 2-furaldehyde, alone or in admixture (curves A, B and C), do not produce significant colorations in the time intervals measured; with longer time these incipient colorations would become significant. The inverted S or sigmoid curve E is that of an admixed equimolar D-xylose and glycine solution. The slow rate of initial color development gives indication of an initial induction period. It is reasonable that this may be due to the time required for the formation of color precursors. The nature of the colored bodies formed is presently unknown but it is believed that they are formed by polymerization reactions in which glycine plays a part. It is possible that the furan ring may be an integral constituent of these polymers. It is not excluded that there may be an initial carbonyl-amino reaction followed by dehydrations to furan or other derivatives.

Since D-galacturonic acid is a constituent of pectins and is an established 2-furaldehyde precursor, its behavior under our selected "browning" conditions was of interest; curve D (0.25 *M* in D-galacturonic acid and glycine) of Fig. 5 is the result. A longer induction period was present. Seaver and Kertesz[15] have shown that D-galacturonic acid is a potent color producer with amino acids and it has been demonstrated[16] that furan intermediates are involved in the browning of dried apricots.

While the pentoses are convertible to 2-furaldehyde, the hexoses are convertible to 5-(hydroxymethyl)-2-furaldehyde and finally to levulinic acid. This reaction is enhanced by acidity but

(14) R. G. Rice, Z. I. Kertesz and E. A. Stotz, THIS JOURNAL, **69**, 1798 (1947).

(15) Joan L. Seaver and Z. I. Kertesz, *ibid.*, **68**, 2178 (1946).

(16) Victoria A. Haas, E. R. Stadtman, F. H. Stadtman and G. MacKinney, *ibid.*, **70**, 3576 (1948); A. Wahhab, 3580; F. H. Stadtman, 3583; G. MacKinney and Odette Temmer, 3586.

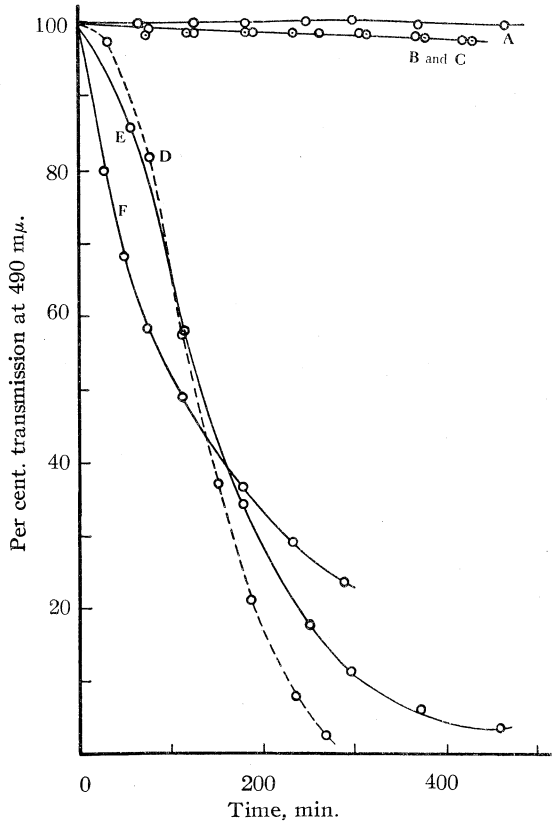


Fig. 5.—Rate of change in the percentage transmission at 490 mμ of D-xylose, D-galacturonic acid and 2-furaldehyde in the presence and absence of glycine; 0.2500 molar (in each constituent) aqueous solutions at reflux temperature (102°): Curve A, D-xylose alone; B, O, 2-furaldehyde alone; C, ⊙, D-xylose and 2-furaldehyde; D, D-galacturonic acid and glycine; E, D-xylose and glycine; F, 2-furaldehyde and glycine; Lumetron (Mod. 402E) photoelectric colorimeter.

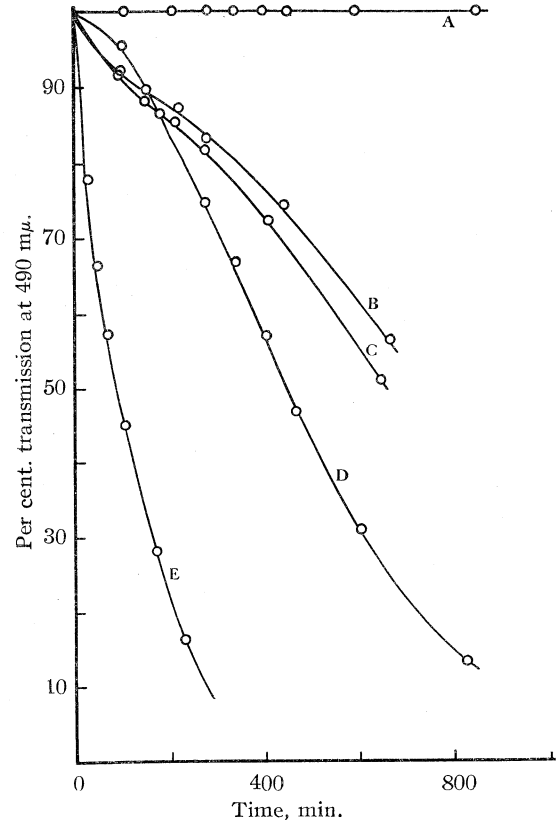
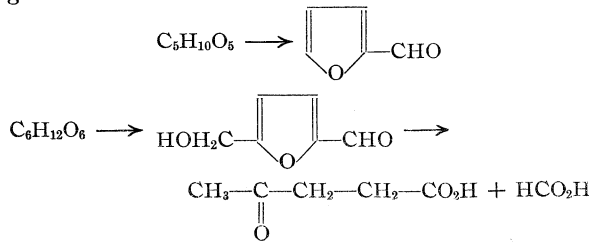


Fig. 6.—Rate of change in the percentage transmission at 490 mμ of D-glucose and 5-(hydroxymethyl)-2-furaldehyde in the presence and absence of glycine; 0.2500 molar (in each constituent) aqueous solutions at reflux temperature (102°): Curve A, D-glucose alone; B, D-glucose and 5-(hydroxymethyl)-2-furaldehyde; C, 5-(hydroxymethyl)-2-furaldehyde alone; D, D-glucose and glycine; E, 5-(hydroxymethyl)-2-furaldehyde and glycine; Lumetron (Mod. 402E) photoelectric colorimeter.

takes place in a refluxing aqueous solution of D-glucose.[17]



The data of Table I show the conversion of D-glucose to 5-(hydroxymethyl)-2-furaldehyde as measured spectroscopically directly in the heated (refluxed for one thousand minutes) solution. It is believed that the main component of the analyzing band is 5-(hydroxymethyl)-2-furaldehyde but the presence of other contributing carbonyl compounds is not excluded. It is noted that the presence of significant amounts of glycine has a promoting effect upon the furan bodies formed. The conversion of the hexose to furan bodies is apparently lower than with the pentose D-xylose but this may be more apparent than real since the 5-(hydroxymethyl)-2-furaldehyde produced is subject to further conversion to levulinic acid. The *p*H of both the hexose and pentose solutions (Table I) drifts downward with time. That 5-(hydroxymethyl)-2-furaldehyde is formed from D-glucose in the presence of glycine was established by isolation from such a mixture.

The degree of conversion of hexoses and pentoses to furan bodies (Table I) is small but the measured figure represents only the amount of substance actually exhibiting the absorption at the wave length employed. This is undoubtedly an intermediate value and the total quantity of hexose or pentose passing through this stage may be much greater.

Singh, Dean and Cantor[18] have shown that the 5-(hydroxymethyl)-2-furaldehyde formed in acid

(17) B. L. Scallet with J. H. Gardner, THIS JOURNAL, **67**, 1934 (1945).

(18) B. Singh, G. R. Dean and S. M. Cantor, *ibid.*, **70**, 517 (1948).

solutions of D-glucose is the prime cause of color development in them. We are then presently concerned with attempting to determine whether this same intermediate is a probable factor in the "browning" of aqueous solutions of D-glucose by glycine. To this end we employed the same color-forming conditions as we used for the pentoses. The results are diagrammed in Fig. 6. D-Glucose alone (Fig. 6, curve A) did not form colored substances as readily as did our sample of D-xylose (Fig. 5, curve A). 5-(Hydroxymethyl)-2-furaldehyde alone is a good source of color (curve C), much more than is 2-furaldehyde. Admixture with D-glucose (curve B) has little effect upon this property. Refluxing of 5-(hydroxymethyl)-2-furaldehyde with glycine (curve E) produces a very rapid color formation. The curve (D) of D-glucose and glycine is similar in general characteristics to that of D-xylose and glycine (curve E of Fig. 5); it exhibits even a more pronounced initial induction period. Thus the behavior of D-glucose is similar to that of D-xylose.

On heating in dilute aqueous solution an equimolar mixture of D-glucose and glycine ethyl ester, the *p*H falls gradually (curve A of Fig. 7).

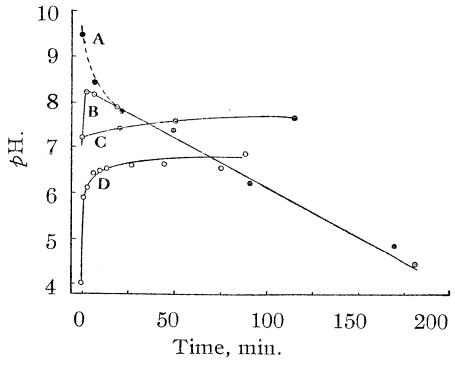


Fig. 7.—Change in *p*H of a 0.001 molar solution of N-D-glucosylglycine ethyl ester: at room temperature (20–25°), curve C; at 90–92°, curve B; in 0.02 *N* hydrochloric acid at room temperature (20–25°), curve D. Change in *p*H of a mixture of D-glucose and glycine ethyl ester at an equivalent concentration, 90–92°, curve A. Measurements of *p*H on the heated solutions were made by rapidly cooling an aliquot to room temperature.

When an equivalent amount of crystalline N-D-glucosylglycine ethyl ester is heated under the same conditions (curve B, Fig. 7), a very rapid initial increase in *p*H occurs followed by a slower drop in *p*H which merges into the *p*H-time curve of the D-glucose–glycine ester system. These data are those predictable should the N-D-glucosylglycine ethyl ester have hydrolyzed largely to D-glucose and glycine ethyl ester with the latter substance then undergoing a slower hydrolysis to glycine. N-D-Glucosylglycine ethyl ester undergoes hydrolysis at room temperature (curve C, Fig. 7) and its instability toward water is shown also by the rapid and essentially quantitative release of the amino group (ninhydrin colorimetric assay) on heating in aqueous solution for only a few minutes. Toward mineral acid, the substance is very unstable at room temperature (curve D, Fig. 7). This hydrolytic behavior shows that only a small amount of N-D-glucosylglycine could possibly be formed by the interaction of D-glucose and glycine in aqueous solution. It is not excluded, however, that this small amount may be a significant factor in a complex equilibrium.

Finally we may state that our findings stand contrary to the statement of Enders[19] that these furan derivatives do not brown with sufficient rapidity to be of significance in the Maillard reaction. When present in sufficient concentration, both 2-furaldehyde and 5-(hydroxymethyl)-2-furaldehyde form deeply colored products with glycine and do so at a high rate of speed.

Experimental

Materials.—The colorless 2-furaldehyde required in this investigation was obtained from a commercial sample that had been freshly triply distilled under reduced pressure. 5-(Hydroxymethyl)-2-furaldehyde was prepared according to the procedure of Middendorp[20] with some modification. An amount of 180 g. (0.527 mole) of sucrose was dissolved in 600 ml. of water. To this was added 0.180 g. (0.00143 mole) of oxalic acid. The resulting solution was refluxed for twenty hours, after which it was cooled to room temperature and the black, insoluble material was removed by filtration. The filtrate was neutralized with 11.0 g. (0.110 mole) of calcium carbonate with mild heating. To the neutralized filtrate was added 2 g. of basic lead acetate and after standing for ninety minutes the solution was again filtered. The 5-(hydroxymethyl)-2-furaldehyde was extracted with a 100-ml. portion of ethyl acetate and then with four 50-ml. quantities. The solvent was removed under reduced pressure from the dried extract and the 5-(hydroxymethyl)-2-furaldehyde was purified by molecular distillation at 2×10^{-3} mm.; m. p. 33.3–33.5° (cor.).

The glycine and the carbohydrates employed were highly purified materials recrystallized in our own laboratories. The D-galacturonic acid used was the α-monohydrate. All aqueous solutions were made with triply distilled water.

Isolation and Characterization of 2-Furaldehyde from the Decomposition of D-Xylose in the Presence of Glycine.—An aqueous solution (100 ml.) of D-xylose and glycine (2.5 molar in each constituent) was refluxed for two hours. It was then steam-distilled, the distillate being led directly into a heated solution of 2 *N* hydrochloric acid saturated with 2,4-dinitrophenylhydrazine. The resulting 2,4-dinitrophenylhydrazone was filtered and recrystallized from pyridine; m. p. 229° (dec., Fisher–Johns apparatus), accepted value 229° (dec., cor.).[21] In an identical manner, a 2,4-dinitrophenylhydrazone of like melting point was isolated from a 2.5 *M* solution of D-xylose alone after refluxing for sixteen hours. Mixed melting points of these two products with an authentic reference compound were unchanged.

Isolation and Characterization of 5-(Hydroxymethyl)-2-furaldehyde from the Decomposition of D-Glucose in the Presence of Glycine.—An aqueous solution (400 ml.) of D-glucose and glycine (2.5 molar in each constituent) was refluxed for twenty hours and then extracted with ethyl acetate for eight to ten hours in a continuous extractor. Crude 5-(hydroxymethyl)-2-furaldehyde was obtained as a light brown oil on solvent removal under diminished

(19) C. Enders, *Biochem. Z.*, **312**, 339 (1942).
(20) J. A. Middendorp, *Rec. trav. chim.*, **38**, 1 (1919).
(21) A. Wahhab, ref. 16.

pressure; yield 1–2 g. Identification was effected by ultraviolet absorption[1,18] and by the preparation of two crystalline derivatives: the 2,4-dinitrophenylhydrazone of m. p. 198–200° (dec., Fisher–Johns apparatus) (after recrystallization from 95% ethanol; in agreement with accepted value[21]) and the condensation product with β-naphthylamine of m. p. 130–131° (after recrystallization from benzene; accepted value[22] 131–132°). These two derivatives showed no depression in melting point on admixture with authentic samples of like melting point.

Preparation of N-D-Glucosylglycine Ethyl Ester.—This compound was first recorded by Euler and Zeile.[23] The following is an improved method of preparation which makes this substance readily available. An amount (66 g.) of freshly prepared glycine ethyl ester was added to a suspension of 115 g. of anhydrous D-glucose in 200 ml. of absolute ethanol and the mixture was mechanically stirred and heated under reflux on a water-bath while protected from moisture by a guard tube. The heating was continued until all of the D-glucose had dissolved, about seventy-five minutes of heating time generally being required. The resultant solution was tea-colored. Approximately 125 ml. of ethanol was then removed under diminished pressure and *ca.* 150 ml. of acetone added to the residual sirup. The resultant solution was nucleated and allowed to stand at room temperature until crystallization was complete (overnight). The crude product was removed by filtration and washed with absolute ethanol; yield 110 g. (64%), m. p. 80°. Quite pure material was obtained on three recrystallizations from equal parts of hot absolute ethanol; yield 50 g. (30%), m. p. 108°, $[\alpha]^{25}D$ −5° (*c* 3, absolute ethanol). A significant purification could be obtained by making a slurry of the crude product with absolute ethanol, filtering and washing with a small amount of ethanol. The filtrate was discarded and the filtered material was crystallized from hot absolute ethanol.

Hydrolytic Breakdown of N-D-Glucosylglycine Ethyl Ester in Water; Ninhydrin Reaction.—An amount (0.26 g.) of D-glucosylglycine ethyl ester was heated on a water-bath in 10 ml. of water containing ninhydrin. The characteristic color developed in a few minutes and heating was continued for a total of thirty minutes. Comparison of this solution (cooled rapidly to room temperature) with a solution containing an equivalent amount of glycine by means of a photoelectric colorimeter revealed that both solutions absorbed to the same extent.

Acknowledgment.—The assistance of Mrs. Clare B. Spitler is gratefully acknowledged. We are also pleased to acknowledge the counsel of Dr. T. L. Tan and of Professors W. R. Brode, M. S. Newman and F. H. Verhoek of this department.

Summary

1. Aqueous solutions of D-xylose form small amounts of 2-furaldehyde on being heated. The presence of a relatively large amount of glycine promotes this conversion as it does the analogous conversion of hexoses to 5-(hydroxymethyl)-2-furaldehyde.

2. The course of the formation of 2-furaldehyde from D-xylose has been followed spectroscopically and on this basis structures are postulated for several intermediates.

3. It is demonstrated that 5-(hydroxymethyl)-2-furaldehyde, in the case of D-glucose, and 2-furaldehyde, in the case of the pentoses and D-galacturonic acid, are important precursors in the formation of the brown colors developed when aqueous solutions of these substances are heated with glycine.

4. Evidence is presented which shows that the carbonyl-amino reaction could occur to only a slight extent if at all in dilute aqueous solutions of D-glucose and glycine.

COLUMBUS, OHIO RECEIVED MAY 31, 1949

(22) W. F. Cooper and W. H. Nuttall, *J. Chem. Soc.*, **101**, 1080 (1912).

(23) H. v. Euler and K. Zeile, *Ann.*, **487**, 163 (1931).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF RUTGERS UNIVERSITY AND THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

A Synthesis for 4-Bromo-7-methoxyhydrindene

BY RODERICK A. BARNES, ELISE R. KRAFT[1] AND LOUIS GORDON[2]

In a previous paper[3] the use of 4-substituted hydrindenes as starting materials for preparation of cyclopentanophenanthrene derivatives has been illustrated. The present work was undertaken in order to extend the scope of this method by making available a new 4-substituted hydrindene (IV).

The method which finally proved successful for the synthesis of IV and which was most readily applicable to large-scale preparation was based on the hydrindone synthesis of von Auwers.[4] Although halogen substituted hydrindones have not previously been prepared by this procedure, we have found that it can be used to synthesize 4-bromo-7-hydroxy-1-hydrindone (II) in 40–50% yield. The Clemmensen reduction (80% yield) to 4-bromo-7-hydroxyhydrindene (III) and methylation of III with diazomethane complete the synthesis.

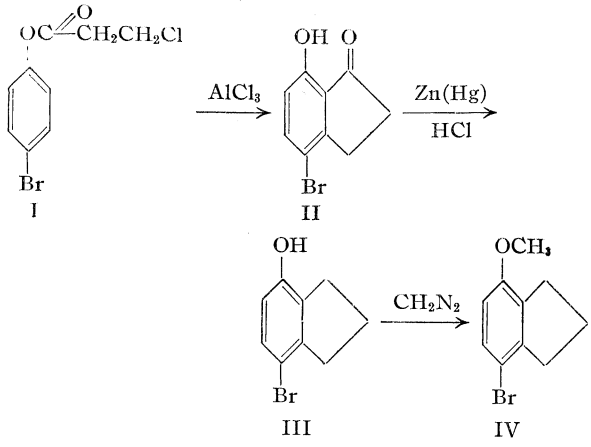
The von Auwers preparation of hydrindones takes place in two steps, first a Fries rearrangement of the phenol ester of an α- or β-halopropionic acid, and second a cyclization of the intermediate haloketone. In harmony with this conception of the reaction we have found that the best yields of II were obtained when I was heated with aluminum chloride at 95–100° for five to six hours to complete the Fries rearrangement and then at 170° for one hour to cause cyclization. Extended heating at the higher temperature results in de-

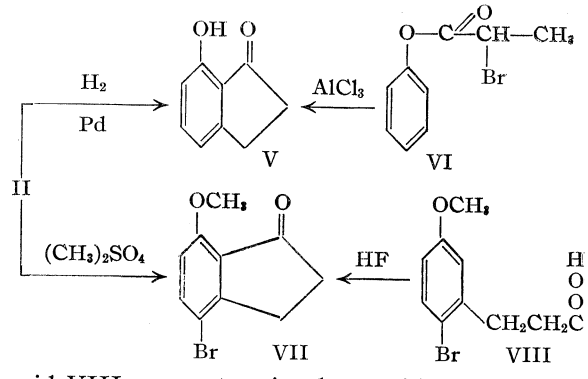
(1) Present address: Chemical Laboratory, Harvard University, Cambridge, Massachusetts.

(2) A portion of this work was taken from a thesis presented by Louis Gordon in partial fulfilment of the requirements for the Ph.D. degree, Columbia University, June 1948.

(3) Barnes and Gordon, THIS JOURNAL, **71**, 2644 (1949).

(4) von Auwers, *Ann.*, **439**, 132 (1924).





struction of II; however, cyclization is very slow at the lower temperature.

The yield of II was less than has been reported[5] for *p*-cresyl β-chloropropionate (60%); however, this may be explained by a comparison of the inductive effect of the bromine atom and the methyl group. Thus, the lower electron density at the cyclization position in our case requires that a higher temperature be used for this step of the reaction with a resultant increase in destructive side reactions. The more readily available *p*-bromophenyl α-chloropropionate gave only a trace of II in spite of the fact that 7-hydroxy-1-hydrindone (V) can be prepared in small yield from phenyl α-bromopropionate (VI).[6]

In view of the rather drastic reaction conditions necessary to produce the hydrindone II, it was important to prove its structure.[7] To show that II had the desired carbon skeleton it was reduced over palladium until no more hydrogen was absorbed. It was anticipated that the known 4-hydroxyhydrindene would be formed; however, the product was 7-hydroxy-1-hydrindone (V).[6] The failure of the carbonyl group to undergo catalytic reduction is believed to be due to chelation.[8]

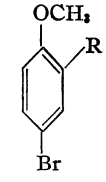
The position of the bromine atom in II was confirmed by an alternate synthesis of 4-bromo-7-methoxy-1-hydrindone from β-(2-bromo-5-methoxyphenyl)-propionic acid (VIII) which was prepared by direct bromination of β-(*m*-methoxyphenyl)-propionic acid in carbon tetrachloride at −5°.

The location of the bromine atom in VIII was determined by oxidation to the known 2-bromo-5-methoxybenzoic acid.[9] The synthesis of IV from acid VIII was not seriously considered as a preparative method because of the greater number of steps and more expensive reagents necessary to prepare VIII from *m*-hydroxybenzaldehyde. The preparation of I from acrylonitrile and *p*-bromophenol requires only two steps.

Additional proof for the position of the bromine atom was furnished by the nitration of III to produce a steam-volatile nitration product whose methyl ether did not react with a boiling alcoholic solution of silver nitrate. The steam volatility of this product indicates that the nitro group must be ortho to the phenolic hydroxyl, and the inactivity of the bromine atom indicates it to be meta to the nitro group. The indicated structure for III, with the bromine atom in the 4-position, is the only one in accord with these facts. Chromic acid oxidation of III produced a small amount of 4,7-hydrindenequinone; the bromine atom would not have been eliminated during oxidation to this product if it were in any but the 4-position.

The first approach to the preparation of IV had been based on the observation of Johnson and Shelberg[10] that β-(*p*-methoxyphenyl)-propionic acid could be cyclized in 85% yield to 5-methoxy-1-hydrindone. To this end β-(2-methoxy-5-bromophenyl)-propionic acid XII was prepared. The condensation of ethyl cyanoacetate with 2-methoxy-5-bromobenzaldehyde produced the cyanoester IX in good yield, but prolonged acid hydrolysis of IX produced only cyanoacid X. The condensation of the aldehyde with malonic acid produced the desired cinnamic acid XI but the reduction with hydrogen and Raney nickel removed the bromine atom.

IX, R = —CH=C(CN)COOEt
X, R = —CH=C(CN)COOH
XI, R = —CH=CH—COOH
XII, R = —CH_2CH_2COOH
XIII, R = —CH_2Cl



The desired acid XII was prepared in an over-all yield of 63% from *p*-bromoanisole by chlorometh-

(5) Krollpfeiffer and Schultze, *Ber.*, **57**, 600 (1924).

(6) von Auwers and Hilliger, *ibid.*, **49**, 2410 (1916).

(7) The migration of the bromine atom during the cyclization was the possibility which seemed most likely to produce a substance isomeric with the desired hydrindone. A discussion of the rearrangement of bromo compounds under acid conditions is presented by Moyle and Smith, *J. Org. Chem.*, **2**, 112 (1937).

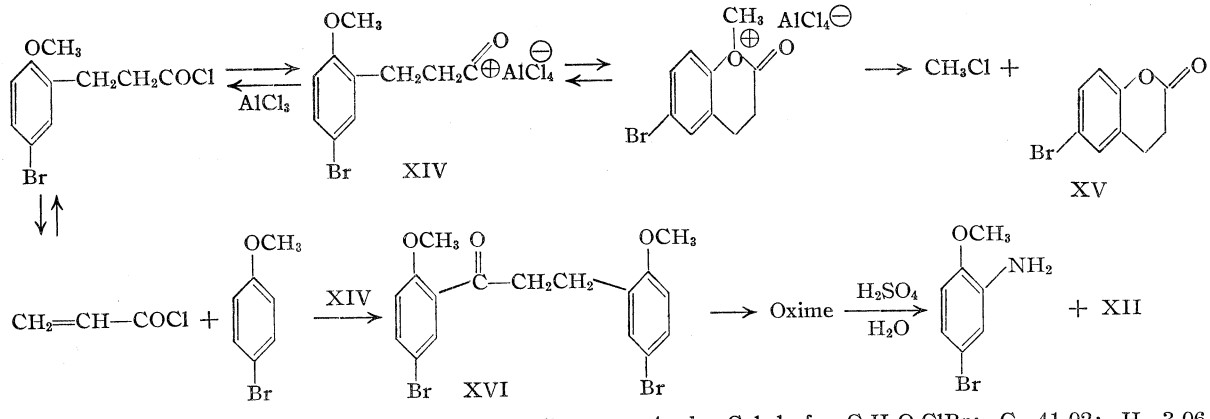
(8) Jarowski and Cramer (Washington A.C.S. Meeting, September, 1948) have observed that the carbonyl group of 2-carbethoxy-5-hydroxy-γ-chromenone is not reduced by hydrogen in the presence of Raney nickel. In this case chelation is also possible.

(9) We are indebted to Dr. Domenick Papa for a generous sample of β-(*m*-hydroxyphenyl)-propionic acid and a melting point sample of 2-bromo-5-methoxybenzoic acid. Schwenk and Papa have reported (Chicago A. C. S. meeting, September, 1948) that bromination of the silver salt of β-(*m*-methoxyphenyl)-propionic acid also produces VIII.

(10) Johnson and Shelberg, THIS JOURNAL, **67**, 1853 (1945).

ylation to 2-methoxy-5-bromobenzyl chloride (XIII) followed by alkylation of malonic ester with XIII.

Using a variety of reaction conditions we have been completely unable to cyclize either β-(2-methoxy-5-bromophenyl)-propionic acid XII or β-(*o*-methoxyphenyl)-propionic acid.[11] Neither stannic chloride nor anhydrous hydrogen fluoride caused any reaction of acid XII. With aluminum chloride in benzene or nitrobenzene the main product was 6-bromo-3,4-dihydrocoumarin (XV). When nitrobenzene was used as a solvent there was also obtained in 18% yield a ketone m. p. 93–94° (XVI). The structure assigned to this ketone is based on the analysis, molecular weight, oxidation by potassium permanganate to 2-methoxy-5-bromobenzoic acid and the Beckmann rearrangement of the oxime.



The results obtained in this attempted cyclization of the acid XII would indicate that the failure of β-(*o*-methoxyphenyl)-propionic acids to cyclize is due to preferential reaction of the positive carbon of the complex XIV with the oxygen of the methoxyl group rather than with the ring carbon meta to the methoxyl group. The relative yield of the dihydrocoumarin XV and the ketone XVI were not materially changed by the addition of a mole of *p*-bromoanisole to the cyclization mixture; this would indicate that the intramolecular reaction with oxygen was faster also than reaction with the ortho position of *p*-bromoanisole.

Acknowledgment.—The authors wish to express their appreciation for a Frederick Gardner Cottrell Research Grant which made possible the successful completion of this work.

Experimental[12]

β-Chloropropionic Acid.—Acrylonitrile (250 g.) was added to concentrated hydrochloric acid (2 liters), and the mixture refluxed for six hours. After cooling the precipitated ammonium chloride was filtered and the filtrate concentrated *in vacuo*. The residue was distilled to yield 384 g. (75%) of acid which boiled at 115–117° (32 mm.) and which solidified on standing for a short time.

***p*-Bromophenyl β-Chloropropionate.**—Phosphorus trichloride (90 ml.) was added dropwise to β-chloropropionic acid (332 g.) and the mixture heated at 110–120° for three hours. Then, a solution of *p*-bromophenol (533 g.) in toluene (500 ml.) was added and the mixture refluxed for an additional three hours. The cool reaction mixture was washed with dilute potassium hydroxide solution, dried and distilled. There was obtained 567 g. (65%) of the ester which boiled at 106–117° (0.4–0.6 mm.).

Anal. Calcd. for $C_9H_8O_2ClBr$: C, 41.02; H, 3.06. Found: C, 41.05; H, 3.11.

***p*-Bromophenyl α-Chloropropionate.**—α-Chloropropionyl chloride[13] (50.9 g.) and *p*-bromophenol (60.5 g.) were refluxed for two hours and the reaction mixture processed as for the previous ester. There was obtained 33.8 g. (53%) of the ester which boiled at 160–167° (26 mm.). This substance crystallized on standing and after recrystallization from ligroin (b. p. 90–110°) melted at 56.2–56.8°.

Anal. Calcd. for $C_9H_8O_2ClBr$: C, 41.02; H, 3.06. Found: C, 40.88; H, 3.20.

4-Bromo-7-hydroxy-1-hydrindone.—A mixture of *p*-bromophenyl β-chloropropionate (131.5 g.) and aluminum chloride (250 g.) was stirred while the temperature was maintained at 95–100° for six hours; the temperature was then raised to 170° and the reaction mixture was heated at this temperature for one hour. After cooling, the mixture was treated with ice water and then steam distilled. The steam distillate was chilled and filtered to yield 70.2 g. of yellow crystals. After drying and recrystallization from ligroin (b. p. 90–110°) there was obtained 49.8 g. (44%) of the hydrindone which melted at 142–145°.[14] This substance was obtained analytically pure by alternate recrystallization from methyl ethyl ketone and ligroin, m. p. 146.2–146.9°.

Anal. Calcd. for $C_9H_7O_2Br$: C, 47.60; H, 3.11; Br, 35.19. Found: C, 47.37; H, 3.18; Br, 35.32.

This compound can be preserved pure only if kept in a sealed evacuated container. Without this precaution surface oxidation of the crystals takes place; however, on standing in air only a small percentage of the compound is oxidized by this process. Thus, a sample left exposed to air for two weeks had the following analysis: C, 46.82; H, 3.20; Br, 33.97.

p-Bromophenyl α-chloropropionate was allowed to react with aluminum chloride at temperatures from 140–185° for periods of time varying from one-half hour to five hours, but the main steam volatile product was an oil.

(11) Heinzelmann, Kolloff and Hunter, THIS JOURNAL, **70**, 1386 (1948), have reported that β-(*o*-methoxyphenyl)-propionic acid could not be cyclized by anhydrous hydrogen fluoride, aluminum chloride or phosphorus pentoxide.

(12) All melting points are corrected. Microanalyses are by W. Manser and Lois E. May.

(13) Prepared by the method of Henry, *Compt. rend.*, **100**, 116 (1885).

(14) These conditions, which produce a maximum yield of the hydrindone, were worked out by Dr. G. L. Shoemaker, Cottrell Grant Research Fellow.

By extraction of an ether solution of the oil with sodium hydroxide and subsequent neutralization of the aqueous solution a very small amount of hydrindone II could be isolated.

4-Bromo-7-hydroxyhydrindene.—4-Bromo-7-hydroxy-1-hydrindone (65 g.) was refluxed with amalgamated zinc (75 g.) and alcohol (200 ml.) while hydrochloric acid (250 ml.) was added in portions during eight hours. After filtration and dilution with water the product was extracted with ether. Recrystallization from ligroin produced 49.6 g. (81%) of product which melted at 106–107°. The pure substance melts at 108–108.8°.

Anal. Calcd. for C_9H_9OBr: C, 50.73; H, 4.26. Found: C, 50.46: H, 4.39.

4-Bromo-7-methoxyhydrindene.—4-Bromo-7-hydroxyhydrindene (15 g.) was allowed to stand with a solution of diazomethane in ether (prepared from 16 g. of nitrosomethylurea) for twenty-four hours. The ether solution was washed with dilute sodium hydroxide (0.2 g. of the phenol was recovered) and the solvent was removed on the water pump. The crystalline residue was recrystallized from petroleum ether (30–60°). There was obtained 13.2 g. (82%) of product which melted at 66–66.5°.

Anal. Calcd. for $C_{10}H_{11}OBr$: C, 52.88; H, 4.88. Found: C, 52.47; H, 4.85.

β-(2-Bromo-5-methoxyphenyl)-propionic Acid.—β-(*m*-Methoxyphenyl)-propionic acid (5.0 g.) prepared by methylation of β-(*m*-hydroxyphenyl)-propionic acid[9] with dimethyl sulfate, was dissolved in carbon tetrachloride (100 ml.) and cooled to −10° while a solution of bromine (4.8 g.) in carbon tetrachloride (15 ml.) was added dropwise with mechanical stirring. On processing of the reaction mixture there was obtained 5.4 g. (75%) of product which melted at 81–83°. The purified acid melted at 83.7–84.4°.[15]

Oxidation of 0.5 g. of this substance by boiling with potassium permanganate solution produced 2-bromo-5-methoxybenzoic acid, melting point and mixed melting point with an authentic sample[9] 160–160.8°.

4-Bromo-7-methoxy-1-hydrindone.—**A.** β-(2-Bromo-5-methoxyphenyl)-propionic acid (4 g.) was dissolved in anhydrous hydrogen fluoride (100 ml.) contained in a copper reaction bottle and allowed to stand at room temperature until all of the hydrogen fluoride had evaporated. Recrystallization of the residual solid from alcohol produced 2.2 g. (60%) of product which melted at 133.6–134.2°.

B. The methylation of 4-bromo-7-hydroxy-1-hydrindone (1.8 g.) by reaction with dimethyl sulfate (2.9 ml.) and a slight excess of sodium hydroxide in methanol solution produced 1 g. of material which melted at 134.5–135°. The melting point of a mixture of this substance and the product obtained in part A was 133.5–134.5°.

Anal. Calcd. for $C_{10}H_9O_2Br$: C, 49.81; H, 3.84. Found: C, 49.67; H, 3.78.

7-Hydroxy-1-hydrindone.—**A.** 4-Bromo-7-hydroxy-1-hydrindone (5 g.) was shaken with hydrogen in the presence of palladium on barium sulfate (1 g.) at atmospheric pressure until no more hydrogen was absorbed (twenty hours). The catalyst was filtered off, the filtrate evaporated and the residue crystallized from petroleum ether. The product melted at 112–113°.[16]

B. Phenyl α-bromopropionate (20 g.) was treated with aluminum chloride (40 g.) according to the procedure of von Auwers.[6] There was obtained 1.55 g. (12%) of the steam-volatile 7-hydroxy-1-hydrindone. The melting point of this substance and also of a mixture of it and the product from part A was 112–113°.

4-Bromo-6-nitro-7-hydroxyhydrindene.—Fuming nitric acid (1 ml.) dissolved in acetic acid (10 ml.) was added dropwise to a solution of 4-bromo-7-hydroxyhydrindene (2.4 g.) in acetic acid (25 ml.) at 5°. When the addition was complete the reaction mixture was allowed to stand fifteen minutes and then poured into cold water. The crude product was filtered and purified first by steam distillation and then by recrystallization from ethanol. There was obtained 2.3 g. (80%) of the bright yellow nitrophenol which melted at 101.8–102.6°.

Anal. Calcd. for $C_9H_8O_3NBr$: C, 41.88; H, 3.12; N, 5.43. Found: C, 41.99; H, 3.23; N, 5.32.

The methyl ether was prepared by allowing the nitrophenol to stand for twenty-four hours with a solution of diazomethane. After recrystallization from ethanol the nearly colorless product melted at 81.7–82.2°.

Anal. Calcd. for $C_{10}H_{10}O_3NBr$: C, 44.14; H, 3.70; N, 5.15. Found: C, 44.16; H, 3.82; N, 5.03.

There was no reaction when this methyl ether was boiled with an alcoholic solution of silver nitrate.

4,7-Dihydroxyhydrindene.—4-Bromo-7-hydroxyhydrindene (1 g.) dissolved in 70% acetic acid (100 ml.) was treated with chromic anhydride (6 g.) for ten minutes at 70–75°. The product was isolated by dilution of the reaction mixture with cold water and ether extraction. The ether extract was concentrated and the quinone sublimed *in vacuo*. The oily sublimate was shaken with ether and aqueous sodium hydrosulfite. Evaporation of the ether left the crystalline hydroquinone (28 mg.) which was purified by crystallization from methyl ethyl ketone and ligroin. When heated under a microscope the product began to melt at 155–160°; however, at this temperature a new crystalline form appeared which melted sharply at 186–187°.

This same behavior was noted with an authentic sample prepared by the method of Arnold and Zaugg[17] and there was no lowering of the melting point when the two samples were mixed and heated.

Ethyl α-Cyano-2-methoxy-5-bromocinnamate.—2-Methoxy-5-bromobenzaldehyde[18] (50 g.) was treated with ethyl cyanoacetate (30 g.), ammonium acetate (3.9 g.), acetic acid (12 g.) and benzene (50 ml.) according to the directions of Cope, *et al.*[19] After recrystallization from ethanol there was obtained 65 g. (91%) of product which melted at 103–104°.

Anal. Calcd. for $C_{13}H_{12}O_3NBr$: C, 50.34; H, 3.90. Found: C, 50.60; H, 4.04.

α-Cyano-2-methoxy-5-bromocinnamic Acid.—Ethyl α-cyano-2-methoxy-5-bromocinnamate (31 g.) was refluxed for thirty hours with a mixture of hydrochloric acid (150 ml.) and acetic acid (300 ml.). After filtration of the cold reaction mixture there was obtained 27 g. (96%) of the acid which crystallized as yellow needles from alcohol, m. p. 240–242° (dec.).

Anal. Calcd. for $C_{11}H_8O_3NBr$: C, 46.83; H, 2.86; N, 4.97; Br, 28.33. Found: C, 46.91; H, 2.79; N, 4.53; Br, 28.16.

A repetition of the treatment with acid produced no further change in this substance. When a solution of this acid in potassium hydroxide was allowed to stand at room temperature, crystals of 2-bromo-5-methoxybenzaldehyde (m. p. and mixed m. p. with an authentic sample 117–118°) were slowly deposited.

2-Methoxy-5-bromocinnamic Acid.—The condensation of 2-methoxy-5-bromobenzaldehyde (13.6 g.) with malonic acid (6.5 g.) produced only 2.1 g. (13%) of the desired acid, m. p. 223–226°.[20] The starting aldehyde was recovered in 62% yield (8.5 g.).

The reduction of 2-methoxy-5-bromocinnamic acid (1 g.) in alkaline solution with hydrogen (40 lb.) and Raney nickel produced β-(*o*-methoxyphenyl)-propionic acid, m. p. and mixed m. p. with an authentic sample 87–88°.

(15) Schwenk and Papa (ref. 9) report a melting point of 83–84° for this substance.

(16) von Auwers and Hilliger, ref. 6, report the melting point of this substance to be 111–112°.

(17) Arnold and Zaugg, THIS JOURNAL, **63**, 1317 (1941), report the melting point to be 184–185°.

(18) Graebe, *Ann.*, **340**, 210 (1905).

(19) Cope, Hoffman, Wyckoff and Hardenbergh, *ibid.*, **63**, 3452 (1941).

(20) Biilmann and Rimbert, *Bull. soc. chim.*, **33**, 1473 (1923), report the melting point of this substance as 222–223°.

β-(2-Methoxy-5-bromophenyl)-propionic Acid.—**A.** 2-Methoxy-5-bromobenzyl chloride[21] (250 g.) was slowly added to a cold (5–10°) solution of sodium (25 g.) and malonic ester (250 g.) in absolute ethanol (800 ml.). The mixture was stirred for twelve hours at room temperature and then refluxed for an additional three hours. The crude alkylated malonic ester was isolated by pouring the reaction mixture into water (3 liters) and extracting with ether. The ether and excess malonic ester were removed by distillation until the vapor temperature of the distillate reached 95° (6 mm.). The residue (371 g.) was refluxed for twenty hours with potassium hydroxide (145 g.) water (100 ml.) and methanol (400 ml.). The mixture was poured into water and extracted with ether. The aqueous solution was acidified and the solid malonic acid filtered and decarboxylated by heating to 180°. The crude acid was purified by dissolving in dilute potassium hydroxide, washing the aqueous solution with ether, reprecipitating with hydrochloric acid and finally recrystallizing from benzene and petroleum ether. There was obtained 226 g. (82%), of the acid which melted at 117–118°.

Anal. Calcd. for $C_{10}H_{11}O_3Br$: C, 46.35; H, 4.28. Found: C, 45.74; H, 4.37.

B. β-(*o*-Methoxyphenyl)-propionic acid was brominated by the same procedure as for the meta isomer. The product from this reaction melted at 117–118° and when mixed with the acid obtained in part A caused no depression of the melting point. The oxidation of this acid with aqueous potassium permanganate produced 2-methoxy-5-bromobenzoic acid, m. p. 119°. A mixture of this oxidation product (m. p. 119°) and β-(2-methoxy-5-bromophenyl)-propionic acid (m. p. 117–118°) melted at 84–95°.

Cyclization Attempts with *o*-Methoxyphenylpropionic Acid.—Seven experiments using variations of the procedure developed by Johnson and Shelberg[10] for the para isomer, were carried out but in each case there was obtained either recovered acid or an amorphous precipitate (m. p. *ca.* 230–280°) which was insoluble in both organic and inorganic reagents (presumably a polymer). In three experiments small amounts (0.5–5%) of an oil were isolated which reacted with 2,4-dinitrophenylhydrazone. The small amounts of partially purified 2,4-dinitrophenylhydrazones obtained (m. p. 113–118°, 153–156° and 245–250°) were not further investigated.

Cyclization Attempts with β-(2-Methoxy-5-bromophenyl)-propionic Acid.—This acid (24 g.) was recovered quantitatively after standing for thirty hours at room temperature with anhydrous hydrogen fluoride (200 g.).

The acid chloride when treated with stannic chloride in benzene solution at room temperature did not undergo any reaction.

The acid chloride (prepared from 79 g. of acid and thionyl chloride) was dissolved in benzene (400 ml.) and aluminum chloride (40 g.) was added slowly to the cold solution. The mixture was stirred for six hours at room temperature, then after washing with water the organic layer was extracted with dilute potassium hydroxide. Acidification of this alkaline solution liberated 21 g. of β-(2-hydroxy-5-bromophenyl)-propionic acid which melted at 139–140°.[22] Evaporation of the benzene and recrystallization of the residue from ethanol produced 18 g. of 6-bromo-3,4-dihydrocoumarin, m. p. 106–106.5°.[23] It was subsequently observed that the dihydrocoumarin can be completely extracted from an organic layer by warm potassium hydroxide solution. Both the dihydrocoumarin and the hydroxy acid were reconverted to β-(2-methoxy-5-bromophenyl)-propionic acid (m. p. and mixed m. p. 117–118°) by reaction with dimethyl sulfate and potassium hydroxide.

The acid chloride (60 g., b. p. 152–155° (3 mm.)) was dissolved in nitrobenzene (200 ml.) and treated with a solution of aluminum chloride (29 g.) in nitrobenzene (100 ml.) at room temperature for nine hours. The dihydrocoumarin was removed by shaking with warm potassium hydroxide solution to yield 37 g. (70%) of β-(2-hydroxy-5-bromophenyl)-propionic acid. After removing solvents and recrystallizing from ethanol there was obtained 9 g. (18%) of a substance melting at 93–94°.

Anal. Calcd. for $C_{17}H_{16}O_3Br_2$: C, 47.69; H, 3.77; Br, 37.33. Found: C, 47.18, 47.72; H, 3.76, 3.79; Br, 36.87.

In an attempt to prepare larger quantities of the above substance β-(2-methoxy-5-bromophenyl)-propionic acid (14 g.) was treated with aluminum chloride in nitrobenzene as above except that one equivalent of *p*-bromoanisole (10 g.) was added. By extraction of the reaction mixture with sodium bicarbonate solution 0.89 g. (6%) of the starting acid was recovered. Most of the dihydrocoumarin was removed by recrystallization from alcohol (7.3 g., 60%), the remainder by washing with warm potassium hydroxide solution (acidification liberated 0.9 g. of crude hydroxy acid). The residual ketone (2.2 g., 9%) was contaminated with a small amount of another substance (0.09 g., m. p. 149–151°) which was obtained by concentration of the mother liquors after most of the ketone (m. p. 92–94°) had been removed.

Structure Proof for β-(2-Methoxy-5-bromophenyl)-ethyl 2′-Methoxy-5′-bromophenyl Ketone.—The molecular weight determined by the depression of the freezing point of benzene was 412 (calcd. 428). Oxidation with aqueous potassium permanganate produced only 2-methoxy-5-bromobenzoic acid, m. p. and mixed m. p. 118–119° (the authentic sample was prepared by oxidation of 2-methoxy-5-bromobenzaldehyde). The following derivatives were prepared by standard procedures; oxime, m. p. 141–142°.

Anal. Calcd. for $C_{17}H_{17}O_3NBr$: C, 46.07; H, 3.87. Found: C, 46.10; H, 4.18.

Phenylhydrazone, m. p. 159–161°.

Anal. Calcd. for $C_{23}H_{22}O_2N_2Br_2$: C, 53.30; H, 4.28. Found: C, 53.07; H, 4.00.

p-Nitrophenylhydrazone, m. p. 187–188°.

Anal. Calcd. for $C_{23}H_{21}O_4N_3Br_2$: C, 49.04; H, 3.76. Found: C, 49.22; H, 3.96.

The oxime (0.4 g.) was mixed with 85% sulfuric acid (10 ml.) and heated to 180° during five minutes. After dilution with water (100 ml.) the solution was boiled for five hours. The cool hydrolysis mixture was extracted with ether and the aqueous layer made alkaline and extracted with ether to remove the amine. There was obtained 0.13 g. of amine which after recrystallization from petroleum ether melted at 94.8–95.6°. The melting point of a mixture of this substance and an authentic sample of 2-amino-4-bromoanisole was 95–96.2°. The 2-amino-4-bromoanisole was prepared by reduction with iron and acetic acid of 2-nitro-4-bromoanisole (m. p. 84–85°) which had been prepared by the method of Reverdin and Düring.[24] The ether extract of the original hydrolysis mixture was shaken with sodium bicarbonate solution to remove the acid. Acidification of the aqueous solution followed by ether extraction and evaporation of the ether yielded 0.04 g. of crude acid. After purification by sublimation and recrystallization from petroleum ether this substance melted at 116–118° and was found by mixed melting to be identical with β-(2-methoxy-5-bromophenyl)-propionic acid.

Summary

A satisfactory method for the preparation of 4-bromo-7-methoxyhydrindene has been worked out using the von Auwers hydrindone synthesis.

The structure of the intermediate 4-bromo-7-hydroxy-1-hydrindone has been proven by an alternate synthesis.

(21) Prepared in 78% yield by the method of Quelet, *Bull. soc. chim.*, [5] **1**, 539 (1934).

(22) Lasch, *Monatsh.*, **34**, 1662 (1913), reports the melting point as 142°.

(23) Fittig and Hochstetter, *Ann.*, **226**, 362 (1884), report the melting point as 106°.

(24) Reverdin and Düring, *Ber.*, **32**, 161 (1899).

It has been established that attempted cyclization of β-(2-methoxy-5-bromophenyl)-propionic acid produces 6-bromo-3,4-dihydrocoumarin as the main product.

The structure of a minor product (β-(2-methoxy-5-bromophenyl)-ethyl 2′-methoxy-5′-bromophenyl ketone) of the cyclization has been proved. This substance must have been formed by the elimination of a propionic side chain in the presence of aluminum chloride.

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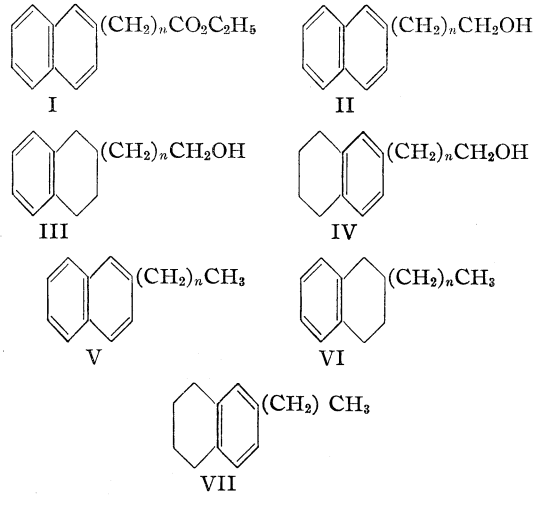
[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Selective Hydrogenation of Esters Containing a Naphthalene Nucleus

BY HOMER ADKINS AND EDWARD E. BURGOYNE[1]

The selective hydrogenation of a carbethoxy to a carbinol group, in an ester containing a naphthalene nucleus, has not seemed a feasible process. This was true because the naphthalene nucleus is rather rapidly and quantitatively hydrogenated to a tetralin over the copper chromium oxide catalyst at 150–190°. A further complication arises from the fact that the unsaturation of the rings labilizes an attached carbinol group toward hydrogenolysis. Thus the hydrogenation of esters of the type shown in I may give one or all of the three types of alcohols II, III and IV, and the hydrocarbons V, VI and VII resulting from hydrogenolysis.



Ethyl and methyl esters where "*n*" has a value of 0, 1, 2 and 3, and the chain is in the 1- or the 2-position of the nucleus, have been subjected to hydrogenation over a copper chromium oxide catalyst.[2] A summary of the numerical results of several of the more significant hydrogenations is given in Table I. The extent of hydrogenation is indicated in the fourth column of the table by stating the percentage to which the carbethoxy group reacted, as well as the moles of hydrogen absorbed during the period of reaction. A hydrogenation of ethyl benzoate to benzyl alcohol is also listed in the table. The result at 125° was similar to that reported at 165° by Mozingo and Folkers, who were the first to hydrogenate a carbethoxy group on a benzenoid nucleus to a carbinol group.[3]

The experimental conditions, as well as the structure of the ester, make important differences in the rates and relative rates of the various types of hydrogenation and hydrogenolysis. The compounds, where *n* equals 1, 2 or 3 in formula I, underwent hydrogenation to alcohols smoothly at 190–200°. The yield of alcohols when *n* equals 1 was lower (77%) than where *n* equals 2 or 3 (90%). There was no significant difference in behavior between the esters containing the 1- as compared with the 2-naphthyl group. However, in all the four esters just mentioned, four moles of hydrogen per mole of ester were absorbed so that the alcohol produced contained a tetrahydronaphthyl, rather than a naphthyl, group. That is to say, the naphthalene nucleus is sufficiently labile toward hydrogenation in the presence of the copper oxide–chromite catalyst so that hydrogenation of the ring took place under the same conditions required for the hydrogenation of the carbethoxy to a carbinol group. The relative distribution of hydrogen between the substituted and unsubstituted rings during catalytic hydrogenation, will be considered in more detail below, but it will suffice for the present to state that the tetrahydronaphthyl alcohols of structure IV predominate with lesser amounts of alcohols of type III.

In compounds where *n* equals zero in I, hydrocarbons are almost the only products resulting when the esters are hydrogenated at 190–200°. Fortunately, the esters where *n* equals 0 or 1, can be hydrogenated under milder conditions than when *n* equals 2 or 3. The naphthoates and naphthylacetates may be hydrogenated at tempera-

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(2) The catalyst was prepared as described by Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, 1937, p. 13, except the decomposition step was carried out by a procedure recommended by Dr. Ralph Mozingo. This consisted of decomposing 2 g. of copper ammonium chromate, stirring in another 2 g. and carefully decomposing, then adding 4 g., etc., each time doubling the amount added and carrying out the decomposition at the minimum temperature with constant stirring until a total of 60–100 g. of material was used.

(3) Mozingo and Folkers, THIS JOURNAL, **70**, 230 (1948).

TABLE I

HYDROGENATION OF ESTERS AT 300 ATMOSPHERES

0.1 mole in 100 ml. of methanol

Temp., °C.	Time, hr.	Catalyst, g.	% Hyd./Moles H_2	Yield of product, %	
			Ethyl γ-(1-naphthyl)-butyrate[a]		
200	7	5	100/0.4	92	4-(Tetrahydro-1-naphthyl)-butanol-1
			Ethyl γ-(2-naphthyl)-butyrate[b]		
200	7	5	100/0.4	92	4-(Tetrahydro-2-naphthyl)-butanol-1
			Methyl β-(1-naphthyl)-propionate[c]		
200	3.5	10	10/0.4	89	3-(Tetrahydro-1-naphthyl)-propanol-1
			Ethyl 1-naphthylacetate[d]		
190	3	5	100/0.4	77	2-(Tetrahydro-1-naphthyl)-ethanol
				17	1-Ethyltetrahydronaphthalene
			Methyl 1-naphthylacetate[e]		
120	0.67	20	41/0.19	40	2-(1-Naphthyl)-ethanol
108	2	20	37/0.23	28	2(1-Naphthyl)-ethanol
			Ethyl 1-naphthoate[f]		
88	3.5	10	40/0.22	5	1-Naphthylcarbinol
				35	1-Methylnaphthalene
80	7	10	66/0.22	51	1-Methylnaphthalene
			Methyl 2-naphthoate[g]		
108	1.5	10	65/0.24	35	2-Naphthylcarbinol
				5	2-Methylnaphthalene
166	7	10	100/0.48	70	2-Methyltetrahydronaphthalene
			Ethyl benzoate		
125	5	10	79/0.37	65	Benzyl alcohol

[a] [7,9] b. p. 139–140° (0.5 mm.), $n^{25}D$ 1.5652. [b] [7,9] b. p. 145–146 (1.5 mm.), $n^{25}D$ 1.5650. [c] [8] b. p. 145–147° (2 mm.), m. p. 34–5°, $n^{25}D$ 1.5832. [d] [5] b. p. 112–117° (0.5 mm.), $n^{25}D$ 1.5795. [e] [4,5,6] b. p. 122–122.5° (1 mm.), $n^{25}D$ 1.5952. [f] [10] b. p. 110° (0.05 mm.), $n^{25}D$ 1.5931, Z 33.5. [g] [11,12] m. p. 75–77°.

tures as low as 80° with an activated catalyst. At temperatures in the range 90–110°, with a high ratio of catalyst to ester, alcohols containing the unhydrogenated naphthalene nucleus were obtained. The best yields, so far obtained, are 35–40% for 2-(1-naphthyl)-ethanol and 2-naphthylcarbinol and only 6% for 1-naphthylcarbinol although the percentage yield of the naphthylethanol would be increased to almost 100% and the others by 50%, if allowance were made for the amount of ester not reacting.

In order to obtain the best yields it is necessary to carefully control the extent of hydrogenation and to stop the reaction after about 70% of the ester has been hydrogenated. If the reaction is allowed to proceed, then the carbinol is destroyed more rapidly than it is produced. Hydrogenolysis of the carbinols and hydrogenation of the naphthalene nucleus do take place over the catalyst even at temperatures below 100°. In fact, if too low a temperature is used in attempting to convert esters to alcohols, the reaction proceeds so slowly that hydrocarbons are produced just as they are at too high a temperature.

Since the hydrogenation of esters of formula I, when n was 3 or 4, gave only alcohols of formulas III and IV rather than of II, it became of interest to attempt to prepare the latter from III and IV through dehydrogenation. Two general methods were used with a palladium on activated carbon catalyst. In one method the dehydrogenation was carried out under pressure of ethylene in a steel reaction vessel at 200–225° for 8–13 hours, with benzene or cymene as the medium.[13] In the other the compound to be dehydrogenated was heated with a palladium catalyst under reflux at 180–185° for 18–29 hours in cymene. The extents of dehydrogenation obtained in both methods seemed to be about 65–80%. However, the yields of naphthyl alcohols were quite poor, both with respect to amount and quality of product. In every case hydrocarbons were produced, even when the dehydrogenations were far from complete. These results are similar to those reported by Newman and Zahm[14] and by others.

The relative rates of hydrogenation of the substituted and unsubstituted rings in esters of the structure of I has apparently not been determined. The isomeric tetrahydro esters or the corresponding alcohols (III and IV), or hydrocarbons (VI and VII) are not readily separated nor the proportions of the isomers in a mixture estimated. Several esters have been hydrogenated over W-6 Raney nickel at room temperature and low pressures, *i.e.*, ethyl γ-(1-naphthyl)-butyrate, ethyl γ-(2-naphthyl)-butyrate, methyl β-(1-naphthyl)-propionate, ethyl 1-naphthoate, and methyl 2-naphthoate. The corresponding tetrahydronaphthyl esters were produced almost quantitatively, four moles of hydrogen per mole of ester being taken up within a few hours.

The saponification of the esters and the separation of the acids showed that the tetrahydro esters from ethyl γ-(1-naphthyl)-butyrate and ethyl γ-(2-naphthyl)-butyrate gave good yields of the 5,6,7,8-tetrahydro (III) acids. The isomeric 1,2,3,4-tetrahydro (IV) acids were not found. The tetrahydro ester from methyl β-(1-naphthyl)-propionate gave both acids, the

(4) Manske and Ledingham, *Can. J. Research*, **17B**, 14 (1939).
(5) Arndt and Eistert, *Ber.*, **68**, 207 (1935).
(6) Grummitt and Buck, "Organic Syntheses," **24**, 30 (1944), John Wiley and Sons, Inc., New York.
(7) Wislicenus and Elvert, *Ber.*, **49**, 2822 (1916).
(8) Fieser and Gates, THIS JOURNAL, **62**, 2335 (1940).
(9) Borsche, *Ber.*, **52**, 2083 (1919).
(10) Whitmore and Loder, "Org. Syntheses," Coll. Vol. II, 282 (1943), John Wiley and Sons, Inc., New York, N. Y.
(11) Newman and Holmes, "Organic Syntheses," Coll. Vol. II, 428 (1943), John Wiley and Sons, Inc., New York, N. Y.
(12) Vieth, *Ann.*, **180** 319 (1876).
(13) Adkins and Reid, THIS JOURNAL, **63**, 741 (1941).
(14) Newman and Zahm, *ibid.*, **65**, 1097 (1943).

TABLE II

PROPERTIES AND ANALYSES OF COMPOUNDS

Compounds	$n^{25}D$	d^{25}_4	M_R Calcd.	M_R Found	B. p. or m. p. °C.	Mm.	Mol. form.	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
4-(5,6,7,8-Tetrahydro-1-naphthyl)-butanol	1.5430	1.0247	62.6	62.8	131–133	0.7	$C_{14}H_{20}O$	82.30	81.85	9.83	9.73
Phenylurethan					M. 87.5–88		$C_{21}H_{25}O_2N$	77.98	78.02	7.79	7.97
3,5-Dinitrobenzoate					M. 88.5–89.5		$C_{21}H_{22}O_6N_2$	63.30	62.88	5.57	5.47
4-(5,6,7,8-Tetrahydro-2-naphthyl)-butanol	1.5385	1.0153	62.6	62.9	131–135	0.8	$C_{14}H_{20}O$	82.30	81.83	9.87	9.99
3,5-Dinitrobenzoate					M. 130–132		$C_{21}H_{22}O_6N_2$	63.30	63.28	5.57	5.71
4-(2-Naphthyl)-butanol 3,5-dinitrobenzoate					M. 139–140		$C_{21}H_{18}O_6N_2$	64.01	63.69	4.60	4.46
3-(5,6,7,8-Tetrahydro-1-naphthyl)-propanol	1.5507	1.0446	58.0	58.5	126–129	0.7	$C_{13}H_{18}O$	82.02	81.74	9.53	9.68
3,5-Dinitrobenzoate					M. 96–98		$C_{20}H_{20}O_6N_2$	62.48	62.12	5.24	4.95
3-(1-Naphthyl)-propanol 3,5-dinitrobenzoate					M. 153–153.5		$C_{20}H_{16}O_6N_2$	63.14	63.05	4.24	4.40
5,6,7,8-Tetrahydro-1-naphthylcarbinol phenylurethan					M. 102–103		$C_{18}H_{19}O_2N$	76.86	76.53	6.81	6.90
1-Naphthylcarbinol phenylurethan					M. 89–89.5		$C_{18}H_{15}O_2N$	77.96	77.50	5.45	5.43
Ethyl γ-(5,6,7,8-tetrahydro-1-naphthyl)-butyrate	1.5194	1.031	71.97	72.94	140–141	1	$C_{16}H_{22}O_2$				
Methyl β-(5,6,7,8-tetrahydro-1-naphthyl)-propionate	1.5303	1.096	62.73	61.6	105–113	0.1	$C_{14}H_{18}O_2$				
Methyl β-(1,2,3,4-tetrahydro-1-naphthyl)-propionate	1.5263	1.109	62.73	60.4	.....		$C_{14}H_{18}O_2$				
Methyl 5,6,7,8-tetrahydro-1-naphthoate	1.5442	1.104	53.49	54.3	.....		$C_{12}H_{14}O_2$				

yield of the 5,6,7,8-tetrahydro acid being three times as large as that of the 1,2,3,4-tetrahydro acid. Similarly ethyl 1-naphthoate gave the 5,6,7,8-tetrahydro acid and the 1,2,3,4-tetrahydro acid in a ratio of 5:3. Methyl 2-naphthoate gave the 5,6,7,8- and the 1,2,3,4-tetrahydro acids in a ratio of 15:1.

The distribution of hydrogen between the rings of an ester or alcohol over a copper chromium oxide catalyst under 300 atm. would not necessarily be the same as over a nickel catalyst at 2–3 atm. However, the evidence available is that the proportion of 1,2,3,4- and 5,6,7,8-tetrahydroalcohols is similar in the two cases. The 2-(1-tetrahydronaphthyl)-ethanol obtained (Table I) gave the 3,5-dinitrobenzoate of 2-(1-(5,6,7,8-tetrahydronaphthyl))-ethanol[15] in good purity and yield.

Saponification of the residual ester in an incomplete hydrogenation of methyl β-(1-naphthyl)-propionate over copper chromium oxide gave 3-(1-tetrahydronaphthyl)-propanol-1 and after saponification of the residual esters, β-[1-(5,6,7,8-Tetrahydronaphthyl)]-propionic acid. This acid constituted at least 70% of the mixture of acids, a proportion in harmony with that obtained in the low pressure hydrogenation over W-6 Raney nickel. Thus the 5,6,7,8 isomers probably predominate in the tetrahydronaphthyl alcohols listed in Table I, although significant amounts of the 1,2,3,4 isomer are no doubt present.

Experimental Part

The esters used were distilled from Raney nickel before they were submitted to hydrogenation. They had the properties indicated in the footnotes to Table I. The ethyl γ-naphthylbutyrates were prepared from naphthalene (154 g.) through the reaction of succinic anhydride with naphthalene[7,9,16,17,18,19]; separation of the isomeric acids (m. p. 120–125° and m. p. 167–172°); their reduction to γ-(1-naphthyl)-butyric acid (m. p. 104–107°) and γ-(2-naphthyl)-butyric acid (m. p. 95–97°); and esterification of the acids. The over-all yield of the esters from naphthalene was approximately 50% of the theoretical, the two esters being obtained in a ratio of 4 parts of 1-naphthyl to 3 parts of the 2-naphthyl ester.

The catalyst was separated by centrifugation; solid potassium hydroxide (5 g.) added to the methanol solution; the solvent distilled off during a period of 3–4 hours; water added to the residue; the alcohols and hydrocarbons extracted with ether; the products dried and distilled; and the acids recovered from their salts. The products were crystallized where possible, or fractionated through a Vigreux column (12 mm. × 15 cm.). The alcohol from ethyl 1-naphthylacetate was characterized as the 3,5-dinitrobenzoate, m. p. 126–127°, of 2-1-(5,6,7,8-tetrahydronaphthyl)-ethanol.[6] The 2-(1-naphthyl)-ethanol from the methyl 1-naphthylacetate (20 g.) was obtained in a yield of crude product of 6.9 g., b. p. 115–121° (0.12 mm.), $n^{25}D$ 1.6105–1.6180. Purification by distillation and crystallization from petroleum ether gave 3.8 g., m. p. 55–58° and recrystallization 3.3 g., m. p. 60.5–61.5°. The phenylurethan had a m. p. 116–116.5°.[20] 1-Naphthylacetic acid (11.0 g.) was recovered after saponification of the residual ester, indicating that the hydrogenation had not been more than 41% complete. Ethyl 1-naphthoate at 80° gave 1-methylnaphthalene (7.3 g., b. p. 97–99° (6.5 mm.), $n^{25}D$ 1.6140, Z 35.0. Ethyl 1-naphthoate at 88° gave products which after several recrystallizations gave 0.6 g. of 2-(1-naphthyl)-ethanol, m. p. 58–59°, and 0.3 g., m. p. 60–61°, with a phenylurethan m. p. 89–89.5°.[21,22] There was also obtained in the usual way 1-naphthoic acid (9.5 g.) and 1-methylnaphthalene (4.9 g.) b. p. about 100° (7 mm.), $n^{25}D$ 1.6120–1.6132.

Methyl 2-naphthoate gave 2-naphthylcarbinol (5.7 g., m. p. 80–81°),[23] 2-methylnaphthalene (0.8 g., m. p.

(15) Cook, Hewett, Mayneord and Roe, *J. Chem. Soc.*, 1736 (1934).

(16) Adams and Thal, "Organic Syntheses," Coll. Vol. 1, 270 (1941), John Wiley & Sons, Inc., New York, N. Y.

(17) Haworth, *J. Chem. Soc.*, 1125 (1932).

(18) Fieser and Peters, THIS JOURNAL, **54**, 4354 (1932).

(19) Martin, "Organic Syntheses," Coll. Vol. II, 499 (1943), John Wiley and Sons, Inc., New York, N. Y.

(20) Shoruigin and Shoruigina, *J. Gen. Chem.* (*U. S. S. R.*), **5**, 555 (1935), *C. A.*, **29**, 6886 (1935).

(21) Bamberger and Lodter, *Ber.*, **21**, 258 (1888).

(22) Rupe and Bretano, *Helv. Chim. Acta*, **19**, 581 (1936).

(23) Sah, *Rec. trav. chim.*, **59**, 461 (1940).

31–32°), and 2-naphthoic acid (5.8 g.) after saponification of the residual ester. The material not accounted for above was apparently a mixture of hydrocarbons which did not crystallize. When the hydrogenation was carried out at 166° the chief product was a hydrocarbon (10.2 g., b. p. 75–85° (6.5 mm.), $n^{25}D$ 1.5335, Z 23.2). The product was apparently predominantly 2-methyl-5,6,7,8-tetrahydronaphthalene.[24]

Hydrogenation of Esters at 2–3 atm. Pressure.—The esters (0.05 mole) in 50–75 ml. of methanol or ethanol, depending upon whether a methyl or ethyl ester was used, were hydrogenated at room temperature, in a pyrex glass centrifuge bottle of 235 ml. capacity, with 5 g. of W-6 Raney nickel,[25] under a pressure of 45 to 30 p. s. i. The esters absorbed 2 moles of hydrogen per mole of ester during a period varying from 1.2 hours for ethyl 1-naphthoate to eight hours for ethyl γ-(2-naphthyl)-butyrate. The other esters ethyl γ-(1-naphthyl)-butyrate, methyl β-(1-naphthyl)-propionate and methyl 2-naphthoate required two to four hours for hydrogenation. The hydrogenations went quantitatively with the formation of the tetrahydro esters. The products were distilled and showed the properties and analyses given in Table II.

Samples of each of the six tetrahydro esters were saponified in the usual way and the acids isolated. The γ-[1-(5,6,7,8-tetrahydronaphthyl)]-butyric acid, 3.5 g., m. p. 96–97°,[26] was obtained by recrystallization from 5.2 g. of acid obtained from the saponification. None of the isomeric 1,2,3,4-tetrahydro acid could be found in the mother liquors. Similarly γ-[2-(5,6,7,8-tetrahydronaphthyl)]-butyric acid, 3.6 g., m. p. 46.5–47.5°,[27] was obtained in turn from 10.8 g. of the acid. The amide, m. p. 135–136°, was prepared.[28] None of the isomeric 1,2,3,4-tetrahydro acid could be found in the mother liquors from which the 5,6,7,8-tetrahydro acid had been obtained.

The saponification of ethyl β-(1-tetrahydronaphthyl)-propionate gave a mixture of acids. From the mixture of acids (3.5 g.) there was obtained by recrystallizations from petroleum ether, β-[1-(5,6,7,8-tetrahydronaphthyl)]-propionic acid, 2.5 g., m. p. 136–137°.[29] The isomeric β-[1-(1,2,3,4-tetrahydronaphthyl)]-propionic acid, 0.5 g., m. p. 75–76°, was also obtained.[30] The ratio of the two isomeric acids was calculated to be about 3:1.

Two acids were obtained by the saponification of a sample of methyl 1-tetrahydronaphthoate. Through the usual procedures 1-(5,6,7,8-tetrahydro)-naphthoic acid, 1.7 g., m. p. 148–150°, was obtained from 2.2 g., m. p. 140–145°, which was in turn obtained from 4.7 g. of the mixture of acids from a saponification. The amide m. p. 185° was prepared.[31,32] There was also obtained from the mixture of acids (4.7 g.) the 1-(1,2,3,4-tetrahydro)-naphthoic acid, 1.3 g., m. p. 74–80°. The amide m. p. 141–143° was prepared.[33]

The chief component of the mixture of acids (8.6 g.) from methyl 2-naphthoate was 5,6,7,8-tetrahydro-2-naphthoic acid, 6.8 g., m. p. 148–151°, 5.8 g., m. p. 152–153.5°. The amide m. p. 137–138° was prepared.[34,35] There was also obtained 0.3 g. of somewhat impure 1,2,3,4-tetrahydro-2-naphthoic acid, m. p. 85–87°, and after recrystallization m. p. 86–88°.[36,37]

Dehydrogenation of Tetrahydronaphthyl Alcohols.—A sample (10.2 g.) of 4-[2-(tetrahydronaphthyl)]-butanol-1 in 50 ml. of *p*-cymene was dehydrogenated with 2 g. of a 5% palladium on activated carbon catalyst,[38] by heating it in a bath held at 185–190°. The apparatus was equipped with ground glass connections and a mechanical stirrer. About 2.5 liters of hydrogen was evolved during a period of 28.5 hours. When the products of the reaction were worked up a hydrocarbon fraction 2.6 g., b. p. 83–116° (0.3 mm.), $n^{25}D$ 1.5718, Z 29.0, d^{25}_4 0.9647; and an alcohol fraction 4.2 g., b. p. 135–137° (0.3 mm.), $n^{25}D$ 1.5664, Z 25.6 were obtained. Upon the basis of the Z values, the mixture of alcohols was estimated to contain 60% of 4-(2-naphthyl)-butanol-1 mixed with 40% of the tetrahydro alcohol. A picrate m. p. 77–78° prepared from the hydrocarbon fraction indicated 2-(*n*-butyl)-naphthalene.[39] 3-[1-(Tetrahydronaphthyl)]-propanol-1 (9.5 g.) was dehydrogenated as described for the butanol above. Similar results were obtained, 2140 ml. of hydrogen was evolved and 5 g. crude γ-(1-naphthyl)-propanol-1, b. p. 131–133° (0.7 mm.), $n^{25}D$ 1.5917, Z 28.5, d^{25}_4 1.0719[10] was obtained. Analysis for carbon and hydrogen as well as the Z values indicated that the product was not more than 80% pure. Hydrocarbons (2 g.) were also produced in the dehydrogenation.

Summary

Esters of formula I where *n* is 0, 1, 2 or 3, and the substituent is in the 1 or 2 position of the naphthalene nucleus, have been submitted to hydrogenation over the copper chromium oxide catalyst at temperatures from 80 to 200°. Through the use of a high ratio of catalyst to ester at 80–120° and by controlling the extent of hydrogenation, alcohols of formula II have been obtained where *n* is 0 or 1. Where *n* has a value of 2 or 3 the temperature required for the hydrogenation of the carbethoxy group was sufficiently high so that tetrahydronaphthyl alcohols of formula III and IV were obtained.

Esters of formula I have been quantitatively hydrogenated to the corresponding tetrahydronaphthyl esters, over W-6 Raney nickel at 2-3 atm. and room temperature. The unsubstituted ring is more susceptible to hydrogenation than the substituted ring in these esters.

MADISON, WISCONSIN RECEIVED APRIL 23, 1949

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(25) Adkins and Billica, THIS JOURNAL, **70**, 695 (1948).
(26) Schroeter, *Ber.*, **57B**, 2025 (1924).
(27) Newman, THIS JOURNAL, **65**, 1097 (1943).
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(33) Newman and O'Leary, THIS JOURNAL, **68**, 258 (1946).
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(37) Pickard and Yates, *J. Chem. Soc.*, **89**, 1107 (1906).
(38) Mozingo, "Organic Syntheses," **26**, 78, John Wiley and Sons, Inc., New York, N. Y., 1946.
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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY AND CHEMOTHERAPY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

The Oxidation of Volemitol by Acetobacter suboxydans and by Acetobacter xylinum

BY LAURA C. STEWART, NELSON K. RICHTMYER AND C. S. HUDSON

Volemitol (I) was discovered by Bourquelot[1] in the mushroom *Lactarius volemus* Fr., by Bougault and Allard[2] in the roots of several species of *Primula*, and more recently by Asahina and Kagitani[3] in the lichen *Dermatocarpon miniatum* (L.) Mann. From the synthetic side this same heptitol has been described by Peirce[4] who called it D-β-mannoheptitol because he had obtained it from D-β-mannoheptose by reduction with sodium amalgam; by LaForge,[5] who isolated it as one of the reduction products of naturally occurring D-mannoheptulose; and by LaForge and Hudson,[6] who called it α-sedoheptitol when they found it to be one of the reduction products of naturally occurring sedoheptulose. LaForge[7] showed that α-sedoheptitol was identical with volemitol, and Ettel[8] later proved the identity of volemitol with D-β-mannoheptitol of known configuration.[4] By our present system of nomenclature, volemitol (I) may be named either D-manno-D-*talo*-heptitol or D-altro-D-*manno*-heptitol.

In a recent contribution from this Laboratory[9] it was established that the "phenyl-volemosazone" which Fischer[10] obtained from the products of oxidation of volemitol by sodium hypobromite was D-mannoheptose phenylosazone, and it was suggested accordingly that the name "volemose" might well be discarded or used only in a historical way. In accord with a previously announced intention,[9] we have now repeated Bertrand's[11] biochemical oxidation of volemitol with *Acetobacter xylinum* and have identified "volemulose," the sirupy ketone sugar formed. Very recently, Ettel and Liebster[12] showed that *A. suboxydans* oxidized volemitol to a mixture of D-mannoheptulose and D-altroheptulose (= sedoheptulose) and estimated that the two sugars were produced in equal amounts. The present independently conceived experiments agree with these results, but they disprove Ettel and Liebster's inference that *A. xylinum* and *A. suboxydans* give the same products from volemitol.

(1) E. Bourquelot, *Bull. soc. mycologique France*, **5**, 132 (1889); *J. pharm. chim.*, [6] **2**, 385 (1895).

(2) J. Bougault and G. Allard, *Compt. rend.*, **135**, 796 (1902); *Bull. soc. chim.*, [3] **29**, 129 (1903).

(3) Y. Asahina and M. Kagitani, *Ber.*, **67**, 804 (1934).

(4) G. Peirce, *J. Biol. Chem.*, **23**, 327 (1915).

(5) F. B. LaForge, *ibid.*, **28**, 511 (1917).

(6) F. B. LaForge and C. S. Hudson, *ibid.*, **30**, 61 (1917).

(7) F. B. LaForge, *ibid.*, **42**, 375 (1920).

(8) V. Ettel, *Collection Czechoslov. Chem. Commun.*, **4**, 504 (1932).

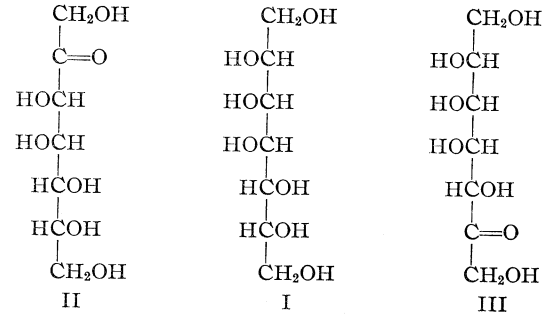
(9) W. T. Haskins and C. S. Hudson, THIS JOURNAL, **69**, 1370 (1947).

(10) E. Fischer, *Ber.*, **28**, 1973 (1895).

(11) (a) G. Bertrand, *Compt. rend.*, **126**, 763 (1898); (b) *Bull. soc. chim.*, [3] **19**, 347 (1898); (c) *Ann. chim.*, [8] **3**, 209, 287 (1904).

(12) V. Ettel and J. Liebster, *Collection Czechoslov. Chem. Commun.*, **14**, 80 (1949).

Because *Acetobacter suboxydans*, in contrast to *A. xylinum*, had previously been found to give excellent yields of ketone sugars from most of the polyhydric alcohols which it attacks, we decided to study first the behavior of *A. suboxydans* toward volemitol. According to the specificity rule of Bertrand[13] for *A. xylinum*, as extended by Hann, Tilden and Hudson[14] to *A. suboxydans*, we should expect that the latter organism would oxidize volemitol (I) to D-mannoheptulose (II), D-altroheptulose (=sedoheptulose) (III), or to a mixture of these two ketoses. Experiments showed that volemitol was indeed oxidized readily by *A. suboxydans*, and reducing sugar was produced in nearly theoretical yield. The resulting solution, from 9 g. of volemitol, was deproteinized, deionized, and concentrated to a sirup from which we were able to isolate 3.8 g. of crystalline D-mannoheptulose. The mother liquor was heated with dilute sulfuric acid to convert any sedoheptulose to its anhydride, and we could then obtain 2.2 g. of crystalline sedoheptulosan. Thus, as might be expected from the presence of the favorable grouping —CHOH—CHOH—CH_2OH at each end of the volemitol molecule, both D-mannoheptulose and D-altroheptulose were formed by the action of *A. suboxydans*.



On the other hand, the oxidation of 4 g. of volemitol by *A. xylinum* proceeded very slowly. A heavy pellicle of cellulosic material was formed, and titration of the solution showed that only 29% of the expected reducing sugar was formed even after fifty-five days. The solution, freed from

(13) G. Bertrand, ref. 11a, 11b and 11c, p. 202.

(14) R. M. Hann, E. B. Tilden and C. S. Hudson, THIS JOURNAL, **60**, 1201 (1938).

protein, ionizable material, and 2.2 g. of unchanged volemitol, was concentrated to a sirup which showed no tendency to crystallize when inoculated with D-mannoheptulose. It was heated with dilute sulfuric acid, with a resulting change in rotation from positive to negative, and 0.22 g. of crystalline sedoheptulosan was isolated. The mother liquor was acetylated and chromatographed, but no evidence could be found to indicate the presence of D-mannoheptulose.[14a] The conclusion is that *A. xylinum* appears to attack only one end of the volemitol molecule to produce a ketoheptose, and that Bertrand's sirupy "volemulose" was in reality the first description of the sugar we now know as D-altroheptulose (=sedoheptulose). The phenylosazone of "volemulose," reported by Bertrand[11a,b] to melt at 205–207° is to be identified as D-altroheptose phenylosazone, even though the melting point of the latter is known to be somewhat lower, namely, 197°[6] or 194–195°.[15]

Experimental

Volemitol.—The material used in these experiments was prepared by Dr. Raymond M. Hann and Mr. John T. Sipes, of this Laboratory, by the reduction of sedoheptulose sirups with sodium amalgam.[16] The recrystallized product melted at 152°.

Oxidation of Volemitol by Acetobacter suboxydans.—After some preliminary experiments had been completed, the following procedure was adopted for the oxidation of the 10-g. sample. A medium was prepared to contain 0.5% of Difco yeast extract, 0.3% of potassium dihydrogen phosphate, 0.05% of D-glucose and 2% of volemitol after dilution to 500 ml. with distilled water. This solution was distributed among five 500-ml. Erlenmeyer flasks, sterilized, and each flask was inoculated with 0.3 ml. of a three-day-old culture of *A. suboxydans*[17] grown on a yeast extract and D-glucose medium. The mixture was incubated in an oven at 30°. The progress of the reaction was followed by deproteinizing 1-cc. aliquots with zinc sulfate and barium hydroxide according to Somogyi,[18] and determining reducing sugar in the filtrate by the method of Hagedorn and Jensen[19] as modified by Hanes.[20] After one hundred and sixty-two hours a reducing value equivalent to 18.1 mg. of mannoheptulose per ml. had been reached, and was unchanged after another twenty-four hours.

The remainder of the material in the five flasks was combined and deproteinized by the addition of 250 ml. of 5% aqueous zinc sulfate solution followed by an equivalent amount of aqueous barium hydroxide solution, so that the resulting reaction mixture was neutral to phenolphthalein. The clear, colorless filtrate was deionized by passage through columns of Amberlite IR-100 and IR-4B, and then concentrated *in vacuo* to 280 ml. At this point, 28 ml. of the solution, corresponding to about 1 g. of reducing sugars, was heated with 2 ml. of phenylhydrazine and 1 ml. of glacial acetic acid for two hours on the steam-bath. The resulting phenylosazone was filtered from the cooled solution, and washed successively with 10% acetic acid, water, ethanol and ether. The yellow, finely crystalline powder weighed 1.1 g. and melted at 180–187° with decomposition. Upon recrystallization from 75 ml. of ethanol the clusters of tiny, yellow needles (0.4 g.) melted at 177–185° with decomposition. The material is evidently a mixture of the phenylosazones[9] of D-altroheptose (194–195°) and D-mannoheptose (199–200°), and no further attempts were made to separate the components.

The main portion of the solution was concentrated *in vacuo* to a dry sirup which was taken up in methanol and allowed to concentrate in a desiccator. Upon inoculation at the thin-sirup stage, D-mannoheptulose separated in a yield of 2.8 g., with an additional 1.0 g. being obtained later. The product, after one recrystallization as prisms from methanol, weighed 2.2 g., melted at 151–152° and showed no depression of melting point when mixed with an authentic sample. The rotation, $[\alpha]^{20}D$ +29.1° in water (*c*, 2.5), was in agreement with the values +29.0 and +29.4° reported by LaForge.[5]

The filtrate from the D-mannoheptulose crystals was concentrated to a sirup which was dissolved in 30 ml. of *N* sulfuric acid and heated on the steam-bath for three hours. The solution was neutralized with excess barium carbonate, filtered, and concentrated *in vacuo* to a thick sirup. By dissolving the sirup in methanol and again concentrating we obtained a total of 2.2 g. of the characteristic prisms of sedoheptulosan.[21] After one recrystallization from hot methanol the product had a rotation, $[\alpha]^{20}D$ −143° in water (*c*, 2), and melting point, 154–155°, in good agreement with the values −146° and 155–156° reported by LaForge and Hudson.[6] A mixture of our product with sedoheptulosan from *Sedum spectabile* showed no depression of melting point.

Oxidation of Volemitol by Acetobacter xylinum.—In view of the experience of Tarr and Hibbert,[22] preliminary studies were made to determine optimal cultural conditions for the growth of *A. xylinum* upon mannitol and perseitol as substrates. A small concentration of ethanol appeared to stimulate the oxidation to some extent, whereas D-glucose and sodium lactate had little or no stimulatory effect. The medium finally selected contained 0.5% of Difco yeast extract, 0.3% of potassium dihydrogen phosphate and 2% of volemitol after dilution to 200 ml. with distilled water. The solution was divided between two 500-ml. Erlenmeyer flasks, sterilized, and to each flask was added 0.7 ml. of ethanol; this was followed by an inoculum of five drops of a twenty-four-hour culture of *Acetobacter xylinum*[23] which had been grown on a yeast extract and D-glucose broth containing 10% of canned cherry juice. After thirty days' incubation at 30° the mixture contained the equivalent of 5.2 mg. of mannoheptulose per ml.; after forty days the value had risen to 5.8 mg./ml., and was unchanged after another fifteen days. The solution was separated from the pellicle of cellulosic material, deproteinized, deionized, and concentrated *in vacuo* to dryness. The solid residue was extracted several times with warm methanol, leaving 2.2 g. of unchanged volemitol. The concentrated methanol solution would not crystallize when inoculated with D-mannoheptulose. Accordingly, the sirup was heated on the steam-bath for three hours with 50 ml. of *N* sulfuric acid; the levorotatory solution was neutralized with excess barium carbonate, filtered, and concentrated to a dry sirup. A methanol extract then yielded 0.22 g. of crystalline sedoheptulosan which was identified, after one recrystallization from methanol, by its rotation of $[\alpha]^{20}D$ −146° in water

(14a) Note added Sept. 29, 1949.—In order to eliminate the possibility that D-mannoheptulose was formed and then oxidized further by *A. xylinum*, it has now been shown in a separate experiment that a 0.5% solution of this ketose was unaffected even by seven weeks' incubation with *A. xylinum* in the usual culture medium.

(15) The melting point reported by Bertrand may have been observed on the Maquenne block.

(16) A. T. Merrill, W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **69**, 70 (1947).

(17) American Type Culture Collection No. 621.

(18) M. Somogyi, *J. Biol. Chem.*, **160**, 69 (1945).

(19) H. C. Hagedorn and B. N. Jensen, *Biochem. Z.*, **135**, 46 (1923).

(20) C. S. Hanes, *Biochem. J.*, **23**, 99 (1929).

(21) Sedoheptulosan monohydrate has recently been obtained in this Laboratory by crystallization of sedoheptulosan from water or aqueous ethanol. In contrast to the anhydrous form it is stable in moist air. Further details will appear later.

(22) H. L. A. Tarr and H. Hibbert, *Can. J. Research*, **4**, 372 (1931).

(23) Obtained through the courtesy of Dr. Reese H. Vaughn of the University of California.

(c, 1.2), and its melting point and mixed melting point of 154–155°.

The mother liquor from the sedoheptulosan still would not crystallize when concentrated and inoculated with D-mannoheptulose. The 0.38 g. of sirup was acetylated with acetic anhydride and pyridine, to yield 0.57 g. of sirupy acetate. Using the technique of flowing chromatography which we had already found could be applied to the acetylated mother liquor of the *A. suboxydans* experiment, we dissolved the 570 mg. of this acetate in ether, poured it on a column containing 10 g. of alumina, and eluted it exhaustively with absolute ether to remove 363 mg. of levorotatory material. Further elution with mixtures of ether and ethyl acetate produced 152 mg., in five fractions, all of which were dextrorotatory, but none could be induced to crystallize when inoculated with hexaacetyl-α-D-mannoheptulose as did certain of the corresponding fractions from the *A. suboxydans* experiment. In this case the dextrorotatory material presumably consists of acetylated sedoheptulose which has not yet been obtained in crystalline form. The combined five fractions were deacetylated, but the small amount of sirup still would not crystallize when inoculated with mannoheptulose.

Summary

The action of *Acetobacter suboxydans* upon volemitol proceeds readily and nearly quantitatively to produce both D-mannoheptulose and D-altroheptulose (=sedoheptulose). This result is in agreement with the specificity rule of Hann, Tilden and Hudson for the action of *A. suboxydans*.

The action of *Acetobacter xylinum* upon volemitol is slow and incomplete; only one end of the molecule appears to be oxidized, and the sirupy ketose, which was first obtained by Bertrand and named "volemulose," has been identified as D-altroheptulose (=sedoheptulose).

BETHESDA, MARYLAND RECEIVED MAY 31, 1949

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Hydrogen Transfer. III.[1] Reaction of *p*-Ethyltoluene and *p*-Propyltoluene with Methylcyclohexene. Synthesis of Diarylalkanes

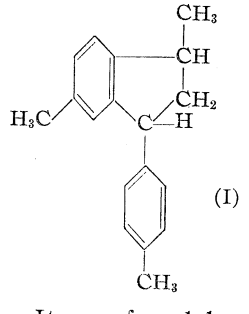
BY HERMAN PINES, D. R. STREHLAU[2] AND V. N. IPATIEFF

In a previous paper it has been shown that an abnormal reaction occurs when *p*-cymene is contacted with methylcyclohexene in the presence of either sulfuric acid or hydrogen fluoride.[3] Instead of the expected cycloalkylation of *p*-cymene, a hydrogen transfer was the main reaction; the methylcyclohexene acted as a hydrogen acceptor, forming methylcyclohexane, while *p*-cymene acted as a hydrogen donor yielding as the main product 1,3,3,6-tetramethyl-1-*p*-tolylindan.

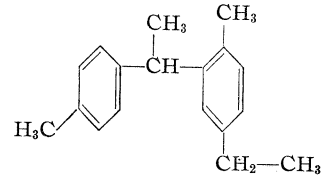
It was of interest to determine whether a para disubstituted benzene ring having an alkyl group containing more than one hydrogen atom on the carbon attached to the benzene ring would also yield products resulting from a hydrogen transfer reaction. For that reason *p*-xylene, *p*-ethyl- and *p*-propyltoluene reacted with methylcyclohexene in the presence of hydrogen fluoride and/or sulfuric acid.

p-Xylene, on reacting with methylcyclohexene in the presence of hydrogen fluoride, yielded only methylcyclohexyl-*p*-xylene. The formation of methylcyclohexane which serves as an indicator of a hydrogen transfer reaction was not observed.

Hydrogen transfer was the main reaction when *p*-ethyltoluene and methylcyclohexene in the molal ratio of two to one reacted in the presence of hydrogen fluoride. Forty-five per cent. of the methylcyclohexene was converted to methylcyclohexane and 20% to a compound corresponding to dimethyldicyclohexyl. Of the converted *p*-ethyltoluene 65% underwent a hydrogen transfer reaction to form a compound (Y) containing 18 carbon atoms boiling at 157° (6 mm.), $n^{20}D$ 1.5540; and 23% underwent condensation with methylcyclohexene, yielding probably 2-(1-methylcyclohexyl)-4-ethyltoluene[3a]; and remainder of the reacted *p*-ethyltoluene corresponded to a condensation product of methylcyclohexene with compound (Y). It was thought at first that *p*-ethyltoluene reacted with methylcyclohexene in a manner similar to the reaction of *p*-cymene and methylcyclohexene, and that 3,6-dimethyl-1-*p*-tolylindan (I), would be formed.



(I)



(II)

It was found however that the physical constants, solid derivatives and infrared absorption spectra (Graph I) of synthetic (I) did not correspond to the compound (Y) (Graph II).

In line with the mechanism proposed for the hydrogen transfer reactions described previously,[1] it

(1) For paper II of this series see H. Pines, A. Weizmann and V. N. Ipatieff, THIS JOURNAL, **70**, 3859 (1948).

(2) Universal Oil Products Company Predoctorate Fellow (1945–1947).

(3) V. N. Ipatieff, H. Pines and R. C. Olberg, THIS JOURNAL, **70**, 2123 (1948)

(3a) This conclusion is based on the observation that during the reaction of *p*-cymene with cyclohexene the carbon atom ortho to the methyl group is substituted[1] and that the reaction between benzene and isomeric methylcyclohexenes, including 4-methylcyclohexene results in the formation of 1-methyl-1-phenylcyclohexane (V. N. Ipatieff, E. E. Meisinger and H. Pines, unpublished work).

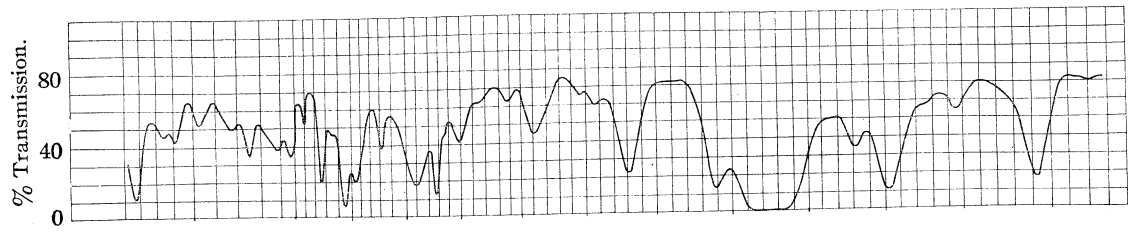


Fig. 1.—Synthetic 3,6-dimethyl-1-*p*-tolylindan.

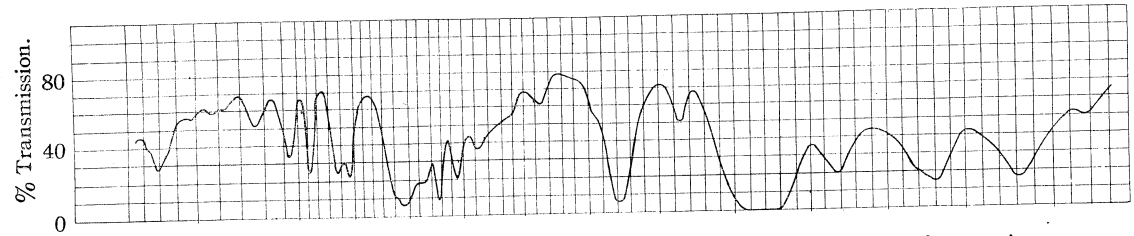


Fig. 2.—1-*p*-Tolyl-1-(2-methyl-ethylphenyl)-ethane obtained from hydrogen transfer reaction.

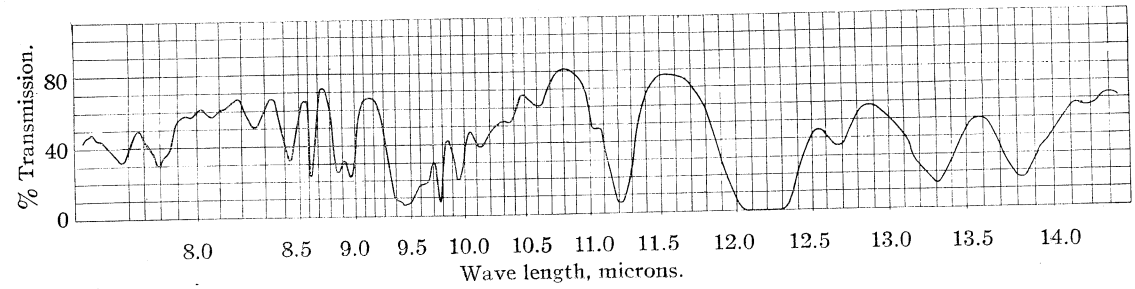


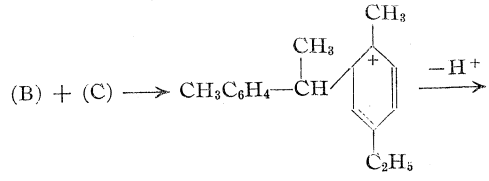
Fig. 3.—Synthetic 1-*p*-tolyl-1-(2-methyl-5-ethylphenyl)-ethane.

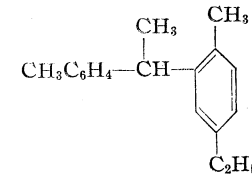
was reasoned that the reaction between *p*-ethyltoluene and methylcyclohexene might have yielded 1-*p*-tolyl-1-(2-methyl-5-ethylphenyl)-ethane (II). Compound II was synthesized, and it was found to be identical with the compound (Y) obtained from the hydrogen transfer reaction (Graphs I and III). Sulfuric acid used as the catalyst caused a similar type of reaction to occur as did hydrogen fluoride; 60% of the olefins used was converted to methylcyclohexane. The higher boiling hydrocarbons obtained from the reaction catalyzed by sulfuric acid were identical with the corresponding fraction obtained from the reaction in the presence of hydrogen fluoride.

To explain these findings, it is assumed that the proton from sulfuric acid or hydrogen fluoride adds to the methylcyclohexene to form a carbonium ion which then acts with *p*-ethyltoluene

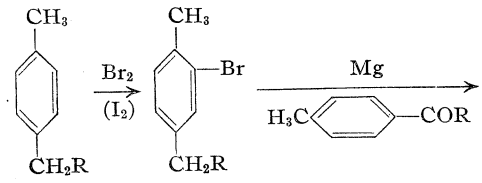
$$CH_3C_6H_9 \xrightarrow{H^+} CH_3C_6H_{10}^+ \qquad (A)$$

$$(A) + CH_3C_6H_4C_2H_5 \rightleftharpoons CH_3C_6H_{11} + CH_3C_6H_4\overset{+}{C}HCH_3$$
(B) (C)

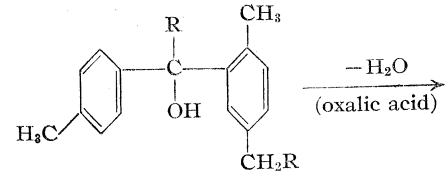




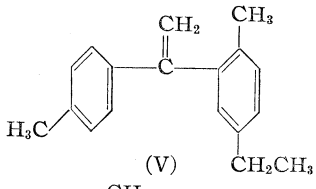
The synthesis of compound II and of a similar compound XVII was carried out according to the equations



R, CH_3 (III)
R, C_2H_5 (XIV)

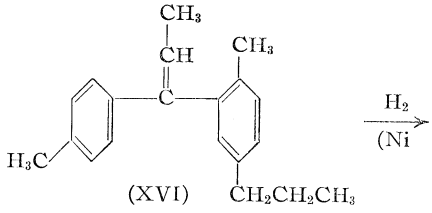


R, CH_3 (IV)
R, C_2H_5 (XV)

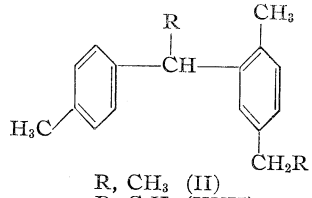


and

(V)

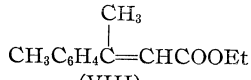


(XVI)

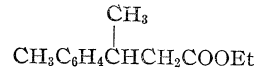


R, CH_3 (II)
R, C_2H_5 (XVII)
R, CH_3, C_2H_5

To synthesize (I) these steps were followed: *p*-methylacetophenone and ethyl bromoacetate were condensed in a Reformatsky reaction into ethyl 3-*p*-tolyl-3-hydroxybutyrate (VII); after dehydration of this compound to VIII, hydrogenation to IX and ring closure to 3,6-dimethyl-1-indanone

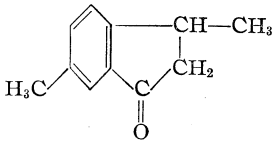


(VIII)

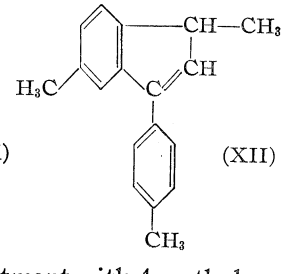


(IX)

(X) using hydrogen fluoride, the indanone was treated with *p*-tolylmagnesium bromide; the intermediary tertiary alcohol (XI) was not isolated but was dehydrated to the substituted indene (XII) which was hydrogenated to (I).



(X)



(XII)

p-Propyltoluene on treatment with 4-methylcyclohexene in the presence of hydrogen fluoride under experimental conditions indicated for *p*-ethyltoluene, yielded also as main reaction products compounds resulting from a hydrogen transfer reaction. Of the methylcyclohexene reacted, 40% was converted to methylcyclohexane and 15% to a compound corresponding to a dimethyldicyclohexyl and only 24% was condensed with *p*-propyltoluene to form methylcyclohexyl-*p*-propyltoluene. Of the *p*-propyltoluene reacted, 50% was converted to 1-*p*-tolyl-1-(2-methyl-5-propylphenyl)-propane; the structure of this compound was proved by comparing its infrared spectra (Graph IV) with that of the corresponding compound prepared by synthesis (Graph V).

The synthesis of 1-*p*-tolyl-1-(2-methyl-5-propylphenyl)-propane was made according to the outline presented above.

The *p*-ethyl- and *p*-propyltoluene used in this reaction were prepared by hydrogenation of the appropriate ketones.[4]

In attempting to prepare acetyl derivatives of compounds II and XVII which could be converted to solid 2,4-dinitrophenylhydrazones, it was found that acetylation causes a split at the aliphatic bridge at the para position of the tolyl and gives rise to *p*-methylacetophenone and tarry products from either II or XVII.

Experimental Part

I. Synthesis of *p*-Ethyltoluene

(a) ***p*-Acetyltoluene (VI).**—This compound was prepared from 275 g. (3.5 moles) of acetyl chloride, 276 g. (3 moles) toluene and 467 g. (3.5 moles) of aluminum chloride in 1800 ml. of carbon disulfide; yield 88%, b. p. 108° (18 mm.), $n^{20}D$ 1.5348. The oxime of this ketone melted at 87–88°.[5]

(b) ***p*-Ethyltoluene.**—*p*-Acetyltoluene was hydrogenated under 100 atmospheres of initial hydrogen pressure and at 180° in the presence of a copper oxide–alumina catalyst[4] (94% CuO, 6% Al_2O_3). The *p*-ethyltoluene which was obtained in a yield of 95% distilled at 161–162°, $n^{20}D$ 1.4943.[6]

II. Reaction of *p*-Ethyltoluene with 4-Methylcyclohexene in the Presence of Hydrogen Fluoride

The reaction was carried out according to a procedure described previously.[3] The following reagents were used: 240 g. (2 moles) of *p*-ethyltoluene, 96 g. (1 mole) of 4-methylcyclohexene and 250 g. of hydrogen fluoride. The hydrocarbon, 310 g. obtained from this reaction, was distilled through a 20–25 plate column at a reflux ratio of 10 to 1 and the following fractions were separated: (1) b. p. 102° (752 mm.), $n^{20}D$ 1.4250, 43 g. (methylcyclohexane); (2) b. p. 160–161° (752 mm.), $n^{20}D$ 1.4944, 99 g. (*p*-ethyltoluene); (3) b. p. 96–98° (5 mm.), $n^{20}D$ 1.4860, 19 g.; (4) b. p. 114–115° (4 mm.), $n^{20}D$ 1.5310, 21 g.; (5) b. p. 142–143° (4 mm.), $n^{20}D$ 1.5560, 100 g.; (6) b. p. 150–230° (4 mm.), $n^{20}D$ 1.5505, 16 g.; (7) residue 10 g.

Fraction 3 was stable toward a nitrating mixture; it corresponds to dimethyldicyclohexyl, d^{20}_4 0.8858; MR_D calcd. 62.4, obsd. 62.8.

Anal. Calcd. for $C_{14}H_{26}$: C, 86.51; H, 13.49. Found: C, 86.23; H, 13.17.

Fraction 4 corresponds to a (methylcyclohexyl)-*p*-ethyltoluene, d^{20}_4 0.9478; MR_D calcd. 70.3; obsd. 70.5.

Anal. Calcd. for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.91; H, 10.70.

Acetyl derivative was prepared according to the method described previously.[1] The 2,4-dinitrophenylhydrazone of the ketone melted at 179–181°.

Anal. Calcd. for $C_{24}H_{30}N_4O_4$: C, 65.72; H, 6.57; N, 12.77. Found: C, 65.75; H, 6.42; N, 12.99.

Fraction 5 corresponds to 1-*p*-tolyl-1-(2-methyl-5-ethylphenyl)-ethane, d^{20}_4 0.9617; MR_D calcd. 78.1, obsd. 79.5.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.75; H, 9.25. Found: C, 91.23; H, 9.19.

(4) V. N. Ipatieff and V. Haensel, THIS JOURNAL, **64**, 520 (1942).
(5) O. Widman and J. A. Bladin, *Ber.*, **19**, 587 (1886).
(6) Egloff, "Physical Constants of Hydrocarbons," Vol. III, Reinhold Publishing Corporation, New York, N. Y., 1946, p. 84.

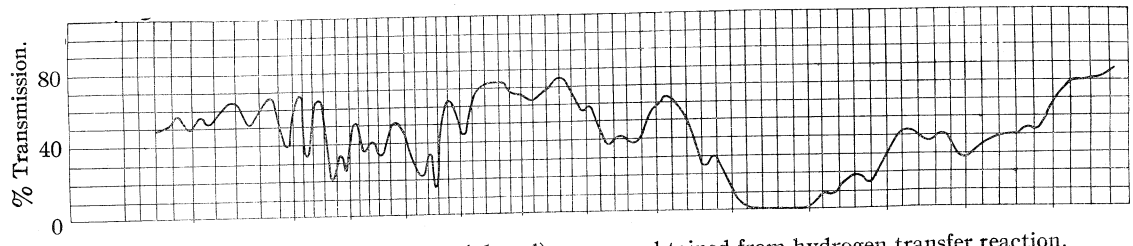


Fig. 4.—1-*p*-Tolyl-1-(2-methyl-5-propylphenyl)-propane obtained from hydrogen transfer reaction.

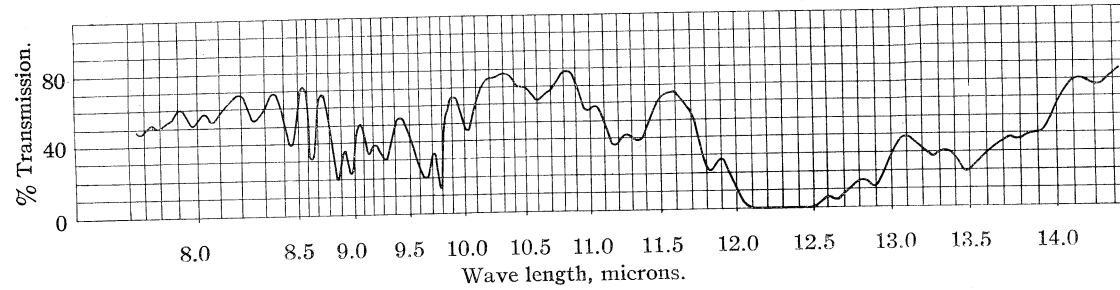


Fig. 5.—Synthetic 1-*p*-tolyl-1-(2-methyl-5-propylphenyl)-propane.

Infrared absorption spectra are given in Graph II.

Nitro Derivative.—Nitration with a nitrating mixture composed of 2 volumes of 96% sulfuric acid and 1 volume of 72% nitric acid gave a tetranitro derivative, m. p. 160–163°.

Anal. Calcd. for $C_{18}H_{18}N_4O_4$: C, 51.67; H, 4.36; N, 13.46. Found: C, 51.80; H, 4.25; N, 13.65.

Acetylation followed by the preparation of the 2,4-dinitrophenylhydrazone resulted in a small yield of solid product, m. p. 263–265°. A mixed melting point with the 2,4-dinitrophenylhydrazone of an authentic sample of *p*-methylacetophenone showed no depression.

Anal. Calcd. for $C_{15}H_{13}N_4O_4$: N, 17.9. Found: N, 17.5.

III. Reaction of *p*-Ethyltoluene with 4-Methylcyclohexene in the Presence of Sulfuric Acid

The reaction was made according to the procedure described previously[3]; 48 g. (0.4 mole) of *p*-ethyltoluene, 20 g. (0.2 mole) of 4-methylcyclohexene and 35 g. of 96% sulfuric acid were used. Fifty-seven grams of product was obtained from which the following cuts were separated: (1) b. p. 102° (751 mm.), $n^{20}D$ 1.4230, 11.8 g., methylcyclohexane; (2) b. p. 159–160° (751 mm.), $n^{20}D$ 1.4943, 16.7 g., *p*-ethyltoluene; (3) b. p. 114–115° (4 mm.), $n^{20}D$ 1.5330, 2-(1-methylcyclohexyl)-4-ethyltoluene; (4) b. p. 136–137° (3 mm.), $n^{20}D$ 1.5562, 11 g. (compound II); (5) residue 10 g.

Cut 3 was identified by the dinitrophenylhydrazone of the acetyl derivative and cut 4 by the infrared absorption spectra and nitro derivative.

IV. Synthesis of 1-*p*-Tolyl-1-(2-methyl-5-ethylphenyl)-ethane

(a) 1-Bromo-2-methyl-5-ethylbenzene (III).—Prepared by the bromination of *p*-ethyltoluene at 0° with bromine in the presence of a small amount of iodine,[7,8] 49 g. of the bromo-compound (83% yield), b. p. 99–101° (14 mm.), $n^{20}D$ 1.5440, was realized from 40 g. of the hydrocarbon.

Compound III on oxidation with a solution of chromic acid, sulfuric acid and water yielded 3-bromo-*p*-toluic acid melting at 203–204°; this agrees with the published data.[7]

(b) 1-*p*-Tolyl-1-(2-methyl-5-ethylphenyl)-ethanol (IV).—This was prepared by the Grignard method using 40 g. of 2-methyl-5-ethylbromobenzene, 4.8 g. of magnesium and 26.8 g. of *p*-methylacetophenone. The carbinol which was obtained and which amounted to 20.6 g. boiled at 162–164° (5 mm.), (64% yield), $n^{20}D$ 1.5655, d^{20}_4 1.0307; MR_D calcd. 79.6, obsd. 79.8.

Anal. Calcd. for $C_{18}H_{22}O$: C, 85.04; H, 8.66. Found: C, 84.88; H, 8.43.

(c) 1-*p*-Tolyl-1-(2-methyl-5-ethylphenyl)-ethane (V).—A solution of 13 g. of compound (IV) in 40 cc. of benzene was refluxed for one hour with 2 g. of oxalic acid to effect the dehydration. The olefins, 12 g., had the following physical constants: b. p. 146–146.5° (4 mm.), $n^{20}D$ 1.5770, d^{20}_4 0.9745; MR_D calcd. 77.7, obsd. 80.2.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.50; H, 8.50. Found: C, 91.20; H, 8.52.

(d) 1-*p*-Tolyl-1-(2-methyl-5-ethylphenyl)-ethane (II) which was prepared by the hydrogenation of compound V in the presence of a nickel–kieselguhr catalyst at 100 atm. and 45° distilled at 148–150° (4 mm.), $n^{20}D$ 1.5540, d^{20}_4 0.9625; MR_D calcd. 78.1, obsd. 79.2. Infrared absorption spectra are given in Graph III. A tetranitro derivative, m. p. 160–162° was obtained by treating compound II with a nitrating mixture consisting of 2 volumes of 96% sulfuric acid and 1 volume of 72% nitric acid.

Anal. Calcd. for $C_{18}H_{18}N_4O_8$: C, 51.67; H, 4.36, N, 13.46. Found: C, 51.80; H, 4.31; N, 13.55.

The nitro compound did not show any depression in melting point when mixed with the corresponding nitro compound obtained from the hydrogen transfer reaction.

VI. Synthesis of 3,6-Dimethyl-1-*p*-tolylindan

(a) 3-*p*-Tolyl-3-hydroxybutyrate (VII) was prepared in 61% yield from 84 g. of *p*-methylacetophenone according to the procedure of Lindenbaum.[9] Compound VII thus prepared was colorless, boiling at 116–117° (4 mm.), $n^{20}D$ 1.5000, d^{20}_4 0.9381; the same compound was reported[7] as being a light yellow oil, boiling at 156–157° (16 mm.).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.22; H, 8.17. Found: C, 69.82; H, 7.91.

(b) Ethyl β-*p*-Tolylcrotonate (VIII).—Sixty-seven grams of compound (VII) was dehydrated in the presence of 12 g. of oxalic acid and 150 ml. of benzene. The following main two fractions were separated: (1) b. p. 116.5–120° (3–4 mm.), 39.6 g., $n^{20}D$ 1.5335; (2) b. p. 120–125° (3–4 mm.), 15.8 g., $n^{20}D$ 1.5455. The yield of VIII amounted to 89%. The dehydrated ester corresponded to a mixture of the two expected isomers.[9]

(7) H. N. Morse and I. Remsen, *Ber.*, **11**, 225 (1878)

(8) G. Defren, *ibid.*, **28**, 2651 (1895).

(9) S. Lindenbaum, *Berg-tech.*, **50**, 1270 (1917).

(c) **β-*p*-Tolylbutyric Acid (IX).**—Compound VIII, 55 g. was hydrogenated in the presence of 69 g. of *n*-pentane and 6 g. of a nickel–kieselguhr catalyst at 48° and under 115 atm. of hydrogen pressure.

The saturated ester was saponified by heating it at a reflux temperature with a solution of alcoholic potassium hydroxide. An 82% yield of the acid was obtained, m. p. 91–92°. It yielded the known *p*-toluidide[10] m. p. 112–113°.

(d) **3,6-Dimethylindanone (X).**—Twenty grams of compound IX was stirred into 200 g. of anhydrous hydrogen fluoride in a copper beaker at 0°. After standing two hours at 0° the hydrogen fluoride was evaporated and the remaining oil was washed with 2% potassium hydroxide. Distillation yielded 15 g. (88.5%) of the cyclic ketone b. p. at 100–102° (5 mm.), $n^{20}D$ 1.5518. The semicarbazone melted at 225° with decomposition.[11]

The following data on the ketone were not previously published: d^{20}_4 1.0454; dinitrophenylhydrazone m. p. 271–273°.

Anal. Calcd. for $C_{17}H_{17}O_4N_4$: C, 59.82; H, 4.99; N, 16.42. Found: C, 59.80; H, 4.92; N, 16.20.

A study of the various methods for cyclization was made with the following results:

Cyclization agent	Yield of ketone, %
Hydrogen fluoride	88.5 (Acid was used directly)
Aluminum chloride	67.0 (Acid chloride was used)
Stannic chloride	48.0 (Acid chloride was used)

(e) **3,6-Dimethyl-1-*p*-tolylindene (XII).**—3,6-Dimethyl-1-*p*-tolyl-1-indanol (XI) was prepared by the Grignard reaction using 2.68 g. of magnesium, 18.8 g. (0.11 mole) of *p*-bromotoluene and 13.0 g. (0.1 mole) of the 3,6-dimethyl-1-indanone (X). Because tertiary alcohol tends to dehydrate, it could not be isolated; 12.6 g. of the olefin (54% yield) was obtained distilling at 157° (5 mm.), $n^{20}D$ 1.6022, d^{20}_4 1.0307; MR_D calcd. 74.7, obsd. 74.4.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.31; H, 7.67. Found: C, 91.75; H, 7.97.

(f) **3,6-Dimethyl-1-*p*-tolylindan (I).**—Twelve grams of the compound XII was hydrogenated under pressure in the presence of a nickel–kieselguhr catalyst at 50°. Distillation gave a colorless fluorescent oil boiling at 144–146° (5 mm.), $n^{20}D$ 1.5700, d^{20}_4 0.9998; MR_D calcd. 75.2, obsd. 77.4.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.53; H, 8.47. Found: C, 91.37; H, 8.46.

The infrared absorption spectra of this compound are given in Graph I.

VII. Synthesis of *p*-Propyltoluene (XIII)

(a) ***p*-Methylpropiophenone.**—This ketone boiled at 114.5° (18 mm.), $n^{20}D$ 1.5287. The semicarbazone of this ketone melted at 187–188° and the oxime melted at 87.5–88° which is identical with the data given in the literature.[12,13] A dinitrophenylhydrazone (not previously reported) melted at 200–202°

Anal. Calcd. for $C_{16}H_{16}N_4O_4$: N, 17.1. Found: N, 17.0.

(b) ***p*-Propyltoluene,** which was obtained by hydrogenation[4] of *p*-methylpropiophenone distilled at 179–180° (750 mm.), $n^{20}D$ 1.4934, d^{20}_4 0.8588; the physical constants agree with those reported in the literature.[13a] A sulfonamide derivative[14] (not previously reported) melted at 79–80°.

Anal. Calcd. for $C_{10}H_{15}O_2NS$: C, 56.34; H, 7.04; N, 6.57. Found: C, 56.53; H, 7.14; N, 6.48.

(10) H. Rupe and Fr. Wiederkehr, *Helv. Chim. Acta*, **7**, 654 (1924).

(11) Th. Wagner-Jauregg and H. Hippchen, *Ber.*, **76B**, 694 (1943).

(12) A. Klage, *Berg-tech.*, **35**, 2245 (1902).

(13) K. Auwers, *Ann.*, **408**, 243 (1915).

(13a) Reference 6, p. 99.

(14) E. H. Huntress and J. S. Autenrieth, THIS JOURNAL, **63**, 3446 (1941).

VIII. Reaction of *n*-Propyltoluene with 4-Methylcyclohexene in the Presence of Hydrogen Fluoride

The reaction was carried out as described above, using the following reagents: *p*-propyltoluene, 240 g. (1.86 moles), 89 g. (0.93 mole) of 4-methylcyclohexene and 250 g. of hydrogen fluoride. The product resulting from this reaction weighed 304 g. The following fractions were separated by distillation: (1) b. p. 102° (750 mm.), $n^{20}D$ 1.4260, 40.5 g., methylcyclohexane; (2) b. p. 179–180° (750 mm.), $n^{20}D$ 1.4930, 109 g., *n*-propyltoluene; (3) b. p. 84–87° (3 mm.), $n^{20}D$ 1.4833, 13 g.; (4) b. p. 116–120° (3 mm.), $n^{20}D$ 1.5300, 34 g.; (5) b. p. 151–153° (3 mm.), $n^{20}D$ 1.5450, 86 g.; (6) b. p. 155–180° (3 mm.), $n^{20}D$ 1.5418, 10.0 g.; (7) residue 9.6 g.

Fraction 3 corresponds to a dimethyldicyclohexyl; it was stable toward a nitrating mixture consisting of 2 volumes of 96% sulfuric acid and 1 volume of 72% nitric acid; d^{20}_4 0.8850; MR_D calcd. 62.4, obsd., 62.6.

Anal. Calcd. for $C_{14}H_{26}$: C, 86.51; H, 13.49. Found: C, 86.19; H, 13.13.

Fraction 4 corresponds to 2-(1-methylcyclohexyl)-4-propyltoluene d^{20}_4 0.9502; MR_D calcd. 74.9; obsd. 74.8.

Anal. Calcd. for $C_{17}H_{26}$: C, 88.63; H, 11.37. Found: C, 89.12; H, 10.90.

The 2,4-dinitrophenylhydrazone of the acetyl derivative melted at 230–233°.

Anal. Calcd. for $C_{25}H_{32}N_4O_4$: C, 66.30; H, 7.13; N, 12.38. Found: C, 66.35; H, 7.05; N, 12.50.

Fraction 5 corresponds to 1-*p*-tolyl-1-(2-methyl-5-propylphenyl)-propane, d^{20}_4 0.9478; MR_D calcd. 89.1, obsd. 88.7.

Anal. Calcd. for $C_{20}H_{26}$: C, 90.16; H, 9.84. Found: C, 90.31; H, 9.93.

The infrared absorption spectra are given in Graph IV.

Nitration yielded a gummy product which could not be crystallized.

Acetylation followed by treatment with 2,4-dinitrophenylhydrazone gave a solid derivative, m. p. 263–265°. A mixed melting point with the dinitrophenylhydrazone of synthetic *p*-methylacetophenone showed no depression.

Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.46; N, 17.83. Found: C, 57.50; H, 4.89; N, 17.40.

IX. Reaction of *n*-Propyltoluene with 4-Methylcyclohexene in the Presence of Sulfuric Acid

p-Propyltoluene, 26.8 g. (0.2 mole), 4-methylcyclohexene, 10 g. (0.1 mole) and 10 g. of 96% sulfuric acid were used for the reaction. The following cuts were separated from 33.6 g. of the hydrocarbon layer: (1) b. p. 103° (750 mm.), $n^{20}D$ 1.4215, 3.6 g., (2) b. p. 179° (750 mm.), $n^{20}D$ 1.4938, 15.8 g.; (3) b. p. 122–129° (5 mm.), $n^{20}D$ 1.5318, 6.5 g.; (4) b. p. 144–150° (5 mm.), $n^{20}D$ 1.5440, 4.2 g.; (5) residue 2 g.

The distillation data and the physical constants show that the results obtained from sulfuric acid catalyzed reaction are comparable to the hydrogen fluoride catalyzed reaction except that no dimethyldicyclohexyl fraction is detectable and more cycloalkylation seems to occur.

X. Synthesis of 1-*p*-Tolyl-1-(2-methyl-5-propylphenyl)-propane

(a) **1-Bromo-2-methyl-5-propylbenzene (XIV).**—The same procedure was used as for bromination of *p*-ethyltoluene. Forty-eight grams (95% yield) of compound XIV was obtained (not previously reported), boiling at 119–120° (20 mm.), $n^{20}D$ 1.5388, d^{20}_4 1.2470; MR_D calcd. 52.4, obsd. 53.5.

Anal. Calcd. for $C_{10}H_{13}Br$: Br, 37.52. Found: Br, 37.48.

The position of the entering bromine atom was proved to be ortho to the methyl group by oxidation with dilute nitric acid to 3-bromo-*p*-toluic acid, m. p. 203–204°, which agrees with the data reported.[7]

(b) **1-*p*-Tolyl-1-(2-methyl-5-propylphenyl)-1-propanol (XV).**—Prepared by means of a Grignard reaction using

4.1 g. of magnesium, 40 g. of the bromide XIV and 28 g. of *p*-propionyltoluene. Distillation gave 26.2 g. of the tertiary alcohol boiling at 160–163° (3 mm.), $n^{20}D$ 1.5540, d^{20}_4 1.0025; MR_D calcd. 88.9, obsd. 90.2.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.1; H, 9.2. Found: C, 84.3; H, 9.4.

(c) **1-*p*-Tolyl-1-(2-methyl-5-propylphenyl)-propene (XVI).**—Prepared by dehydration of compound XV in benzene solution in presence of oxalic acid. The olefin was obtained in 87% yield, b. p. 149–150° (3 mm.), $n^{20}D$ 1.5695, d^{20}_4 0.9616; MR_D calcd. 86.9, obsd. 89.9.

Anal. Calcd. for $C_{20}H_{24}$: C, 90.84; H, 9.16. Found: C, 90.80; H, 9.20.

(d) **1-*p*-Tolyl-1-(2-methyl-5-propylphenyl)-propane (XVII).**—The olefin, compound XVI, was hydrogenated under pressure in the presence of a nickel–kieselguhr catalyst at 45°. The hydrocarbon obtained (XVII) boiled at 143–144° (3 mm.), $n^{20}D$ 1.5455, d^{20}_4 0.9480; MR_D calcd. 87.3, obsd. 86.6.

Anal. Calcd. for $C_{20}H_{26}$: C, 90.16; H, 9.84. Found: C, 90.29; H, 9.80.

The infrared absorption spectra are given in Graph V.

Acetylation followed by treatment with 2,4-dinitrophenylhydrazone gave a solid derivative m. p. 263–265°. A mixed melting point with the dinitrophenylhydrazone of synthetic *p*-methylacetophenone showed no depression.

XI. Reaction of *p*-Xylene with 4-Methylcyclohexene

Forty-two grams (0.4 mole) of *p*-xylene was treated with 19.2 g. (0.2 mole) of 4-methylcyclohexene in the presence of 50 g. of hydrogen fluoride by the usual procedure described above. The hydrocarbon layer after washing and drying weighed 52 g. The following products were separated by fractional distillation through a 20-plate column: (1) 135–137° (750 mm.), 22 g., $n^{20}D$ 1.4960 (*p*-xylene); (2) 131–134° (10 mm.), 18 g., $n^{20}D$ 1.5260; (3) > 135° (4 mm.), 9 g., $n^{20}D$ 1.5310.

Fraction 2 corresponded to (1-methylcyclohexyl)-*p*-xylene, d^{20}_4 0.9363; MR_D calcd. 65.7, obsd. 66.2 (new compound).

Anal. Calcd. for $C_{15}H_{22}$: C, 89.11; H, 10.89. Found: C, 89.05; H, 10.77.

Acetylation yielded a ketone from which 2,4-dinitrophenylhydrazone was prepared. Crystallization from the chloroform–ethanol solution produced orange needles m. p. 172–174° (new compound).

Anal. Calcd. for $C_{23}H_{28}N_4O_4$: N, 13.21. Found: N, 13.70.

Nitration of the hydrocarbon with a solution of 2 volumes of 96% sulfuric acid gave a sirupy product which could not be crystallized.

Acknowledgment.—The authors wish to thank Dr. W. S. Gallaway, Universal Oil Products Company, for the infrared absorption spectra, and Miss Patricia Craig, Northwestern University, for microanalyses.

Summary

When *p*-ethyltoluene and *p*-propyltoluene react with methylcyclohexene in the presence of hydrogen fluoride and sulfuric acid, the main products formed result from a hydrogen transfer in which the aromatic hydrocarbons acted as a hydrogen donor and methylcyclohexene as a hydrogen acceptor.

The products obtained from the respective aromatic hydrocarbons through a hydrogen transfer were: 1-*p*-tolyl-1-(2-methyl-5-ethylphenyl)-ethane and 1-*p*-tolyl-1-(2-methyl-5-propylphenyl)-propane.

A mechanism for the hydrogen transfer reaction has been proposed; *p*-xylene on reaction with methylcyclohexene yields the expected cycloalkylation products.

The following new compounds and their derivatives were prepared; 1-*p*-tolyl-1-(2-methyl-5-ethylphenyl)-ethanol, 1-*p*-tolyl-1-(2-methyl-5-ethylphenyl)-ethene, 1-*p*-tolyl-1-(2-methyl-5-ethylphenyl)-ethane, 3,6-dimethyl-1-*p*-tolylindene, 3,6-dimethyl-1-*p*-tolylindan, 1-bromo-2-methyl-5-propylbenzene, 1-*p*-tolyl-1-(2-methyl-5-propylphenyl)-propanol, 1-*p*-tolyl-1-(2-methyl-5-propylphenyl)-propene, 1-*p*-tolyl-1-(2-methyl-5-propylphenyl)-propane and (1-methylcyclohexyl)-*p*-xylene.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 19, 1948

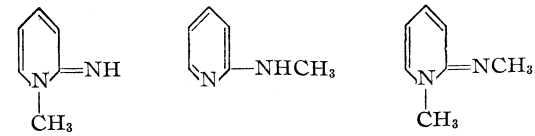
NOTES

2-Triphenylmethylaminopyridine

BY ROGER ADAMS AND JOHN B. CAMPBELL

The direct interaction of 2-aminopyridine and methyl iodide yields almost entirely the hydroiodide of N-methyl-2-pyridoneimide (I).[1] The reaction of the sodio derivative of 2-aminopyridine and methyl iodide yields principally 2-methylaminopyridine (II). The reaction of I or II with methyl iodide gives the dimethyl derivative (III). The same general behavior occurs when benzyl chloride is used rather than methyl iodide.

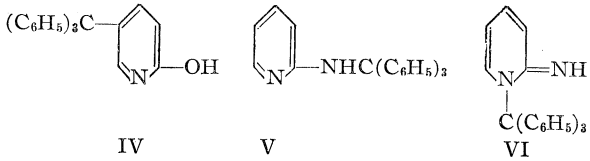
(1) Chichibabin, Konovalova and Konovalova, *Ber.*, **54**, 814 (1921).



I II III

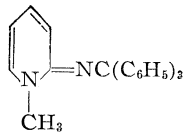
Triphenylcarbinol was condensed with 2-aminopyridine in the presence of a trace of acid in an attempt to obtain 5-triphenylmethyl-2-aminopyridine. Diazotization of the product in an effort to get the known 5-triphenylmethyl-2-hydroxypyridine (IV) resulted in cleavage of the molecule to yield triphenylcarbinol. Cleavage was also readily effected by means of concentrated

sulfuric acid. This behavior indicated that N-alkylation had occurred to produce V or VI. The attempted condensation of triphenylcarbinol with 2-aminopyridine using larger amounts of acidic catalyst gave only dark tarry products which could not be crystallized.



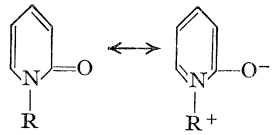
IV V VI

The product obtained was shown to be 2-triphenylmethylaminopyridine (V) by reaction with methyl iodide to yield N-methyl-2-pyridonetriphenylmethylimide(VII), the latter also being obtained in low yield by the reaction of N-methyl-2-pyridoneimide(I) with triphenylchloromethane. Thus, triphenylcarbinol reacts differently than do the methyl and benzyl halides.



VII

It is noteworthy that the free bases having the quinoid structure, as shown by I, III and VII, have a yellow color. The color is lost upon preparing the hydrochlorides. Since color is lacking in N-alkyl-2-pyridones (VIII), the color in the imide-type structures may be because the latter do not have as great a tendency to exist in a "zwitterion" structure as do the N-alkyl-2-pyridones as shown by IX. The zwitterion structure results in the loss of the quinoid structure and the attendant color.



VIII IX

Experimental

2-Triphenylmethylaminopyridine.—A mixture of 40 g. of 2-aminopyridine, 26 g. of triphenylcarbinol and 0.1 g. of *p*-toluenesulfonic acid was refluxed gently for two hours, steam being passed through the condenser to remove the water formed. The cooled mixture was recrystallized from 90% ethanol to yield 18.2 g. (54%) of light cream-colored crystals. Recrystallization from 95% ethanol gave glistening white crystals, m. p. 152–153° (cor.).

Anal. Calcd. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.57; H, 6.02; N, 8.18.

Cleavage of 2-Triphenylmethylaminopyridine. (A) By Nitrous Acid.—A suspension of 4.97 g. of powdered 2-triphenylmethylaminopyridine in 25 ml. of concd. hydrochloric acid was stirred at room temperature as a solution of 1.1 g. of sodium nitrite in 15 ml. of water was dropped in over a period of fifteen minutes. The mixture was stirred for one hour after the addition was complete. The white product was then collected on a filter and washed well with water. The yield was 3.50 g. (91%). Two recrystallizations from 95% ethanol gave pure triphenylcarbinol, m. p. 162°, as shown by the melting point of a mixture with an authentic sample.

(B) By Sulfuric Acid.—Upon dissolving 2-triphenylmethylaminopyridine in concd. sulfuric acid and pouring the solution into water, a nearly quantitative yield of triphenylcarbinol resulted.

N-Methyl-2-pyridonetriphenylmethylimide. (A) From 2-Triphenylmethylaminopyridine.—A solution of 1 g. of 2-triphenylmethylaminopyridine and 5 ml. of methyl iodide in 20 ml. of absolute ethanol was refluxed for five hours and then diluted with 50 ml. of petroleum ether. The precipitate of hydroiodide was collected on a filter and washed well with petroleum ether. It was then dissolved in 50 ml. of a 3:2 mixture of hot ethanol and water and the solution made basic with dilute aqueous sodium hydroxide. The mixture was warmed and stirred a few minutes and then cooled overnight in the ice-box. The yellow crystalline precipitate was collected on a filter and washed well with 50% ethanol. The yield was 0.52 g. (50%). Two recrystallizations from 95% ethanol gave yellow crystals, m. p. 151–152° (cor.). A melting point of this compound mixed with 2-triphenylmethylaminopyridine gave a large depression.

Anal. Calcd. for $C_{25}H_{22}N_2$: C, 85.67; H, 6.33; N, 8.00. Found: C, 85.84; H, 6.46; N, 7.98.

(B) From N-Methyl-2-pyridoneimide.—To a suspension of 2.36 g. of the hydroiodide of N-methyl-2-pyridoneimide[1] in 50 ml. of hot benzene was added 5 ml. of 10% aqueous sodium hydroxide and the mixture quickly shaken. The benzene layer was separated, dried over anhydrous sodium sulfate and the benzene removed on the steam-cone. To the green residual oil was added 2.8 g. of triphenylchloromethane and the mixture heated on the steam-cone one hour. Then 30 ml. of benzene was added and the mixture boiled a few minutes. After cooling overnight in the ice-box, the precipitate of hydrochloride was collected on a filter, washed well with benzene and dried. It was then taken up in 10 ml. of boiling ethanol and the solution made basic with the addition of 10% aqueous sodium hydroxide. After cooling in the ice-box, 0.20 g. of dark yellow crystalline material was collected on a filter. Recrystallization from 95% ethanol gave yellow crystals, m. p. 151–152° (cor.), identical with the product obtained above, as shown by a melting point of the mixture.

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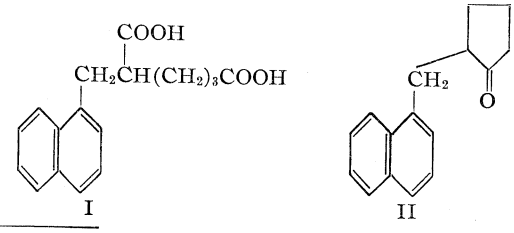
RECEIVED JULY 5, 1949

Preparation of the Isomeric 2-(Naphthylmethyl)-cyclopentanones

BY W. E. BACHMANN AND N. C. DENO[1]

Condensation of α-chloromethylnaphthalene with the sodio derivative of 2-carbethoxycyclopentanone gave the substituted cyclic keto ester, which was hydrolyzed by alkali with ring cleavage to α-(1′-naphthylmethyl)-adipic acid (I). Cyclization of the diacid with the aid of acetic anhy-



I II

(1) Present address: Department of Chemistry, The Ohio State University, Columbus, Ohio.

dride or by dry distillation with calcium oxide yielded 2-(1′-naphthylmethyl)-cyclopentanone (II). The ultraviolet absorption spectrum of II was similar to that of 1-methylnaphthalene.

2-(2′-Naphthylmethyl)-cyclopentanone was prepared in a similar manner from β-chloromethylnaphthalene. An excellent yield of the crystalline ketone was obtained by cyclization of the intermediate α-(2′-naphthylmethyl)-adipic acid with acetic anhydride. The ketone was obtained also by acid hydrolysis of 2-carbethoxy-2-(2′-naphthylmethyl)-cyclopentanone.

Experimental[2]

α-(1′-Naphthylmethyl)-adipic Acid (I).—A mixture of 15.6 g. (0.1 mole) of 2-carbethoxycyclopentanone, sodium methoxide (prepared from 2.3 g. of sodium and dried at 100° and 20 mm.), and 150 cc. of dry benzene was refluxed for five minutes; any lumps present were crushed with a spatula. After the addition of 17.6 g. (0.1 mole) of α-chloromethylnaphthalene, the mixture was refluxed for six hours. After the removal of the benzene under reduced pressure, 40 cc. of 40% aqueous potassium hydroxide and 60 cc. of methanol were added and the solution was refluxed for eighteen hours. After being cooled and diluted with water to 300 cc., the solution was washed twice with ether and then acidified with hydrochloric acid. The substituted adipic acid, which was isolated by extraction with two 200-cc. portions of ether and removal of the ether, was triturated with 30 cc. of benzene; yield of colorless granular crystals, 15 g., m. p. 116–121°. An additional 1.17 g. of the acid (m. p. 110–118°) was obtained by further treatment of the non-crystalline portion with 40 cc. of 20% aqueous potassium hydroxide at 100° for twenty-four hours; total yield, 56%. After several recrystallizations from benzene the acid melted at 126–127.4°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.30, H, 6.33; neut. equiv., 143. Found: C, 71.42; H, 6.37; neut. equiv., 144.

2-(1′-Naphthylmethyl)-cyclopentanone (II).—The acetic anhydride was distilled slowly from a solution of 0.5 g. of the aforementioned acid in 1.5 cc. of acetic anhydride. After the apparatus had been filled with nitrogen, the temperature was raised to 300° in the course of five minutes; the pressure was then lowered to 30 mm. in order to complete the distillation; yield of colorless liquid, 71%. **The 2,4-dinitrophenylhydrazone** (m. p. 232.2–233.2°), which was prepared in 76% yield by addition of 1 cc. of concentrated hydrochloric acid to a refluxing solution of 100 mg. of the ketone and 150 mg. of 2,4-dinitrophenylhydrazine in ethanol, crystallized in fine, yellow needles.

Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.99. Found: C, 65.47; H, 5.16.

When the diacid alone was distilled, the yield of ketone was low and much acid was recovered. By dry distillation of an intimate mixture of 2 g. of the diacid and 0.4 g. of powdered calcium oxide under nitrogen and redistillation of the dark distillate at 130–170° and 0.1 mm., 1.02 g. of the ketone was obtained.

2-(2′-Naphthylmethyl)-cyclopentanone.—The cyclic keto ester prepared from 11.2 g. of β-chloromethylnaphthalene and an equivalent amount of 2-carbethoxycyclopentanone was completely hydrolyzed and cleaved by refluxing with aqueous methanolic alkali for eighteen hours. Recrystallization of the crude diacid from acetone–benzene gave two crops: 12.8 g., m. p. 149–150°, and 2 g., m. p. 144–146°; total yield, 81%. The highest m. p. obtained for α-(2′-naphthylmethyl)-adipic acid was 152.3–152.8°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.30; H, 6.33; neut. equiv., 143. Found: C, 71.50; H, 6.50; neut. equiv., 142.5.

(2) All melting points are corrected.

By the procedure described for the isomer, 3.63 g. (93%) of the cyclic ketone (m. p. 57–63°) was obtained from 5 g. of the diacid and 15 cc. of acetic anhydride. The **2-(2′-naphthylmethyl)-cyclopentanone** crystallized from ether–petroleum ether in colorless glistening flakes; weight, 2.9 g. (75%), m. p. 70.3–71.3°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.66; H, 7.19. Found: C, 85.78; H, 7.45.

A 38% yield of the ketone (m. p. 65.5–67°) was obtained when the diacid was distilled from calcium oxide and a 53% yield of ketone (m. p. 57–65°) resulted from refluxing a solution of 3.6 g. of the 2-carbethoxy-2-(2′-naphthylmethyl)-cyclopentanone in 10 cc. of acetic acid and 10 cc. of concentrated hydrochloric acid for twelve hours and evaporatively distilling the neutral product up to 180° at 0.1 mm.

The 2,4-dinitrophenylhydrazone (prepared in quantitative yield as described for the isomer except that the mixture was refluxed for five minutes and then allowed to stand for several days) crystallized in fine, short yellow needles; m. p. 138–139°, raised to 144.2–145° by recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.99. Found: C, 65.48; H, 4.95.

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RECEIVED JUNE 30, 1949

Derivatives of Indole-2-carboxylic Acid

BY WARREN J. BREHM

This report of work originally aimed at a synthesis of lysergic acid, but now discontinued, is prompted by Uhle's successful synthesis of 5-keto-1,3,4,5-tetrahydrobenz[cd]indole.[1] It was hoped that an abrine suitably protected at the 2-position to permit closure of the (α-methylamino)-propionic acid side-chain into the 4-position could be prepared by following the tryptophan syntheses developed by Snyder[2] or Robson.[3] The choice of the carboxypiperidide as the protective group made subsequent decarboxylation or its equivalent a necessary step. In an attempt to avoid the difficulties often attendant upon decarboxylation of indole-2-acids, 2-hydroxymethylindole was prepared. When this compound did not lose formaldehyde on treatment with base this alternate scheme had to be abandoned.

Experimental

Ethyl Indole-2-carboxylate.—Crude ethyl *o*-nitrophenylpyruvate, obtained as an oil by the method of Wislicenus and Thoma,[4] was dissolved in glacial acetic acid (35 g. of ester in 225 cc. of solvent). It was reduced with hydrogen at a pressure of 3 atm. over Adams catalyst (0.2 g.). At the end of the very rapid reduction the catalyst was filtered off and the solution diluted with water. This gave 22 g. (80%) of ethyl indole-2-carboxylate, m. p. 121–123°.

2-Hydroxymethylindole.—Lithium aluminum hydride (4.75 g.) was dissolved in 180 cc. of dry ether. With mechanical stirring a solution of 18.9 g. of ethyl indole-2-carboxylate in 250 cc. of dry ether was added dropwise at a rate sufficient to keep the solution boiling. When the addition was complete, stirring was continued for fifteen minutes, and then 100 cc. of water added slowly to decompose the excess reducing agent. The ether layer was

(1) Uhle, THIS JOURNAL, **71**, 761 (1949).
(2) Snyder and Smith, *ibid.*, **66**, 351 (1944).
(3) Miller and Robson, *J. Chem. Soc.*, 1910 (1938).
(4) Wislicenus and Thoma, *Ann.*, **436**, 45 (1924).

separated, washed with water and dried over magnesium sulfate. The ether was boiled off and the residue twice recrystallized from benzene–hexane; 10.0 g. (68%) of colorless plates, m. p. 74–77°. Analytical sample sublimed *in vacuo*, m. p. 75–77°. *Anal.* Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.79; H, 6.24; N, 9.52.

A solution of 1.0 g. of 2-hydroxymethylindole in 60 cc. of alcohol was treated with 3.0 g. of barium hydroxide in 60 cc. of water. The solution was heated on the steam-bath for three hours, diluted with 400 cc. of water and extracted with ether. The ether was dried over sodium sulfate. After removal of the ether and recrystallization from hexane the residue weighed 0.7 g., m. p. 76–77°. This melting point was not depressed when the sample was mixed with starting material.

2-Carboxypiperidinoindole.—(a) Ethyl indole-2-carboxylate (3.8 g.) was suspended in 50 cc. of 1 *N* sodium hydroxide and the mixture was heated on the steam-bath for one hour when complete solution had been attained. The solution was treated with charcoal, filtered and acidified with hydrochloric acid. The precipitated indole-2-carboxylic acid was filtered off, 2.9 g. (90%), m. p. 206–208°. A solution of 2.85 g. of this acid in 100 cc. of dry ether was treated with 3.0 cc. of thionyl chloride. After standing at room temperature for one hour the solvents were removed *in vacuo*. The residue was twice treated with 60 cc. of dry ether and taken to dryness to remove traces of hydrogen chloride. Finally it was dissolved in 90 cc. of dry ether, filtered and treated with 3.5 cc. of piperidine. There was an immediate precipitation of a gum which gradually crystallized. After recrystallization from ethanol–water, 0.4 g. of 2-carboxypiperidinoindole, m. p. 161–164° separated. After three recrystallizations from hexane the white needles melted at 165–166°. *Anal.* Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.07; N, 12.27. Found: C, 73.63; H, 6.86; N, 12.45.

(b) Ethyl indole-2-carboxylate (36 g.) was suspended in 480 cc. of piperidine, and the mixture was treated with 90 cc. of glacial acetic acid. The mixture was heated to boiling, giving a complete solution, and maintained at reflux for two days. The hot solution was diluted with 200 cc. of water and filtered. The filtrate was treated with 2 liters of water to precipitate the 2-carboxypiperidinoindole, 36 g. (83%), m. p. 163–166°.

3-Dimethylaminomethylindole-2-carboxypiperidide.—A suspension of 10.0 g. of 2-carboxypiperidinoindole in 65 cc. of glacial acetic acid, 24 cc. of 25% aqueous dimethylamine and 14 cc. of 40% aqueous formaldehyde was heated on the steam-bath for one hour and then kept at room temperature overnight. After diluting the solution with 700 cc. of water it was extracted with 100 cc. of benzene. The aqueous layer was made basic with concentrated ammonium hydroxide, and the oily product was extracted into ether (one 400-cc. and three 250-cc. portions of solvent). The combined extracts were washed twice with 150 cc. of water and dried over sodium sulfate. After removal of the ether on the steam-bath the oily residue weighed 17 g. Since the theoretical yield was only 12 g. there was considerable contamination, but the material was suitable for further work as it stood.

When a small amount of this oil was heated with 10% chloroplatinic acid a crystalline chloroplatinate precipitated which contained two organic residues per atom of platinum. After recrystallization from water this melted at 208° (dec.). *Anal.* Calcd. for $C_{34}H_{46}N_6O_2$–H_2PtCl_6: C, 41.63; H, 4.93; N, 8.57; Cl, 21.69. Found: Cl, 41.60; H, 4.97; N, 8.53; Cl, 20.83.

2-Carboxypiperidinoskatylacetylaminomalonic Ester.—The 17 g. of crude 3-dimethylaminomethylindole-2-carboxypiperidide (see above) was treated with 150 cc. of xylene and the solution distilled until the distillate was no longer cloudy. The volume of the solvent was replenished, and there was added 9.6 g. of acetylaminomalonic ester (prepared according to the method of Snyder and Smith[2]) and 0.6 g. of powdered sodium hydroxide. With stirring, the mixture was heated to its boiling point while dry nitrogen was passed over the system. Bubbles appeared in the reaction mixture as soon as it became warm, and the exhaust gases became basic. This was presumably due to the evolution of dimethylamine. After twenty hours the evolution of amine had ceased, and the reaction mixture was filtered, washed with 50 cc. of water, twice with 50 cc. of 10% hydrochloric acid and again with 50 cc. of water. The xylene solution was dried over sodium sulfate. After removing the xylene *in vacuo* the residue was crystallized by boiling with ether. The insoluble crystalline residue of 2-carboxypiperidinoskatylacetylaminomalonic ester weighed 10.0 g., m. p. 146–149°; after recrystallizations from ethyl acetate–hexane, ethanol–water and ethyl acetate–isopropyl ether, m. p. 149–152°. *Anal.* Calcd. for $C_{24}H_{31}N_3O_6$: C, 63.00; H, 6.83; N, 9.18. Found: C, 63.22; H, 6.88; N, 8.77.

When this preparation was repeated the ether-insoluble residue melted at 197–200°. It was recrystallized from acetic acid–water, acetone–water and ethanol–water, m. p. 200.2–201.6°. *Anal.* Calcd. for $C_{24}H_{31}N_3O_6$: C, 63.00; H, 6.83; N, 9.18. Found: C, 63.11; H, 6.92; N, 9.17. A sample of the lower melting material, m. p. 149–152°, was recrystallized from ethanol–water and seeded with a crystal of this latter form. The product melted at 200–202°.

2-Carboxypiperidinoindole-3-aldehyde.—To a cold solution of 5.4 g. of N-methylformanilide and 3.66 cc. of phosphorus oxychloride in 35 cc. of *o*-dichlorobenzene there was added gradually 9.1 g. of 2-carboxypiperidinoindole. The resulting suspension was kept at room temperature for forty-three hours although solution was complete after fifteen hours. The solution was poured into a slurry of 30 g. of ice and 20 g. of 35% sodium hydroxide solution. The organic layer was separated, washed with 20 cc. of water and dried over sodium sulfate. The solvent was removed *in vacuo*, the residue dissolved in ethanol, and the solution diluted with water. The precipitated product was recrystallized from benzene–hexane; 6.6 g. (65%), m. p. 149–155°. Five recrystallizations from benzene–hexane gave white needles, m. p. 155.5–156.5°. *Anal.* Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.38; H, 6.09; N, 11.20.

The compound gave a red-orange 2,4-dinitrophenylhydrazone; recrystallized from dioxane, m. p. 310° (dec.). *Anal.* Calcd. for $C_{21}H_{20}N_6O_5$: C, 57.79; H, 4.62; N, 19.26. Found: C, 57.98; H, 4.48; N, 18.68.

5-(3′-α-Carboxypiperidinoindolal)-1-methylhydantoin.—A solution of 1.8 g. of 1-methylhydantoin (prepared according to the method of Miller and Robson[3]) and 2.86 g. of 2-carboxypiperidinoindole-3-aldehyde in 5 cc. of piperidine was heated under reflux for one hour. Some solid yellow material had precipitated during this period. The reaction mixture was treated with 30 cc. of hot water, made slightly acidic with acetic acid, cooled and the solid product filtered off; 3.0 g. (76%), m. p. 289–295°. After seven recrystallizations from pyridine–water the light yellow plates melted at 306–307.5° (dec.). *Anal.* Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 65.08; H, 5.81; N, 16.03.

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Acylation of Some Thiophenes with Crotonyl Chloride[1]

BY CHARLES K. BRADSHER, FRANCES C. BROWN AND R. J. GRANTHAM

Recently Hartough, Kosak and Sardella[2] have shown that thiophene in the presence of activated montmorillonite clay may be acylated with crotonyl chloride to yield 2-crotonylthiophene.

(1) This note consists of a report of work done under contract with the Medical Division, Chemical Corps, U. S. Army.

(2) Hartough, Kosak and Sardella, THIS JOURNAL, **69**, 1014 (1947).

TABLE I

2-CROTONYLTHIOPHENES

Substituents	B. p., °C.[a] (14 mm.)	$n^{25}D$[a]	Yield,[b] %	Formula	Analyses,[c] % Calcd.	Found
.....	134.5–135.5	1.5949	64[d]	C_8H_8OS	S, 21.07	21.04
5-Chloro	151–152	....[f]	55	C_8H_7OSCl	C, 51.47	51.34
					H, 3.78	4.14
3(?)-Methyl	135–136.5	1.5836	49	$C_9H_{10}OS$	S, 19.29	19.50
5-*t*-Butyl[e]	168–169	1.5592	53	$C_{21}H_{16}OS$	C, 69.18	68.87
					H, 7.74	7.74

[a] Constants are for analytical sample. [b] Yields based on product obtained in first fractionation; average boiling range seven degrees. [c] Analyses by Clark Microanalytical Laboratory. [d] Previously reported b. p. 109–116° (5 mm.); yield 22% (ref. 2). [e] The 2-butylthiophene used was obtained by refractionation of a sample obtained from the Midland Chemical Company. On the basis of the work of Appleby, Sartor, Lee and Kapranos (THIS JOURNAL, **70**, 1552 (1948)) this starting material, $n^{20}D$ 1.4981, may have contained 6 ± 3% of 3-*t*-butylthiophene. [f] M. p. 72–73°.

In a similar reaction, using stannic chloride as the catalyst we have produced the crotonylthiophene in a somewhat better yield. Acylation of the 2-chloro-, 2-*t*-butyl- and 3-methylthiophenes with crotonyl chloride was likewise effected successfully, but 2,5-dichlorothiophene appeared unreactive.[3]

General Procedure.—A solution containing 0.15 mole of the thiophene and an equimolecular quantity of crotonyl chloride in 200 ml. of dry benzene was cooled to 0°, and 18 ml. (about 0.15 mole) of anhydrous stannic chloride was added dropwise over a period of one hour. The temperature was allowed to rise slowly to room temperature and stirring continued for an additional hour. The reaction mixture was decomposed with one molar hydrochloric acid and the benzene layer was separated, washed, dried and concentrated. The residue was fractionated under reduced pressure. The results are summarized in Table I.

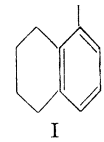
(3) *Cf.* Steinkopf and Kohler, *Ann.*, **532**, 265 (1937).

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA RECEIVED MAY 7, 1949

The Rate of Dissociation of 1,1,1,2-Tetraphenyl-2-(4′-hydrindenyl)-ethane

BY ROBERT G. CHRISTIANSEN[1] AND REUBEN B. SANDIN

In an attempt to relate the ease of preparation and properties of certain polynuclear hydrocarbons to a possible steric effect, the rate of dissociation of 1,1,1,2-tetraphenyl-2-(4′-hydrindenyl)-ethane has been determined. This has been done following the very convenient method of Bachmann and co-workers.[2] The rate constant and half-life period in the reaction with iodine at 80° have been found to be 0.0246 and 28.3 minutes, respectively. Recently Bachmann and Brockway[3] have determined the dissociation rate of 1,1,1,2-tetraphenyl-2-(1′-tetralyl)-ethane. For this hydrocarbon k = 0.0728 and $t^{1/2}$ = 9.5 minutes.[4] It is evident that the 1-tetralyl group (I) shows a somewhat greater effect than the 4-hydrindenyl group (II).



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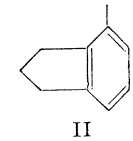

II

This is in agreement with the interesting work of Arnold and co-workers[5] wherein they have presented evidence to prove that the steric effect of the methylene groups in five membered rings (*i. e.*, hydrindene) is smaller than that in the corresponding six-membered rings (*i. e.*, tetralin).

Experimental

4-Benzoylhydrindene.—This ketone prepared in 65% yield by the reaction of the Grignard reagent from bromobenzene and 4-cyanohydrindene[6] was obtained as a viscous oil which did not solidify on long standing; b. p. 177–180° at 2 mm.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.44; H, 6.35. Found: C, 86.76; H, 6.47.

Phenyl-4-hydrindenylcarbinol.—The carbinol prepared in 53% yield by the aluminum isopropoxide reduction of the ketone, was obtained as a viscous liquid; b. p. 180° at 4 mm.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.69; H, 7.19. Found: C, 85.84; H, 7.17.

1,1,1,2-Tetraphenyl-2-(4′-hydrindenyl)-ethane.—The phenyl-4-hydrindenylmethyl bromide from 9.0 g. of the carbinol and acetyl bromide was coupled at once with triphenylmethylsodium by the standard procedure. The resulting hydrocarbon crystallized from benzene–methanol as colorless crystals; yield, 60%; m. p. in air, 185–190°.

Anal. Calcd. for $C_{35}H_{30}$: C, 93.29; H, 6.71. Found: C, 93.44; H, 6.90.

Rate Measurements.—These were carried out according to the procedure of Bachmann and Osborn.[2b] Methanol was used in the place of ethanol in the *o*-dichlorobenzene, iodine and pyridine mixture.

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(2) (a) Bachmann and Wiselogle., *J. Org. Chem.*, **1**, 354 (1936); (b) Bachmann and Osborn, *ibid.*, **5**, 29 (1940); (c) Bachmann, Hoffman and Whitehead, *ibid.*, **8**, 320 (1943).

(3) Bachmann and Brockway, *ibid.*, **13**, 384 (1948).

(4) The present authors have found values which agree with those of Bachmann and Brockway.

(5) Arnold and Rondestvedt, THIS JOURNAL, **67**, 1264 (1945); *ibid.*, **68**, 2176 (1946); Arnold and Craig, *ibid.*, **70**, 2791 (1948).

(6) Fieser and Hershberg, *ibid.*, **59**, 394 (1937).

Proportions of Cymenes from Propylation of Toluene

BY FRANCIS E. CONDON

A mechanism advanced to explain the formation of considerable *m*-dialkylbenzene in the aluminum chloride-catalyzed alkylation of a monoalkylbenzene, in apparent opposition to the well-known ortho–para directing influence of an alkyl group, is alkylation to 1,2,4-trialkylbenzene, followed by dealkylation.[1] In an experimental test of this hypothesis, as part of the present investigation of the proportions of cymenes produced by propylation of toluene under homogeneous liquid-phase conditions, pure *p*-cymene was alkylated with propylene at 65° in the presence of aluminum chloride and of benzene and nitromethane[2] as solvents, in order to determine whether any *m*-cymene would result from *p*-cymene under conditions that produced considerable *m*-cymene from toluene. The experimental data are presented in Table I.

No *o*-cymene and no *m*-cymene were produced when *p*-cymene was alkylated with propylene, whereas 38% *o*-cymene, 27% *m*-cymene, and 35% *p*-cymene were produced from toluene under the same conditions. These results show that all the isomeric cymenes were produced by direct alkylation of toluene at the available positions, rather than by isomerization or by alkylation-dealkylation of *p*-cymene. The considerable proportion of *m*-cymene means that a methyl group exerts a relatively feeble ortho–para orienting influence during propylation. (During nitration of toluene, only about 4% of *m*-nitrotoluene is produced.[3])

The proportions of cymenes produced at 5 and at 65° are slightly different. These differences appear real, and probably should not be considered within the experimental error (*cf.* ref. 3).

The proportions of cymenes appear to be independent of whether the catalyst is aluminum chloride or boron fluoride. Noteworthy, too, is their apparent independence of the extent of conversion (measured by the mole ratio of propylene to aromatics given in Table I). Some dependence at high conversions would be expected from inequalities in the rates of further propylation of the different isomers.

TABLE I

PROPORTIONS OF CYMENES FROM PROPYLATION OF TOLUENE

Temperature, °C.		65	65	5	5	65
Charge compn., mole fract.	Benzene	0.300	0.467	0.304	0.442	0.613
	Toluene	.300	.368	.296	.380	.217[a]
	$AlCl_3$	...	.012	...	.030	.012
	Nitromethane	...	.153	...	.148	.158
	$BF_3 \cdot Et_2O$	.400	...	.400	...	...

Experiment	1	2	3	4	5	6	7	8	9	10
C_3H_6/aromatics, (mole/mole)	0.14	0.24	0.15	0.36	0.11	0.08	0.08	0.13	0.29	0.45
Cymene fraction, vol. %[b] Cumene	0	0	0	0	0	0	0	0	1	5
o-Cymene	38.4	35.8	36.1	36.4	35.9	37.2	34.0	35.9	0	0
m-Cymene	25.9	28.1	27.0	28.2	27.0	27.6	30.0	31.4	0	0
p-Cymene	36.8	34.3	33.2	34.6	32.4	32.0	30.4	32.3	96	91
m-Diisopropylbenzene	0.5	0.0	2.9	2.5	0.5	2.9	0.7	0.0	3	4
Total	101.6	98.2	99.2	101.7	95.8	99.7	95.1	99.6	100	100
Cymenes, average wt. % *o*-Cymene		37.6 ± 0.6				37.5 ± 1.0			0	
m-Cymene		27.5 ± 1.0				29.8 ± 1.6			0	
p-Cymene		34.9 ± 0.6				32.7 ± 0.6			100	

[a] *p*-Cymene. [b] Infrared analyses. Values of log I_0/I for cumene, *o*-cymene, *m*-cymene, *p*-cymene and *m*-diisopropylbenzene, respectively, in a 0.017-mm. cell were: at 14.21 μ: 0.4700, 0.0205, 0.9640, 0.0130, 0.4788; at 13.75 μ: 0.0510, 0.9350, 0.0225, 0.0310, 0.0215; at 12.61 μ: 0.0200, 0.0175, 0.1240, 0.0320, 0.5755; at 12.27 μ: 0.0120, 0.0243, 0.0395, 1.3030, 0.0470; at 11.04 μ: 0.1030, 0.0243, 0.0438, 0.0165, 0.0280; (absorption maxima underlined).

Acknowledgments.—Messers. Harold Price and Richard Sonnenfeld made the infrared analyses. Mr. Stanley Turk supplied pure isomeric cymenes for calibration of the infrared spectrometer. Phillips Petroleum Company granted permission to publish the data.

(1) Price and Ciskowski, THIS JOURNAL, **60**, 2499 (1938); Price, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 10.

(2) Schmerling, *Ind. Eng. Chem.*, **40**, 2072 (1948); Condon, THIS JOURNAL, **70**, 2265 (1948).

(3) Jones and Russell, *J. Chem. Soc.*, 921 (1947).

RESEARCH DEPARTMENT
PHILLIPS PETROLEUM COMPANY
BARTLESVILLE, OKLAHOMA RECEIVED JANUARY 14, 1949

[CONTRIBUTION FROM THE NATIONAL BUREAU OF STANDARDS]

The Dissociation Constant of Dimethylaniline Hydrochloride in Chloroform

BY MARION MACLEAN DAVIS

Recently Moede and Curran[1] described the determination of the dissociation constant, K_c, for

(1) J. A. Moede and C. Curran, THIS JOURNAL, **71**, 852 (1949).

the sulfur dioxide addition compounds of several amines in benzene, *n*-butyl chloride or chloroform, by measurement of dielectric properties or ultraviolet absorption spectra. The reaction assumed was

$$\text{C (addition compound)} \rightleftarrows \text{A (amine)} + \text{B (sulfur dioxide)}$$

The correctness of this assumption was supported by the good agreement of values for K_c at various concentrations.

In the same paper, data and calculations were presented for the dissociation of dimethylaniline hydrochloride in chloroform. The equilibrium postulated in this case was

$$C_8H_{11}NH^+ + Cl^- \rightleftarrows C_8H_{11}N + HCl \quad (1)$$

Values obtained for K_c showed a progressive increase with dilution, varying from 0.38×10^{-6} for 0.008442 molar solution to 31×10^{-6} for 0.001203 molar solution. The salt effect of the hydrochloride was suggested as a possible explanation of the trend toward higher values of K_c as the solutions became more dilute. This interpretation of the reaction seemed erroneous to the writer, because spectrophotometric data obtained at the National Bureau of Standards for various acid–base reactions in benzene[2] and measurements of the effect of dilution on the dielectric polarization of tribenzylammonium picrate in benzene[3] have been interpreted satisfactorily on the assumption of *negligible* ionic dissociation, and the dielectric constant of chloroform (~4.7) is nearly as low as that of benzene (~2.3). Provisional calculations of the dissociation constant for dimethylaniline hydrochloride, using the data in Moede and Curran's Table V and interpolating in their Fig. 6 to obtain ϵ_C (169) and ϵ_A (11,000), but considering the reaction to be

$$C_8H_{11}NHCl \rightleftarrows C_8H_{11}N + HCl \quad (2)$$

gave nearly constant values with the mean value 6.0×10^{-8} for K_c at all concentrations. These provisional values for K_c were reported to Professor Curran, who graciously furnished the experimental values at 255 mμ for ϵ_C (192) and ϵ_A (10,530), and also stated that the same equilibrium (2) had originally been considered by him and Dr. Moede but that because the resulting values for K_c showed a decrease with increasing concentration, the alternative equation (1) was adopted. However, when the values for K_c computed according to both equations are compared (see Table I), it is evident that the data are more consistent with equation (2). According to either formulation, the dissociation of the salt into dimethylaniline and hydrogen chloride occurs to so slight an extent, in the range of concentrations concerned, that a small experimental error will have a large effect on the constancy of K_c. Therefore, the slight trend in the values shown in column 3 of Table I does not appear significant, particularly since the first two values correspond to transmittancies outside the range recommended by Mellon for reliable measurement.[4] The correct value for K_c thus appears to be $\sim 1.5 \times 10^{-8}$.

TABLE I

DISSOCIATION CONSTANT OF DIMETHYLANILINE HYDROCHLORIDE IN CHLOROFORM AT 24 ± 3°

c	$K_c \times 10^{8a}$	$K_c \times 10^{8b}$
0.008442	0.38	0.3
.008120	0.71	0.6
.005627	1.9	1.1
.005413	1.4	0.8
.004221	5.3	2.2
.004060	3.2	1.0
.003248	4.5	1.5
.002814	4.6	1.3
.002707	8.2	2.2
.001407	14	2.0
.001203	31	3.7
		Mean 1.5

[a] Computed by Moede and Curran according to equation (1); see ref. (1), Table V. [b] Computed by M. M. Davis, according to equation (2).

To consider that dimethylaniline hydrochloride exists mainly as an addition compound in chloroform is contrary to the rather common belief that salts are largely dissociated into the free ions in all non-aqueous solvents as well as in water. However, Kraus and his associates have found that the ionic dissociation of a salt drops off rapidly as the dielectric constant of the solvent approaches very low values.[5] Moreover, both Walden[6] and Kraus[7] have pointed out that salts which appear equally strong in water may exhibit pronounced differences in strength when dissolved in solvents of low dielectric constant and that, for example, incompletely substituted ammonium salts are distinctly weaker than quaternary ammonium salts in such solvents. This decrease in strength appears to be caused in part by the presence of a hydrogen bridge in salts of the former type.[7]

Moede and Curran report that the conductance of a 0.1 molar solution of dimethylaniline hydrochloride was observed to be about a thousand times that of hydrogen chloride in chloroform.[1] This does not necessarily imply a significant concentration of dimethylanilinium and chloride ions. Kraus has stated that hydrogen chloride in nitrobenzene, of dielectric constant ~35, is a very weak electrolyte.[7] In chloroform, therefore, the

(2) M. M. Davis and P. J. Schuhmann, *J. Research Nat. Bur. Standards*, **39**, 221 (1947); M. M. Davis and E. A. McDonald, *ibid.*, **42**, 595 (1949).

(3) A. A. Maryott, *ibid.*, **41**, 7 (1948).

(4) M. G. Mellon, "Colorimetry for Chemists," G. Frederick Smith Chemical Co., Columbus, Ohio, 1945, p. 56.

(5) See, for example, R. M. Fuoss and C. A. Kraus, THIS JOURNAL, **55**, 1019 (1933); C. A. Kraus, *J. Chem. Education*, **12**, 567 (1935).

(6) P. Walden, "Salts, Acids, and Bases: Electrolytes: Stereochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1929, Chapter X.

(7) C. A. Kraus, *J. Phys. Chem.*, **43**, 231 (1939); see also discussion by M. Kilpatrick and K. Fajans, *ibid.*, **43**, 288 (1939).

ionic dissociation of hydrogen chloride must be practically negligible. The approximately linear relationship between $-\log K_c$ and $\sqrt{c} \times 10^2$ shown in Moede and Curran's Fig. 8 is probably fortuitous and is somewhat uncertain because of the scattering of the experimental points. A nearly linear relationship also appears to hold if $-\log K_c$ is plotted against $c \times 10^3$ or $\sqrt[3]{c}$. Moreover, these authors found that $k = 14$ in the relationship $-\log K_c = -\log K_a + 2k\sqrt{\mu}$, instead of the expected value, 32.8, and stated that the "low value appears to be due in part to the presence of a large number of $C_8H_{11}NH^+$–Cl^- ion pairs, which reduces the ionic strength below the calculated value." However, in view of the considerations outlined above, it seems more probable that in the chloroform solutions of dimethylaniline hydrochloride under discussion less than 0.6% of the salt was dissociated into $C_8H_{11}N$ and HCl, that the extent of dissociation into $C_8H_{11}NH^+$ and Cl^- was practically negligible, and that the salt existed almost entirely as hydrogen-bonded ion pairs, $C_8H_{11}NH^+$–Cl^-, in effect analogous to the amine–sulfur dioxide addition compounds. The importance of this interpretation is apparent when one observes that equilibrium (2) represents an association as well as a dissociation. More explicitly, I believe the results of Moede and Curran provide new evidence that the product of the reaction of a base with either a "Lewis" acid or a "Brønsted" acid is essentially the same thing, namely, a highly polar addition compound, when the solvent has a low dielectric constant and solvation is not a factor.

WASHINGTON, D. C. RECEIVED MAY 13, 1949

An Improvement on the Process for Making Amidone

BY JOHN W. CUSIC

One of the difficult steps in the synthesis of Amidone is the preparation of the intermediate 4-dimethylamino-2,2-diphenylvaleronitrile.

This has usually involved the use of a hazardous chemical such as sodium amide.[1] Cheney[2] has used lithium amide which, however, is a fairly expensive chemical.

I have found that the condensation of 1-dimethylamino-2-chloropropane hydrochloride with diphenylacetonitrile can be carried out with sodium hydroxide, which is both cheap and safe.

Experimental

Sixty grams (1.5 moles) of commercial sodium hydroxide flake, 77.2 g. (0.4 mole) of diphenylacetonitrile and 79.0 g. (0.5 mole) of 1-dimethylamino-2-chloropropane hydrochloride were mixed in an erlenmeyer flask and heated with occasional stirring for six to seven hours on the steam-bath. The reaction mixture was extracted with ether and the ether in turn extracted with dilute hydrochloric acid. The acid solution was made strongly alkaline with sodium hydroxide and the liberated base extracted with ether. The ether solution was dried over anhydrous potassium carbonate, filtered and after removal of the ether the product was distilled to yield 89 g. of product, b. p. 173–174° at 1 mm. It was then crystallized from petroleum ether (60–71°) to give 49 g. (45.7%) melting at 89–90°.

Anal. Calcd. for $C_{19}H_{22}N_2$: N, 10.3. Found: N, 9.91.

G. D. SEARLE AND CO., BOX 5110
CHICAGO, ILL. RECEIVED MAY 18, 1949

(1) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188, 2454 (1947).

(2) Cheney, Smith and Binkley, *ibid.*, **71**, 52 (1949).

Some 1,2-Dialkylcyclohexanes[1,2]

BY J. R. DICE, L. E. LOVELESS, JR., AND H. L. CATES, JR.[3]

There is a surprising paucity of data concerning 1,2-dialkylcyclohexanes where neither substituent group is methyl. Our original intention was to synthesize an extensive series of these compounds, but the poor yields encountered in many of the steps limited the number prepared.

The crucial intermediates 2-ethyl- and 2-propylcyclohexanone were prepared by the interaction of 2-chlorocyclohexanone and the appropriate Grignard reagent.[4] Propyllithium was used in one experiment. The improvement in yield was more than offset by the increased difficulty of preparation. Attempts to prepare 2-(1-methylethyl)-cyclohexanone by the Grignard method were unsuccessful, although this preparation (without any experimental details) is reported by Bouveault and Chereau.[4] Addition of cobaltous chloride did not affect the yield of 2-propylcyclohexanone. Direct alkylation of cyclohexanone using sodium amide or sodium in liquid ammonia as catalysts gave a complex mixture of products.

The addition of various Grignard reagents to 2-ethyl- and 2-propylcyclohexanone gave a series of 1,2-dialkylcyclohexanols which were dehydrated to the corresponding 1,2-dialkylcyclohexenes by distillation from iodine. The double bond was believed to be in the ring because of the difficulty of hydrogenating the unsaturated products.[5] It also has been proved[6] that the dehydration of 1,2-dimethylcyclohexanol by this method yields 1,2-dimethylcyclohexene. Hydrogenation of the dialkylcyclohexenes using Raney nickel as a catalyst gave the desired 1,2-dialkylcyclohexanes.

Experimental

2-Ethylcyclohexanone.[7]—To the Grignard reagent prepared from 25.6 g. of magnesium, 114 g. of ethyl bromide and 600 ml. of dry ether was added 122 g. of 2-chlorocyclo-

(1) From the M.A. theses of L. E. Loveless, Jr., and H. L. Cates, Jr., The University of Texas, 1948.

(2) This work was generously supported by grants from the University of Texas Research Institute (Project 186).

(3) Present address: Department of Chemistry, The Ohio State University, Columbus, Ohio.

(4) Bouveault and Chereau, *Compt. rend.*, **142**, 1087 (1906); Vavon and Mitchtovitch, *Bull. soc. chim.*, [4] **45**, 961 (1929).

(5) Gilman, "Organic Chemistry," Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 797.

(6) Signaigo and Cramer, THIS JOURNAL, **55**, 3326 (1933).

(7) For other methods for the preparation of 2-ethylcyclohexanone see (a) ref. 4; (b) Tiffeneau, Tchoubar and Le Tellier, *Compt. rend.* **216**, 856 (1943); and (c) Ruzicka and Peyer, *Helv. Chim. Acta*, **18** 676 (1935).

TABLE I

1,2-DIALKYLCYCLOHEXANOLS

Substituted cyclohexanol	Yield, %	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4	Formula	Composition,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1,2-Diethyl-[b]	83	72–73	3	1.4653	0.919	$C_{10}H_{20}O$	76.9	77.2	12.9	12.9
1-Ethyl-2-propyl-	75	60–68	2	1.4640	.907	$C_{11}H_{22}O$	77.6	77.3	13.0	12.9
1,2-Dipropyl-[c]	27	70–74	7	1.4641	.928	$C_{12}H_{24}O$	78.2	78.0	13.1	13.7
1-(1-Methylethyl)-2-propyl-	20	83–85	10	1.4605	.938	$C_{12}H_{24}O$	78.2	78.3	13.1	12.6
1-Butyl-2-propyl-	48	84–85	4	1.4642	.898	$C_{13}H_{26}O$	78.7	78.7	13.2	12.8

[a] Difficulties were encountered in adapting the semi-micro analytical procedure outlined by Horning and Horning, *Ind. Eng. Chem., Anal. Ed.*, **19**, 688 (1947), to the analysis of these compounds. The use of small glass bulbs consistently led to rather vigorous "flashing" and low results. Open platinum boats were impractical due to the volatility of the compounds. Reasonably satisfactory results were finally obtained by increasing the size of the sample to approximately 40 mg. and adding 75 mg. of potassium chlorate to the open boat. [b] Ruzicka and Peyer, ref. 7c, prepared but did not isolate this compound. [c] Vavon and Barbier, *Bull. soc. chim.*, [4] **49**, 4567 (1931), report a *cis-cis*-dipropylcyclohexanol. The positions occupied by the alkyl groups are not indicated, nor is the method of synthesis given.

TABLE II

1,2-DIALKYLCYCLOHEXENES

Substituted cyclohexene	Yield, %	B. p. °C.	Mm.	$n^{25}D$	d^{25}_4	Formula	Composition,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1,2-Diethyl-[b]	85	170–175	747	1.4598	0.831					
1-Ethyl-2-propyl-	76	180–184	746	1.4559	.843	$C_{11}H_{20}$	86.8	86.3	13.2	13.4
1,2-Dipropyl-	60	162–167	748	1.4557	.868	$C_{12}H_{22}$	86.7	86.6	13.3	13.1
1-(1-Methylethyl)-2-propyl-	45	167.5–168.5	746	1.4535		$C_{12}H_{22}$	86.7	86.7	13.3	13.1
1-Butyl-2-propyl-	72	210–211	746	1.4609	.868	$C_{13}H_{24}$	86.6	86.6	13.4	13.5

[a] See footnote *a*, Table I. [b] Reported, ref. 7c, b. p. 60–61° (10 mm.).

TABLE III

1,2-DIALKYLCYCLOHEXANE

Substituted cyclohexane	Yield, %	B. p., °C.	Mm.	$n^{25}D$	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1,2-Diethyl-[a,b]		170–175	746	1.4453	$C_{10}H_{20}$	85.6	85.6	14.4	14.3
1-Ethyl-2-propyl-[b]	60	190–197	746	1.4448	$C_{11}H_{22}$	85.6	85.7	14.4	14.3
1,2-Dipropyl-[c]	25	225–228	748	1.4524	$C_{12}H_{24}$	85.6	86.0	14.4	14.0
1-Butyl-2-propyl-[c]	30	236–240	750	1.4531	$C_{13}H_{26}$	85.6	85.7	14.4	14.1

[a] Prelog and Zalan, *Helv. Chim. Acta*, **27**, 535 (1944), prepared this compound by a different method and reported a boiling range (heating-bath temperature) of 132–197°. [b] Analysis by C. W. Beazley, Micro-Tech Laboratories, Skokie, Illinois. [c] Analysis by the authors. See footnote *a*, Table I.

hexanone[8] over a period of two hours. Most of the ether was replaced by 500 ml. of dry benzene and the mixture was refluxed for five hours. After hydrolysis the product was distilled through a 60-cm. fractionation column to yield 52 g. (41%) of a colorless liquid boiling at 42° (2 mm.) (reported[4] 67° (13 mm.)); $n^{16}D$ 1.4530 (reported[4] 1.4528); semicarbazone, m. p. 161–162° (reported,[4,7b] 161, 165°).

2-Propylcyclohexanone[9] using Propylmagnesium Bromide.—Using the method described previously 2-propylcyclohexanone was prepared from 13.4 g. of magnesium, 67.5 g. of 1-bromopropane and 66.7 g. of 2-chlorocyclohexanone. The colorless distillate (14 g., 20%) boiled at 80–81° (12 mm.) (reported[9a,9c] 83–84° (13 mm.) and 94–95° (25 mm.)), semicarbazone m. p. 119–120° (reported[9a] 133.5–134.0°), semicarbazide m. p. 101–103° (reported[9a] 103–104°), semicarbazide hydrochloride m. p. 146–148° (reported[9a] 146–148°).

2-Propylcyclohexanone Using Propyllithium.—To a stirred mixture of 7.6 g. of freshly-cut lithium and 300 ml. of dry ether was added a solution of 67.5 g. of 1-bromopropane in 200 ml. of dry ether over a three-hour period. The mixture turned black and was refluxed for twelve hours. To the stirred propyllithium reagent was added 61.5 g. of 2-chlorocyclohexanone over a two-hour period; a green color formed. After standing eight hours the mixture was filtered from excess lithium and the filtrate was hydrolyzed by means of an ice–hydrochloric acid slurry. The mixture was extracted with ether and the organic layer was washed with dilute sodium hydroxide and dilute hydrochloric acid and dried over sodium sulfate. The ether was removed by means of a current of air and the residue was distilled at 86–88° (16–17 mm.), yield 22.2 g. (30%), semicarbazone m. p. 119–120°, mixture m. p. with semicarbazone from Grignard method, 119–120°.

Preparation of 1,2-Dialkylcyclohexanols.—To the Grignard reagent prepared from 0.23 mole of magnesium and 0.23 mole of the appropriate alkyl halide in 200–300 ml. of dry ether was added 0.20 mole of the desired 2-alkylcyclohexanone over a period of two hours. The mixture was refluxed with stirring for twelve hours and then poured on an ice–hydrochloric acid slurry. The combined ether extracts were washed with saturated sodium bisulfite solution and twice with water. After drying over sodium sulfate and evaporation of the solvent the alcohols were distilled *in vacuo*. Yields, physical constants and other pertinent data are given in Table I.

Preparation of 1,2-Dialkylcyclohexenes.—Two to 25 g. batches of the various 1,2-dialkylcyclohexanones were distilled from 0.05 to 0.20 g. of iodine. The distillate was washed with sodium thiosulfate solution, dried over calcium chloride and then refluxed with sodium from ten to sixty minutes. Distillation from the sodium gave colorless liquids. Table II contains the data relative to these compounds.

(8) Newman, Barbman and Hipsher, *Org. Syntheses*, **25**, 22 (1945).

(9) For other preparations of 2-propylcyclohexanone see (a) Vavon and Aziani, *Bull. soc. chim.*, [4] **41**, 1642 (1927); (b) ref. 4; (c) Cornubert and Marvel, *Bull. soc. chim.*, **49**, 1498 (1931).

Preparation of 1,2-Dialkylcyclohexanes.—Preliminary tests showed that the 1,2-dialkylcyclohexenes were resistant to hydrogenation at room temperature and 1–2 atmospheres of hydrogen using platinum as catalyst. Hydrogenation occurred smoothly in a bomb at 150° and a starting hydrogen pressure of 2400 p. s. i. using 0.5–1.0 g. of Raney nickel catalyst for 2–5 g. of cyclohexene. Absolute ethanol (30–50 ml.) was used as solvent in all cases. After filtration the solution was evaporated to approximately 10 ml. and poured into water. The mixture was extracted with benzene and the combined extracts dried over sodium sulfate. After evaporation of the solvent the residue was treated with concentrated sulfuric acid to remove any cyclohexenes. The mixture was diluted with water and was extracted with benzene which was washed with dilute sodium hydroxide and water and dried over sodium sulfate. On distillation colorless liquids were obtained. Data on the cyclohexenes prepared are given in Table III.

DEPARTMENT OF CHEMISTRY
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Preparation of 2-Pyridylmethanol[1]

BY WALTER M. EDWARDS[2] AND PEYTON C. TEAGUE[3]

Harries and Lenart[4] and Graf, *et al.*,[5] have reported the preparation of 2-pyridylmethanol by methods which require several steps beginning with readily obtainable derivatives of pyridine. This report describes a simple method of preparation of 2-pyridylmethanol from 2-picoline, which does not involve the isolation of any intermediate product. 2-Picolyllithium was prepared by the hydrogen–metal interchange reaction between 2-picoline and phenyllithium. The picolyllithium was oxidized with a slow current of air to form the desired 2-pyridylmethanol.

A compound, $C_{12}H_{12}N_2$, was obtained as a by-product of the reaction. This compound was not identified but is probably 1,2-dipyridylethane, which would be expected[6] as the coupling product of two pyridyl radicals.

Experimental[7]

2-Picolyllithium was prepared by the procedure of Finkelstein and Elderfield[8] from 46.5 g. of 2-picoline. When the reaction was complete, the source of nitrogen was removed. Dry, carbon dioxide-free air was drawn at the rate of 2 cc. per minute into the flask and over the surface of the solution. The oxidation was carried out with stirring and without heating or cooling for eight hours, at which time the bright red color had disappeared and the mixture was light yellow. From time to time, more anhydrous ether was added to replace that lost by evaporation.

For the separation of the product, 6 *N* hydrochloric acid was added until the solution was acid to congo red. The aqueous layer was separated, made alkaline with sodium carbonate, saturated with sodium chloride, and extracted several times with chloroform. After the chloroform layer had been dried over anhydrous calcium sulfate for twenty-four hours, the chloroform and 2-picoline was distilled from the mixture at atmospheric pressure. The picoline boiled at 128° and was identified by the melting point of its picrate (168°). It weighed 11.3 g. or 24% of the original amount added.

The mixture of free bases was then fractionally distilled under reduced pressure. The following fractions were obtained: Fract. 1 (70–103° at 3–4 mm.), 11.2 g.; fract. 2 (103–136° at 3–4 mm.), 8.0 g., fract. 3 (138–170° at 1–2 mm.), 0.9 g.; residue, 16 g.

Identification of 2-Pyridylmethanol.—Fraction 1 on redistillation boiled completely at 111–115° at 16 mm. *Anal.* Calcd. for C_6H_7NO: N, 12.84. Found: N, 12.64. The picrate melted at 150° and the chloroplatinate at 179°. These data are in agreement with the values of Harries and Lenart.[4]

The yield of 11.2 g. was 20.5% based on the 2-picoline added or 27.0% on the basis of 2-picoline consumed in the reaction.

Compound $C_{12}H_{12}N_2$.—Fraction 2 redistilled at 112–114° at 1–2 mm. The distillate solidified on standing. After recrystallization from ligroin, its melting point was 49°. *Anal.* Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 77.98; H, 6.67; N, 15.05. Molecular weight determination by the Rast camphor method. Calcd.: 184. Found: 197, 196, 193; av. 195. This product was not further characterized.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF GEORGIA
ATHENS, GEORGIA

RECEIVED APRIL 27, 1949

Polyvinyl Bromide[1]

BY DAVID EDELSON AND RAYMOND M. FUOSS

In connection with our work on polyelectrolytes,[2] we attempted to prepare a polymeric quaternary compound by the addition of tertiary amines to polyvinyl bromide. The desired product was not obtained, but the results of some of our experiments seem worth reporting. Vinyl bromide is one of the earliest known vinyl compounds; Regnault[3] prepared it by treating ethylene dibromide with alkali. Staudinger[4] studied its polymerization and noted that the polymer readily loses hydrogen bromide.

We heated 0.5 cc. of 30% hydrogen peroxide and 10 g. of vinyl bromide[4a] in a bomb at 47° for twenty-four hours and obtained no polymer, although Güyer and Schütze[5] report complete conversion in twenty hours at 60°. About 30% conversion was obtained in two days at 60° from a (deoxygenated) solution of vinyl bromide (10 g.) in toluene (8 g.) saturated with benzoyl peroxide. The product was white, but darkened on drying under vacuum at 30°; Parr bomb bromine averaged to 70.2% (theoretical 74.77%). Fair results were obtained by photochemical

(1) Abstracted from the thesis of Walter M. Edwards, submitted in partial fulfilment of the requirements for the M.S. degree at the University of Georgia, Athens, Georgia.

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(4) Harries and Lenart, *Ann.*, **410**, 107 (1915).

(5) Graf, *et al.*, *J. prakt. Chem.*, **146**, 88 (1936).

(6) Gilman and Pacevitz, THIS JOURNAL, **61**, 1603 (1939).

(7) All melting points and boiling points are corrected.

(8) Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939).

(1) Project NR 054-002 of the Office of Naval Research.

(2) R. M. Fuoss and G. I. Cathers, *J. Polymer Sci.*, **2**, 12 (1947); **4**, 97 (1949); R. M. Fuoss and U. P. Strauss, *ibid.*, **3**, 246 (1948); G. I. Cathers and R. M. Fuoss, *ibid.*, **4**, 121 (1949).

(3) V. Regnault, *Ann. chim.*, [II] **59**, 358 (1935).

(4) H. Staudinger, M. Brunner and W. Feisst, *Helv. Chim. Acta* **13**, 805 (1930).

(4a) We are indebted to the Dow Chemical Company for the sample of vinyl bromide on which these experiments were made.

(5) A. Güyer and H. Schütze, *Helv. Chim. Acta*, **17**, 1544 (1934).

polymerization[6] in ether solution in a sealed quartz tube placed in front of a 100-watt quartz mercury arc, but the product darkened in the tube unless precautions were taken to shield the polymer from the ultraviolet radiation.

Oxidation-reduction polymerization[7] using the recipe: 75 cc. of deoxygenated water, 2 g. of Cetab, 10 cc. of 1.0 *N* sulfuric acid, 13 g. of vinyl bromide, 1 cc. of 0.01 *N* ferrous sulfate in *N*/10 sulfuric acid and 1 cc. of 0.01 *N* hydrogen peroxide gave no yield, possibly as a consequence of the difficulty of deoxygenating a monomer which boils at 15.8°. Some conversion was obtained with potassium persulfate as catalyst, using the procedure described by Kolthoff and Dale.[8]

The polyvinyl bromide obtained by solution polymerization was insoluble in Bu_3N (cohesive energy density 44), petroleum ether (52), carbon tetrachloride (73), nitromethane (143), ethyl alcohol (260), and methyl alcohol (346); swelled in toluene (75), benzene (81) and acetone (91); and dissolved in methyl ethyl ketone (80), dioxane (91), $C_6H_5NO_2$ (102) and C_5H_5N (105). From these data, we estimate that the cohesive energy density[9] of polyvinyl bromide is about 90, approximately the same as that of polyvinyl chloride.[10]

Addition of polyvinyl bromide to pyridine in a conductance cell at 25° produced electrolyte, as shown by a rapid increase in conductance. Reaction with triethylamine and with trimethyl amine in methanol also lead to electrolyte formation. No polyelectrolyte was produced, however; in every case, an insoluble red-to-dark-brown precipitate was obtained, and tertiary amine hydrobromide was found in the supernatant liquid. This result shows that tertiary amines dehydrohalogenate polyvinyl bromide[11] in preference to adding to it to form a polymeric quaternary salt. Two facts favor the elimination of hydrogen bromide: first, steric hindrance militates against the insertion of an R_3N group at every other carbon of the polymer chain; and, second, any single elimination of hydrobromic acid produces labile allylic bromines (—CHBr·CH=CH—) in the chain, which are more reactive than the original bromine atoms of the polymer. The tendency thus is to produce conjugated segments in the polymer chain. If the elimination of hydrogen bromide is purely statistical,[12] occasional methylene groups will be isolated, which will break the conjugation. From the deep color and the insolubility of the product, however, we conclude that the conjugated segments must be quite long, in analogy to the higher members[13] of the $R(CH{=}CH)_nR'$ series.

(6) C. S. Marvel and E. H. Riddle, THIS JOURNAL, **62**, 2666 (1940).

(7) J. H. Baxendale, M. G. Evans and J. K. Killiam, *J. Polymer Sci.*, **1**, 466 (1946); A. G. Evans and E. Tyrrall, *ibid.*, **2**, 387 (1947).

(8) I. M. Kolthoff and W. J. Dale, THIS JOURNAL, **67**, 1672 (1945).

(9) J. H. Hildebrand, "Solubility of Non-Electrolytes," A. C. S. Monograph 17, Reinhold Publishing Corp., New York, N. Y., 1936.

(10) P. M. Doty and B. H. Zimm, Bulletin of the High Polymer Clinic, Polytechnic Institute of Brookyn, N. Y., 1946.

(11) C. R. Noller and R. Dinsmore, THIS JOURNAL, **54**, 1025 (1932).

(12) R. F. Boyer, *J. Phys. Colloid Chem.*, **51**, 80 (1947).

(13) R. Kuhn and A. Winterstein, *Helv. Chim. Acta*, **11**, 87 (1928); G. Compton and W. Bergmann, *J. Org. Chem.*, **12**, 363 (1947).

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Inhibition of Growth of *Escherichia coli* by 4-Aminopteroylglutamic Acid and its Reversal

BY A. L. FRANKLIN, E. L. R. STOKSTAD, C. E. HOFFMANN, M. BELT AND T. H. JUKES

Recent investigations[1-5] have shown that thymidine and certain other desoxyribosides can replace vitamin B_{12} as a growth factor for various lactic acid bacteria. In the present study, the relation of these desoxyribosides to the reversal of the inhibitory effect of 4-aminopteroylglutamic acid[6] (4-amino PGA), a potent antagonist of PGA, was measured. It was found that the growth of *Escherichia coli* was inhibited by high levels of 4-amino PGA in spite of the fact that the organism does not need PGA for growth. The inhibition was found to be reversed by liver extract or thymidine but not by PGA, *p*-aminobenzoic acid, vitamin B_{12}, thymine, guanine, hypoxanthine, adenosine, adenylic acid, cytidylic acid or the desoxyribosides of guanidine and hypoxanthine (Table I).

It was also found that *Lactobacillus leichmannii* 313, which needs both PGA (or *p*-aminobenzoic acid) and vitamin B_{12} for growth, was inhibited by 4-amino PGA. This inhibition was reversible by PGA at low levels of 4-amino PGA, up to 5 γ per ml., but at high levels of 4-amino PGA, 25 γ per ml., PGA was ineffective while thymidine produced a reversal. The desoxyribosides of guanine and hypoxanthine were ineffective as reversing agents, although these two compounds produced approximately maximum growth in the presence of PGA if 4-amino PGA and B_{12} were omitted. In the absence of 4-amino PGA, thymidine produced an incomplete growth response, about 50% of maximum, if PGA and *p*-aminobenzoic acid were omitted, with or without the addition of vitamin B_{12}. The response to guanine desoxyriboside or hypoxanthine desoxyriboside under these conditions was 25 to 33% of maximum.

Experimental

The liver extract was a commercial antipernicious-anemia preparation, 10 units per ml. The medium used

(1) Shive, Ravel and Eakin, THIS JOURNAL, **70**, 2614 (1948).

(2) Snell, Kitay and McNutt, *J. Biol. Chem.*, **175**, 473 (1948).

(3) Hoffmann, Stokstad, Franklin and Jukes, *ibid.*, **176**, 1467 (1948).

(4) Kitay, McNutt and Snell, *ibid.*, **177**, 993 (1949).

(5) Hoff-Jorgensen, *ibid.*, **178**, 525 (1949).

(6) Seeger, Smith and Hultquist, THIS JOURNAL, **69**, 2567 (1947).

TABLE I

EFFECT OF VARIOUS SUPPLEMENTS ON GROWTH OF *E. coli* ON COMPLETE MEDIUM PLUS 4-AMINO PGA

Addition per ml. basal medium[a]	Optical density after 16 hours at 37° Expt. 1	Expt. 2	Addition per ml. basal medium[a]	Optical density after 16 hours at 37° Expt. 1	Expt. 2
None	0.09	0.05	100 γ thymidine	..	0.32
3.0 c. mm. liver extract	.16	.20	10 γ guanine desoxyriboside	0.10	.06
10 c. mm. liver extract	.27	.28	100 γ guanine desoxyriboside	..	.09
100 c. mm. liver extract	..	.38	10 γ hypoxanthine desoxyriboside	.09	.06
3 γ thymine	.06	..	100 γ hypoxanthine desoxyriboside	..	.08
50 γ thymine	..	.08	0.01 γ vitamin B_{12}	.08	.07
0.1 γ thymidine	.14	.12	0.1 γ vitamin B_{12}	..	.10
1.0 γ thymidine	.24	.18	0.4 mg. pteroylglutamic acid	..	.08
10 γ thymidine	..	.26	0.5 mg. *p*-aminobenzoic acid	..	.06

[a] Landy–Dicken[b] medium with dextrose in place of sucrose *plus* 0.15 mg. (Expt. 1) or 0.25 mg. (Expt. 2) 4-amino PGA per ml. of culture medium. Final volume 2 ml. per tube. Inoculum: 24 hour culture on broth,[c] washed once and diluted 1:10. Reading with 4-amino PGA omitted, about 0.4. [b] Landy and Dicken, *J. Lab. Clin. Med.*, **27**, 1086 (1942). [c] Teply and Elvehjem, *J. Biol. Chem.*, **157**, 303 (1945).

with *Lactobacillus leichmannii* was similar to that of Snell and co-workers[2] but with thioglycolic acid, 0.2 mg. per ml.[7] When 25 γ of 4-amino PGA per ml. and 0.2 γ of PGA were added, the following are typical of optical densities obtained at 18 hours: no supplement, 0.02; 200 γ PGA, 0.04; 0.01 γ B_{12}, 0.05; 2 γ thymidine, 0.58; 2 γ guanine desoxyriboside, 0.08; 2 γ hypoxanthine desoxyriboside, 0.04; 100 γ thymine, 0.10; 100 γ thymine *plus* 2 mγ vitamin B_{12}, 0.29. The addition of 2 mγ of vitamin B_{12} did not augment the growth obtained with the desoxyribosides. When 4-amino PGA, PGA and *p*-aminobenzoic acid were omitted from the basal medium the following optical densities were obtained: no supplement, 0.03; 2 mγ B_{12}, 0.27; 2 γ guanine desoxyriboside, 0.37; 2 γ hypoxanthine desoxyriboside, 0.37; 2 γ thymidine, 0.52; 2 mγ B_{12} *plus* 0.2 γ PGA, 1.5; 2 γ guanine desoxyriboside *plus* 0.2 γ PGA, 1.1; 2 γ hypoxanthine desoxyriboside *plus* 0.2 γ PGA, 1.1; 2 γ thymidine *plus* 0.2 γ PGA, 1.2.

Discussion.—The inhibitory effects of low levels of 4-amino PGA for certain organisms are reversible by PGA but high levels of the antagonist produce toxic effects which are not so reverse.[8,9,10] The present investigation shows that these toxic effects may in certain instances be reversed by thymidine, which may indicate that PGA has a role in the formation of thymidine. The inhibitory effect of 4-amino PGA on the growth of *E. coli* conceivably may be due to the entrance of this substance into the cell to displace endogenously-formed PGA from this role. The inhibitory effect of "x-methyl-PGA" upon *Leuconostoc mesenteroides* 8293 was found by Shive and co-workers[11] to be reversed by either PGA or thymidine. After the present experiments were completed, Sauberlich[12] reported inhibition of the growth of *Leuconostoc citrovorum* 8081 by 4-amino PGA and reversal by thymidine. We are indebted to Dr. J. O. Lampen for thymidine, to Dr. H. M. Kalckar for guanine desoxyriboside and to Dr. E. E. Snell for hypoxanthine desoxyriboside.

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LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

RECEIVED MAY 9, 1949

(7) Stokstad, Dornbush, Franklin, Hoffmann, Hutchings and Jukes, *Fed. Proc.*, **8**, 257 (1949).

(8) Franklin, Stokstad and Jukes, *Proc. Soc. Exp. Biol. Med.*, **67**, 398 (1948).

(9) Oleson, Hutchings and SubbaRow, *J. Biol. Chem.*, **175**, 359 (1948).

(10) Philips and Thiersch, *J. Pharmacol.*, **95**, 303 (1949).

(11) Shive, Eakin, Harding, Ravel and Sutherland, THIS JOURNAL, **70**, 2299 (1948).

(12) Sauberlich, *Fed. Proc.*, **8**, 247 (1949).

The Reduction of 2-Acetylpyridine to 2-Ethylpyridine

BY ARTHUR FURST

Recently Gregg and Craig[1] reported that the melting point of the picrate of 2-ethylpyridine made by two different methods—hydrogenation of 2-vinylpyridine and the action of methyl iodide on lithium picoline—did not agree with that obtained by Bergstrom and McAllister[2] who made it by the addition of ethylmagnesium bromide to pyridine. In confirmation of the work of the former authors 2-acetylpyridine was reduced to 2-ethylpyridine by three different methods, namely, Clemmensen, Wolff–Kishner, and Huang-Minlon. The results of the boiling points, melting points, mixed melting points, and fusion analysis[3] show that these reduction products agree in all respects with each other and with the compound obtained by Gregg and Craig by hydrogenation of 2-vinylpyridine.

Experimental

The 2-acetylpyridine, from Dougherty Chemical Co., was redistilled: picrate m. p. 131°; lit. 131°.[4]

Clemmensen Reduction.—A solution of 2-acetylpyridine (0.12 mole) in 70 ml. of concentrated hydrochloric acid was vigorously refluxed in contact with amalgamated zinc (0.77 mole).[5] After ten hours 50 ml. more acid was added, and refluxing was continued an additional five hours. The solution was made basic with solid hydroxide, filtered through a stainless steel funnel, extracted with benzene, dried and fractionated. The colorless distillate that came over at 144° was caught in a 50% alcoholic solution

(1) E. C. Gregg and D. Craig, THIS JOURNAL, **70**, 3138 (1948).

(2) F. W. Bergstrom and S. H. McAllister, *ibid.*, **52**, 2845 (1930).

(3) N. Goetz-Luthy, *J. Chem. Education*, **26**, 159 (1949).

(4) H. Maier-Bode and J. Altpeter, "Das Pyridin und seine Derivative," Edwards Brothers, Inc., Ann Arbor, Mich., 1934, p. 197.

(5) E. L. Martin in "Organic Reactions," Vol. I, R. Adams, Ed. John Wiley and Sons, Inc., New York, N. Y., 1942, p. 163.

of picric acid. The solid was isolated as described below (yields).

Anal. Calcd. for $C_{13}H_{12}O_7N_4$: N, 16.7. Found: N, 16.7.

Wolff–Kishner.—A yield of 7.8 g. (83.5%) of the semicarbazide hydrochloride of 2-acetylpyridine was obtained by the method of Woodward, *et al.*,[6] using ten equivalents of hydrochloric acid, m. p. 202° (uncor.).

Anal. Calcd. for $C_8H_{10}ON_4 \cdot HCl$: N, 26.2; Cl, 16.6. Found: N, 26.6; Cl, 17.0, 16.9.

The reduction was carried out by heating the semicarbazide hydrochloride with eight equivalents of sodium ethylate in an oil-bath at 180°. The distillate was caught in a 50% alcoholic solution of picric acid.

Huang–Minlon.[7]—A mixture of 2-acetylpyridine (0.06 mole), 5 ml. of 85% hydrazine hydrate, 5 g. of sodium hydroxide, and 80 ml. of diethylene glycol was heated for six hours. No attempt was made to remove the water. The solution was cooled, extracted with benzene, and converted into the picrate.

Yields.—No attempt was made to obtain maximum yields. The solid picrates were isolated from the alcoholic solution, dissolved in hot acetone, treated with decolorizing carbon, crystallized by cooling and finally recrystallized from alcohol. From the weights of the crude products, and the purified picrates the following estimates of yields were made: Clemmensen 80%, Wolff–Kishner 50% and Huang-Minlon 65%.

Melting Points and Fusion Analysis.—Using a copper block[8] and raising the temperature at a rate no faster than 1–2° per minute each picrate, and all possible combinations of picrate mixtures melted at 107–107.5° (uncor.). When the picrate of the Clemmensen reduction product was mixed with (a) the picrate of 2-acetylpyridine a depression of 20° in the melting point was noted; (b) the picrate of the hydrogenation product of Gregg and Craig the melting point was 107.5°. A fusion analysis showed these last pair to be identical also, for no eutectic melt was noted at the boundary. This in contrast with the eutectic melt shown in the fusion analysis of the first pair.

Acknowledgments.—I should like to acknowledge thanks to Robert Seiwald for the analytical data, and Dr. Luthy for a sample of the picrate of the hydrogenation product of 2-vinylpyridine and for the fusion analysis.

(6) C. F. Woodward, A. Eisner and P. G. Hains, THIS JOURNAL, **66**, 911 (1944).

(7) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(8) F. W. Bergstrom, *Ind. Eng. Chem., Anal. Ed.*, **9**, 340 (1937).

UNIVERSITY OF SAN FRANCISCO
SAN FRANCISCO 17, CALIFORNIA RECEIVED MAY 14, 1949

The Reaction of Propyl Disulfide with Decyl Mercaptan

BY GEORGE GORIN,[1] GREGG DOUGHERTY AND ARTHUR V. TOBOLSKY

It is known that thioglycolic acid reacts with cystine in solution to give cysteine[2]; indeed, a quantitative study of the reaction has been made.[3] We wish to report some results which indicate that a similar reaction occurs between simple alkyl disulfides and mercaptans.

Mixtures of propyl disulfide and decyl mercaptan were heated in sealed Pyrex glass tubes for varying lengths of time. The samples were then cooled, the mercaptans were titrated with standard silver nitrate solution to an amperometric end-point, and the precipitated silver mercaptides weighed.[4] It was found that the number of moles of total mercaptan did not change during the reaction, but that the weight of the precipitate decreased continuously to an equilibrium value. It was thus indicated that there had taken place a mole per mole exchange of propyl for decyl mercaptan. The data obtained in a run at 138–139° are given in Table I.

TABLE I

MIXTURES OF PROPYL DISULFIDE AND DECYL MERCAPTAN HEATED AT 138–139°

Time, hr.	Moles SH found	Av. mol. wt. of AgSR	% PrSH
0		280	1
3	275	268	13
6	282	260	21
9	276	253	29
12	278	248	34
36	277	243	39
62	277	226	56

At 180° the reaction proceeded more quickly, and after a few hours heating considerable amounts of propyl mercaptan could be isolated directly by distillation of the cooled reaction mixture.

We believe the reaction proceeds by a stepwise exchange which at first gives rise to a mixed disulfide. We made no attempt to isolate this compound but hope to obtain evidence on this question in future work.

Experimental

Material.—The propyl disulfide was an Eastman Kodak Co. "white label" product which had been redistilled at least once, b. p. 93.3–94.6° at 30 mm. The decyl mercaptan was a Connecticut Hard Rubber Co. product, which had been redistilled at least once; b. p. 102–106° at 15 mm., $n^{30}D$ 1.4534, molecular weight[4] 171 (calculated 174).

Approximate Rate Measurements.—Equal volumes (1.00 ml.) of a mixture of one mole of propyl disulfide and one mole decyl mercaptan were sealed in several tubes of nearly equal volumes (1.5 ml.) and heated in a vapor bath for some time (*p*-xylene used at 138–139°; *p*-cymene at 176°). At the end of the appropriate period each tube was withdrawn and cooled, and the contents washed into 375 ml. of 95% alcohol containing 25 ml. of 0.2 *M* alcoholic ammonium acetate as supporting electrolyte. The solution was then titrated with standard 0.1 *N* alcoholic silver nitrate to an amperometric end-point. The precipitate was transferred to Gooch-type filters consisting of a layer of asbestos placed over a medium Pyrex glass fritted filter disk, and dried *in vacuo* at 60–70° to constant weight.

Acknowledgments.—The authors are indebted to Dr. F. O. Davis and Mr. E. M. Fettes of the Thiokol Corporation for their active interest and valuable advice.

FRICK CHEMICAL LABORATORY
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PRINCETON, NEW JERSEY RECEIVED MAY 7, 1949

(1) Thiokol Corporation Fellow 1946–1948.

(2) Goddard and Michaelis, *J. Biol. Chem.*, **106**, 605 (1934).

(3) Bersin and Steudel, *Ber.*, **71B**, 1015 (1938).

(4) Laitinen, O'Brien and Nelson, *Ind. Eng. Chem., Anal. Ed.*, **18**, 471 (1946).

Measurement of Ion Hydration by the Diffusion Method

BY A. HUNYAR

C. H. Hale and T. de Vries have recently reported[1] that the hydration of quaternary ammonium salts cannot be determined by the Nernst–Washburn method[2] because the reference substance as well as water is transported during electrolysis. This fact was previously demonstrated by T. Erdey-Gruz and A. Hunyar[3] using a modified form of the diffusion method developed by J. W. McBain and T. H. Liu.[4] They usually employed allyl alcohol of various concentrations as a reference substance and hydrochloric acid, potassium bromide, potassium chloride, lithium chloride, lithium acetate and tetramethylammonium chloride as electrolytes. They found that the concentration of the reference substance decreased, with one exception, in that part of the apparatus from which the electrolyte diffused and increased in that part into which it diffused.[5] The remarkable fact concerning these experiments was that the amount of allyl alcohol transported increased nearly linearly with the concentration of alcohol in the range 0.2 to 25% from 0.003 to 0.31 mole of allyl alcohol per mole of potassium chloride. The amount of alcohol transported decreased from 0.033 mole of allyl alcohol per mole of potassium chloride on the first day to 0.023 on the fourth day which was mathematically shown to be due to the back diffusion of the alcohol. The following results were obtained.

Electrolyte	Hydration numbers by Remy[6]	Mole of allyl alcohol per mole electrolyte
$LiC_2H_3O_2$	22.0	0.041
LiCl	15.6	.033
$N(CH_3)_4Cl$	7.6	.015
KCl	7.1	.031
KBr	6.2	.025
HCl	4.0	.005

Pogány[7] also observed that the electrolytes carried more reference substance than water, using the diffusion method. In the electrolysis of a solution of silver nitrate with pyridine as reference substance, Morgan and Kanolt[8] reported that a large proportion of the pyridine was combined with silver ions.

RECEIVED DECEMBER 8, 1948

(1) Hale and De Vries, THIS JOURNAL, **70**, 2473 (1948).

(2) Washburn, *ibid.*, **31**, 322 (1909); *Z. physik. Chem.*, **66**, 513 (1909).

(3) Ph.D. Dissertation of A. Hunyar, Budapest, 1937.

(4) McBain and Liu, THIS JOURNAL, **53**, 59 (1931).

(5) The exception was the case of arsenic trioxide as a reference substance with potassium chloride as electrolyte, when it was observed that more water than arsenic trioxide was transported. An average of 1.4 mole of water per mole of potassium chloride was carried.

(6) "Handbuch f. Exp. Phys.," Vol. XII, part 1, p. 293.

(7) Pogány, *Magyar Chêm. Folyoirat*, **48**, 85 (1942); *C. A.*, **38**, 3186 (1942).

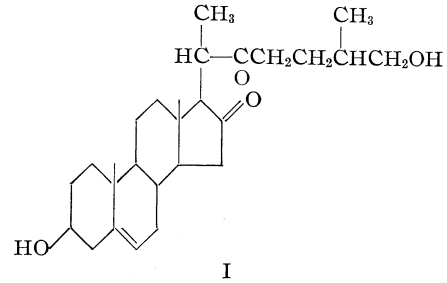
(8) Morgan and Kanolt, THIS JOURNAL, **28**, 572 (1906).

Steroidal Sapogenins. III. 16-Alkylsapogenins[1]

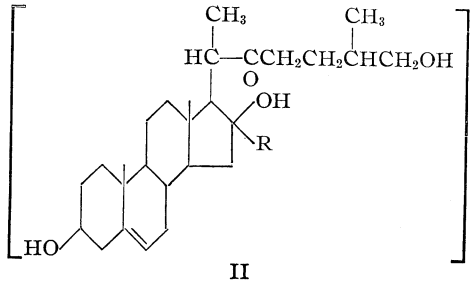
BY ST. KAUFMANN AND G. ROSENKRANZ

Through our recent work[1] it became evident that the two keto groups of the open-side-chain sapogenin, kryptogenin, possess different reactivity and that the conversion into sapogenins of the spiroketal form can easily be achieved as soon as the hydroxy group is introduced in the 16-position: we prepared[2] the 16-dihydrokryptogenin, a very unstable compound which can easily be transformed into diosgenin.

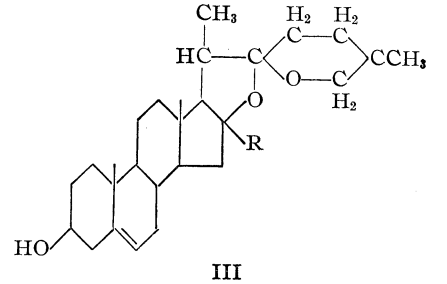
Based on this selective behavior of the 16-keto group we now reacted kryptogenin (I) with alkylmagnesium halides and obtained the respective 16-alkyldiosgenins (III) in good yield. The intermediate compound is very probably a 16-alkyl derivative of 16-dihydrokryptogenin (II)



I



II



III

The same reaction occurs with the esters of kryptogenin. If an excess of alkylmagnesium halide is used, the ester groups also react, thus yielding the free compounds.

In analogous manner, 5,6-dihydrokryptogenin or its esters can be transformed into the 16-alkyltigogenins. These latter compounds can be obtained also from the respective 16-alkyldiosgenins

(1) For Paper II in this series see Rosenkranz, Kaufmann, Landa, Corona and Olalde, THIS JOURNAL, **70**, 3518 (1948).

(2) Kaufmann and Rosenkranz, *ibid.*, **70**, 3502 (1948).

by catalytical hydrogenation with platinum oxide as catalyst.

Since it is known that the neosapogenins can be converted by acids into the corresponding normal side-chain sapogenins, while the compounds obtained with alkylmagnesium halide are stable against acids, we suggest that the normal side chain should be ascribed to the 16-alkylsapogenins described above.

The unsaturated 16-alkylsapogenins behave like diosgenin and the saturated like tigogenin inasmuch as they form mono-esters and as the 3-hydroxy group can easily be converted into a keto-group. The transformation and degradation of the side chain, as well as the resulting 16-alkylpregnane and androstane derivatives shall be dealt with in a forthcoming paper.

Experimental[3,4]

16-Methyldiosgenin.—To a solution of 10 g. (about 0.02 mole) of kryptogenin diacetate in 200 cc. of dry benzene, a diluted solution of 0.2 mole of methylmagnesium bromide in ether was added. The mixture was refluxed for three hours under anhydrous conditions, then poured into water and ice containing hydrochloric acid, and subsequently extracted with ether. After washing the ether solution with water until neutral it was dried and evaporated. After recrystallization from ether–methanol, about 7 g. of 16-methyldiosgenin was obtained m. p. 174–175°, $[\alpha]^{20}D$ −105° (in chloroform). *Anal.* Calcd. for $C_{28}H_{44}O_3$: C, 78.45; H, 10.34. Found: C, 78.46; H, 10.39.

The same product can be obtained from free kryptogenin, utilizing anhydrous dioxane instead of benzene as a solvent. After refluxing 16-methyldiosgenin with hydrochloric acid in alcoholic solution for ten hours, it can be recovered unaltered.

Acetate.—M. p. 171–172°, $[\alpha]^{20}D$ −100° (in chloroform). *Anal.* Calcd. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85. Found: C, 76.74; H, 9.75.

Benzoate.—M. p. 218–218.5°, $[\alpha]^{20}D$ −70° (in chloroform). *Anal.* Calcd. for $C_{35}H_{48}O_4$: C, 78.94; H, 9.02. Found: C, 78.89; H, 9.30.

16-Methyl-4,5-dehydrotigogenone.—16-Methyldiosgenin was oxidized with cyclohexanone and aluminum *t*-butylate to 16-methyl-4,5-dehydrotigogenone; m. p. 182.5–186°, $[\alpha]^{20}D$ −8° (in chloroform). *Anal.* Calcd. for $C_{28}H_{42}O_3$: C, 78.82; H, 9.92. Found: C, 78.78; H, 9.98.

16-Ethyldiosgenin.—The Grignard reaction with ethylmagnesium bromide led to 16-ethyldiosgenin; m. p. 171–172°, $[\alpha]^{20}D$ −107° (in chloroform). *Anal.* Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.59; H, 10.51.

Acetate.—M. p. 176.5–177.5°, $[\alpha]^{20}D$ −105° (in chloroform). *Anal.* Calcd. for $C_{31}H_{48}O_4$: C, 76.81; H, 9.98. Found: C, 76.81; H, 9.91.

Benzoate.—M. p. 208–211°, $[\alpha]^{20}D$ −72° (in chloroform). *Anal.* Calcd. for $C_{36}H_{50}O_4$: C, 79.07; H, 9.21. Found: C, 79.12; H, 9.14.

16-Ethyl-4,5-dehydrotigogenone.—Prepared as the lower homolog, m. p. 171–173°, $[\alpha]^{20}D$ −7° (in chloroform). *Anal.* Calcd. for $C_{29}H_{44}O_3$: C, 78.86; H, 10.04. Found: C, 79.12; H, 10.01.

16-Methyltigogenin.—(a) This saturated compound was prepared from 5,6-dihydrokryptogenin-diacetate and methylmagnesium bromide under analogous conditions as described for 16-methyldiosgenin; m. p. 215–216.5°, $[\alpha]^{20}D$ −56° (in chloroform). *Anal.* Calcd. for $C_{28}H_{46}O_3$: C, 78.07; H, 10.76. Found: C, 78.08; H, 10.75.

(3) The microanalyses were carried out by Dr. Carl Tiedcke, New York, N. Y., and in our microanalytical laboratory under the direction of Miss Amparo Barba.

(4) All the melting points were determined on the Kofler micro-melting point apparatus.

(b) The same product was obtained by catalytical hydrogenation of 16-methyldiosgenin in glacial acetic acid with platinum oxide as catalyst; m. p. 215–216.5°. The mixed m. p. with the 16-methyltigogenin obtained by method (a) showed no depression.

Acetate.—M. p. 186.5–189.5°, $[\alpha]^{20}D$ −65° (in chloroform). *Anal.* Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.23. Found: C, 76.28; H, 9.98.

Benzoate.—M. p. 207–212°, $[\alpha]^{20}D$ −50° (in chloroform). *Anal.* Calcd. for $C_{35}H_{50}O_4$: C, 78.60; H, 9.42. Found: C, 78.50; H, 9.47.

16-Methyltigogenone.—It was prepared by oxidation of 16-methyltigogenin with chromic anhydride in glacial acetic acid; m. p. 175–178°, $[\alpha]^{20}D$ −45° (in chloroform). *Anal.* Calcd. for $C_{28}H_{44}O_3$: C, 78.45; H, 10.34. Found: C, 78.43; H, 10.52.

16-Ethyltigogenin.—The Grignard reaction of 5,6-dihydrokryptogenin with ethylmagnesium bromide led to 16-ethyltigogenin. The catalytical hydrogenation of 16-ethyldiosgenin with platinum oxide gave the same product; m. p. 194.5–197°, $[\alpha]^{20}D$ −60° (in chloroform). *Anal.* Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.32; H, 10.86.

Acetate.—M. p. 197–199°, $[\alpha]^{20}D$ −62° (in chloroform). *Anal.* Calcd. for $C_{31}H_{50}O_4$: C, 76.47; H, 10.35. Found: C, 76.66; H, 10.29.

Benzoate.—M. p. 178.5–181°, $[\alpha]^{20}D$ −49° (in chloroform). *Anal.* Calcd. for $C_{36}H_{52}O_4$: C, 78.78; H, 9.55. Found: C, 78.59; H, 9.66.

16-Ethyltigogenone.—Prepared as the lower homolog; m. p. 169–173°, $[\alpha]^{20}D$ −44° (in chloroform). *Anal.* Calcd. for $C_{29}H_{46}O_3$: C, 76.68; H, 10.47. Found: C, 76.58; H, 10.59.

LABORATORIES SYNTEX, S. A.
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The Exchange of Mercury(I) and Mercury(II) Ions

BY EDWARD L. KING

The exchange of mercury(I) and mercury(II) ions in solution is of interest because this involves breaking the bond in dimeric mercury(I) ion. Unpublished work[1a,b] indicates that this exchange proceeds rapidly at room temperature. It seemed desirable to carry out further experimental studies on this reaction using several techniques for separation of the two oxidation studies of mercury.

The separation of the two oxidation states has been effected by the precipitation of mercury(I) chloride, mercury(I) chromate and mercury(I) sulfate. In addition a partial separation has been effected by the diffusion technique[2] although no exchange experiments were run using this technique.

Experiments of three types were run using the precipitation of mercury(I) chloride and mercury(I) chromate. These differed in the order of addition of reagents: (a) the precipitating agent was added to a solution containing mercury(I) and mercury (II) perchlorates immediately after the two valence states had been brought together, (b) a solution containing mercury(II) perchlorate and the precipitating reagent was added to the solu-

(1) (a) Ruben and Nahinsky, reported by G. T. Seaborg in *Chem. Rev.*, **27**, 199 (1940); (b) Professor Arthur F. Scott, private communication.

(2) Van Alten and Rice, THIS JOURNAL, **70**, 883 (1948).

tion of mercury(I) perchlorate, and (c) the solution containing mercury(II) perchlorate was added to a slurry of the freshly precipitated mercury(I) compound. Using mercury(I) sulfate precipitation, the procedure corresponding to (a) was the only type experiment performed.

The results of experiments of type a and b are reported in Table I. It is seen that the exchange is essentially complete even in experiments of type (b).

TABLE I

EXCHANGE OF MERCURY(I) AND MERCURY(II) IONS

Exp. type	Ppt.	Composition (moles/liter) (Hg^{++})	(Hg_2^{++})	(H^+)	Extent of exchange
a	Hg_2Cl_2	0.0031	$0.0016^{\otimes a}$	0.5[b]	94, 98
a	Hg_2Cl_2	$10^{-5\otimes a}$	10^{-3}	0.5[b]	>98
b	Hg_2Cl_2	$10^{-5\otimes a}$	10^{-3}	0.5[b]	97[c], 98[d]
b	Hg_2Cl_2	$10^{-5\otimes a}$	10^{-3}	3	97–98[e]
a	Hg_2CrO_4[f]	0.0044	$0.0069^{\otimes a}$	0.1	94, 98
b	Hg_2CrO_4[f]	$0.0048^{\otimes a}$	0.0067	0.1	92, 102
a	Hg_2SO_4[g]	0.0093	$0.0059^{\otimes a}$	0.16[h]	~100%
a	Hg_2SO_4[g]	$0.0136^{\otimes a}$	0.0064	0.16[h]	

[a] ⊗ at concentration indicates activity started here. [b] Solutions also contain 3 *M* sodium perchlorate. [c] Two experiments. [d] Two experiments at 0°. [e] Three experiments; Cl^- concentration 0.04–0.06 *M*. [f] Composition of solid not established. [g] Precipitation incomplete; results of two experiments coupled lead to listed conclusion. [h] Not corrected for HSO_4^- formation.

The results of the experiments of type b involving mercury(I) chromate are consistent with a mechanism involving rapid homogeneous exchange and a rapid rate of recrystallization of the freshly precipitated solid. The concentration conditions in the chloride experiments are such that no conclusions may be drawn in this regard.

Experiments of type c are relevant to this question. The extent to which mercury(II) ion exchanges with precipitated mercury(I) chloride varies. The extent of exchange is approximately 30% if the mercury(II) is added within a few seconds after precipitation and then stirred with the precipitate for 2.5 minutes; it is 10% if the mercury(II) is added 7.5 minutes after precipitation and then stirred for 2.5 minutes. These represent extremes in the results of the seven experiments of this type performed. Contrasted with this are the results of this type experiment involving mercury(I) chromate. It was found that mercury(II), added in an amount comparable to the mercury(I), present as long as one minute after the precipitation of the mercury(I) chromate, exchanges completely with the precipitate upon stirring an additional two minutes. If, however, six minutes elapse between the time of precipitation and the addition of the mercury(II), essentially no exchange occurs upon stirring two minutes. This behavior, too, is consistent with a mechanism involving a rapid homogeneous exchange coupled with a relatively high recrystallization rate for freshly precipitated mercury(I) chromate and a much lower recrystallization rate for the coagulated solid. Visual observations reveal the change in the nature of the precipitate at times approximately one minute after precipitation. It was found that mercury(I) chromate precipitated under these conditions would dissolve completely in approximately thirty seconds upon treatment with excess iron(II) if only thirty seconds elapsed between the time of precipitation and addition of iron(II), while many minutes were required if this time interval was increased to three minutes.

This work doesn't discount the possibility that the exchange observed is in reality being induced during the precipitation. Under the conditions of these experiments it appears that the bond in dimeric mercury(I) is readily broken.

It has been shown that mercury(I) ion diffuses approximately 10% more rapidly than mercury(II) under certain concentration conditions. This observation is consistent with the relative diffusion coefficients determined by Kolthoff and Miller.[3] The condition under which this separation is achieved ($(Hg_2^{++})_0/(Hg^{++})_0 = 0.5$) is such that the counting rate of the diffusate would vary by only 5% depending upon whether the extent of exchange is 0% or 100%. The analytical and counting rate uncertainties are such that it does not appear worthwhile to use this technique in the exchange study.

Experimental

The radioactive mercury was prepared by the $Hg(n, \gamma)$ reaction in the Oak Ridge pile and allocated by the United States Atomic Energy Commission. The work was all performed after the Hg^{197} had decayed; thus the mercury isotope present was $Hg^{205,203}$. Solutions of active mercury(II) perchlorate were prepared by dissolving active mercury(II) oxide in perchloric acid. Solutions of active mercury(I) perchlorate were prepared by allowing a solution of mercury(I) perchlorate to exchange for several days with a small amount of active mercury(II) perchlorate. Other reagents were all analytical reagent grade and all solutions were prepared using doubly distilled water.

The mercury(I) fraction was generally counted in the form precipitated while the mercury(II) was counted as the oxide or a basic salt. The samples were mounted for counting on filter paper by suction filtering.

(3) Kolthoff and Miller, THIS JOURNAL, **63**, 2732 (1941).

DEPARTMENTS OF CHEMISTRY
OF HARVARD UNIVERSITY AND
THE UNIVERSITY OF WISCONSIN RECEIVED MAY 31, 1949

β-Ketosulfides

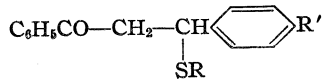
BY FRANK KIPNIS[1] AND JOHN ORNFELT

In the course of studies on certain sulfur-containing ketones, it became desirable to prepare a series of β-ketosulfides. This type of compound had been synthesized previously,[2] but those com-

(1) Present address: Oxford Products, Inc., Cleveland, Ohio.

(2) Ruhemann, *J. Chem. Soc.*, **87**, 461 (1905); Posner, *Ber.*, **35**, 809 (1905); Nicolet, THIS JOURNAL, **53**, 3066 (1931); **54**, 1998 (1932); **57**, 1098 (1935); Nicolet, *J. Biol. Chem.*, **95**, 389 (1932); Morgan and Friedman, *Biochem. J.*, **32**, 733 (1938); Fromm and Hubert, *Ann.*, **394**, 301 (1912); Frank and Smith, THIS JOURNAL, **68**, 2104 (1946).

TABLE I



R	R'	Yield, %	M. p., °C.	Recryst. solvent	Formula	Analyses,[a] % Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
Methyl	H	98	47–48	Ethanol–water	$C_{16}H_{16}OS$	74.96	6.29	12.51	75.44	6.26	12.46
Ethyl	H	90	66–67	Hexane	$C_{17}H_{18}OS$	75.51	6.71	11.86	76.10	6.68	12.19
n-Dodecyl	H	95	52	Methanol	$C_{27}H_{38}OS$	78.97	9.32	7.81	79.06	9.41	7.93
Methyl	OCH_3	90	54–56	Hexane	$C_{17}H_{18}O_2S$	71.30	6.33	11.20	71.13	6.16	10.99
n-Propyl	OCH_3	94	65–66	Hexane	$C_{19}H_{22}O_2S$	72.57	7.05	10.20	72.82	7.05	10.37
n-Dodecyl	OCH_3	91	41–41.5	Methanol	$C_{28}H_{40}O_2S$	76.31	9.15	7.28	75.98	9.32	7.53
Phenyl	OCH_3	93	86.8	Methanol	$C_{22}H_{20}O_2S$	75.83	5.78	9.20	75.63	5.77	9.56
Benzyl	OCH_3	96	58	Hexane	$C_{23}H_{22}O_2S$	76.21	6.12		76.35	5.96	
Pyridine-2-ethyl	OCH_3	98	75–76	Methanol–water	$C_{23}H_{23}NO_2S$	43.18	6.14		72.99	6.06	

[a] Analyses by Oakwold Laboratories, Alexandria, Va.

pounds reported here are new. The general method involved the treatment of an α,β-unsaturated ketone with the appropriate mercaptan in the presence of catalytic amounts of sodium ethoxide. Yields were excellent, ranging from 85 to 100%, and all the compounds studied were crystalline.

Experimental

β-Ketosulfides.—Directions are given for the preparation of one compound only. Others may be synthesized in a similar manner.

Benzylacetophenone β-*n*-Dodecylsulfide.—In a 125-ml. erlenmeyer flask were mixed 10.4 g. (0.05 mole) of benzylideneacetophenone, 10.1 g. (0.05 mole) of *n*-dodecyl mercaptan and 40 ml. of benzene. One-half ml. of 2 *N* sodium ethoxide was added and the mixture was vigorously shaken, a considerable amount of heat developing. After standing for twelve hours, glacial acetic acid was added dropwise until the solution was acid to phenolphthalein, and the solvent was removed under reduced pressure, leaving a crystalline residue which was recrystallized from methanol, giving a product melting at 52°[3] in 95% yield. The properties and analyses of the new compounds are listed in Table I.

(3) All melting points were taken with a Fisher–Johns apparatus.

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2-Substituted-1,3-oxathiolanes

BY FRANK KIPNIS[1] AND JOHN ORNFELT

A search of the literature has indicated that surprisingly little information is available relating to the preparation and properties of 1,3-oxathiolanes. Sjoberg[2] discussed the preparation of 2,2,5-trimethyl-1,3-oxathiolane from acetone and 1-sulfhydryl-2-hydroxypropane in the presence of phosphorus pentoxide and sand. Other information[3] has indicated the possibility of the formation of oxathiolanes from the interaction of aldehydes or ketones with 2-mercaptoethanol in the presence of hydrochloric acid, but no specific data were given.

A method for the preparation of a number of hitherto unreported oxathiolanes is given here. These compounds are liquids with fresh, aromatic aromas, insoluble in water and soluble in most organic solvents, fairly stable to bases, but completely decomposed into the starting materials by very dilute acid. Table I summarizes the properties of three new oxathiolanes.

TABLE I

2-SUBSTITUTED-1,3-OXATHIOLANES

2-Substituent	Phenyl	*i*-Propyl	Methylene-3′,4′-dioxyphenyl
Yield, %	76.6	60.0	50.4
B. p. °C.	86–87	29	118
B. p. Mm.	5	2.5	1.5
Empirical formula	$C_9H_{10}OS$	$C_6H_{12}OS$	$C_{10}H_{10}O_3S$
Carbon, % Calcd.	65.02	54.50	....
Carbon, % Found[a]	64.74	54.00	....
Hydrogen, % Calcd.	6.06	9.15	....
Hydrogen, % Found[a]	5.97	9.26	....
Sulfur, % Calcd.	19.29	...	15.25
Sulfur, % Found[a]	18.89	...	15.64

[a] Analyses by Oakwold Laboratories, Alexandria, Virginia.

Experimental

All the oxathiolanes were prepared by the same method. Directions are given for one compound only.

2-Isopropyl-1,3-oxathiolane.—In a 1000-ml. 3-neck interjoint flask fitted with a sealed Hershberg stirrer, dropping funnel and Dean–Stark adapter and condenser, was placed 39 g. (0.5 mole) of 2-mercaptoethanol, 36 g. (0.5 mole) of isobutyraldehyde and 250 ml. of dry benzene. The stirrer was started and a solution of 250 mg. of hydrogen chloride in 10 ml. of anhydrous ether was added from the dropping funnel during five minutes. A considerable amount of heat was produced and water was evolved. The mixture was refluxed for ninety minutes, and at the end of which time the theoretical amount of water (9 ml.) had been removed. The solution was cooled, washed thoroughly with 10% potassium carbonate, dried over calcium sulfate, filtered and the solvent stripped from the filtrate. The residue was fractionated at 29–31° (2.5 mm.) through a 35-cm. Vigreux column to give 39.6 g. (60%) of a colorless oil with a pleasant aroma.

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(1) Present address: Oxford Products, Inc., Cleveland, Ohio.
(2) Sjoberg, *Ber.*, **75**, 13 (1942).
(3) Reference Form 5427A, Carbide and Carbon Chemicals Corporation, June 20, 1944.

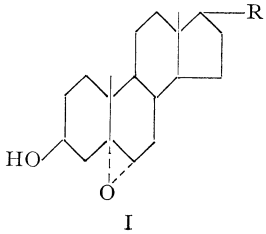
A Method for Reduction of Steroid Oxides

BY L. CARROLL KING AND J. ALLAN CAMPBELL

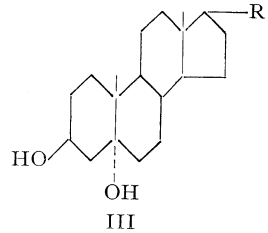
Recent interest in the reduction of steroid oxides[1] impels us to record a method for reduction of these substances which has been under investigation in this Laboratory.

(α)-Cholesteryl oxide (I) reacts with thiourea and *p*-toluenesulfonic acid in alcoholic solution to give 3(β),5(α)-dihydroxycholestanyl-6-isothiuronium tosylate (II) in 73–92% yield. An alcoholic solution of II on shaking with an equivalent amount of sodium hydroxide and an excess of standard nickel catalyst[2] was reduced to 3(β),5(α)-dihydroxycholestane (III), yield 88–95%. The identity of III was established by conversion to 3(β)-acetoxy-5(α)-hydroxycholestane.

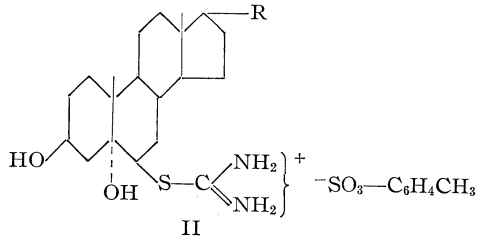
The application of this method of reduction to the preparation of 17-hydroxysteroids from the corresponding 16,17- or 17,20-oxido compounds is in progress.



I



III



II

3(β),5(α)-Dihydroxycholestane-6-isothiuronium Tosylate (II).—Prepared from (α)-cholesteryl oxide by refluxing with thiourea and *p*-toluenesulfonic acid in alcoholic solution; yield 73–92%, m. p. 228–229°. *Anal.* Calcd. for $C_{35}H_{58}N_2O_5S_2$: C, 64.57; H, 8.98. Found: C, 64.57; H, 8.39%.

3(β),5(α)-Dihydroxycholestane (III).—Prepared from II by action of standard nickel catalyst and an equivalent of sodium hydroxide in alcoholic solution; yield 88–95%, m. p. 222–224°. *Anal.* Calcd. for $C_{27}H_{48}O_2$: C, 80.13; H, 11.96. Found: C, 80.03; H, 11.93.

3(β)-Acetoxy-5(α)-hydroxycholestane.—From III by warming with acetic anhydride; m. p. 182–184°. *Anal.* Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 76.94; H, 10.91.

(1) Plattner, Heusser and Feurer, *Helv. Chim. Acta.*, **31**, 2210 (1948); *ibid.*, **32**, 587 (1949); Julian, Meyer and Ryden, THIS JOURNAL, **71**, 756 (1949).

(2) Adkins, "Reactions of Hydrogen with Organic Compounds, etc.," The University of Wisconsin Press, Madison, Wis., 1937, p. 20.

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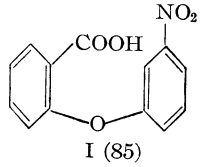
RECEIVED AUGUST 19, 1949

Camps Reaction with 1-Xanthonamine[1]

BY C. F. KOELSCH AND F. J. LUCHT

This paper describes a synthesis of [1]benzopyrano[4,2,de]quinoline (IX) and some reactions designed to yield its 6-methoxy derivative. It is planned to use these substances in experiments which it is hoped will furnish 4-*o*-hydroxyphenylquinolinic acid and ultimately morphine analogs.[2]

The synthesis involved intermediates I–VIII, formulated below. The route from VI to IX through X and XI instead of VII and VIII gave poorer yields. Yield of each substance is indicated by the figure in parentheses.



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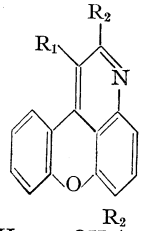
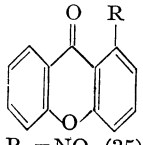




II, R = NO_2 (35)
III, R = NH_2 (100)
IV, R = $NHCOCH_2$-$COOC_2H_5$ (86)

	R_1	R_2
V	$COOC_2H_5$	OH (90)
VI	COOH	OH (94)
VII	H	OH (98)
VIII	H	Cl (89)
IX	H	H (28 from VIII; good from XI
X	COOH	Cl (25)
XI	COOH	H (59)

Experimental

***o*-(*m*-Nitrophenoxy)-benzoic Acid, I.**—The substance has been prepared but not isolated by Dhar.[3] In the present work it was obtained by heating and stirring a mixture of 62 g. of *o*-chlorobenzoic acid, 63 g. of *m*-nitrophenol, 50 g. of sodium carbonate, 5 g. of copper filings, 0.2 g. of cuprous chloride, and 150 ml. of *n*-amyl alcohol for three hours in an oil-bath at 160–170°. The crude crystalline product (55 g.) was suitable for cyclization. Crystallization from benzene gave pale yellow prisms, m. p. 138–139°.

Anal. Calcd. for $C_{13}H_9NO_5$: C, 60.2; H, 3.5. Found: C, 60.2; H, 3.8.

Xanthone Ring Closure.—A solution of 55 g. of crude nitrophenoxybenzoic acid in 300 ml. of sulfuric acid was heated on a steam-bath for thirty minutes and then poured into water. Acidic materials were removed, and the crude neutral residue (25 g., m. p. 160–170°) was separated by crystallization from acetic acid into 18 g. of 1-nitroxanthone (II), pale yellow prisms m. p. 206–207° (reported[3] 210°), and 7 g. of brown crystalline material, m. p. 155–160°. The latter contained the still unknown 3-nitroxanthane, for by reducing it with stannous chloride and alcoholic hydrochloric acid, and fractionally crystallizing the product from alcohol, there was obtained 3.7 g. of 3-xanthonamine, m. p. 231–232° (reported[4] 232°).

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3. Found: C, 74.0; H, 4.4.

1-Xanthonamine, III.—Reduction of 11.5 g. of 1-nitroxanthone with 45 g. of stannous chloride in 115 ml. of alcohol containing 50 ml. of hydrochloric acid and crystallization of the product from alcohol gave 9.5 g. of yellow prisms, m. p. 150–151°.

(1) From the Ph.D. Thesis of Fred J. Lucht, submitted to the Graduate Faculty of the University of Minnesota, September, 1946.

(2) Koelsch, THIS JOURNAL, **67**, 569 (1945).

(3) Dhar, *J. Chem. Soc.*, **117**, 1061 (1920).

(4) Ullmann and Wagner, *Ann.*, **355**, 359 (1907).

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3. Found: C, 73.9; H, 4.5.

All the isomeric xanthonamines are now known: 2 (m. p. 205°),[5] 3 (m. p. 232°),[4] and 4 (m. p. 201°).[6] The structure of the substance, m. p. 175°, formerly thought to be a xanthonamine of uncertain orientation,[7] is thus rendered still more uncertain.

1-(Carbethoxyacetamido)-xanthone, IV.—A solution of 12.5 g. of 1-xanthonamine in 125 ml. of ethyl malonate was boiled for twenty minutes, then most of the ester was removed by rapid distillation. Crystallization of the residue from alcohol gave 16.5 g. of pale tan powder, m. p. 122–123°.

Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.4; H, 4.7. Found: C, 66.5; H, 4.7.

Pyridone Ring Closure.[8]—A solution of sodium ethoxide from 3 g. of sodium in 100 ml. of alcohol was added during fifteen minutes to a boiling suspension of 16 g. of IV in 300 ml. of alcohol. The mixture was boiled for an additional fifteen minutes and then cooled. The solid product was stirred for some time with dilute hydrochloric acid, then washed and dried, giving 13.5 g. of ethyl 2-hydroxy[1]-benzopyrano[4,2-de]quinoline-1-carboxylate (V), m. p. 279–282°. Recrystallization from acetic acid gave fine pale yellow plates, m. p. 285–287°.

Anal. Calcd. for $C_{18}H_{13}NO_4$: C, 70.3; H, 4.3. Found: C, 70.3; H, 4.2.

2-Hydroxy[1]benzopyrano[4,2-de]quinoline-1-carboxylic Acid, VI.—The ester (3.4 g.) was saponified by boiling it six hours with excess 5% aqueous sodium hydroxide. The solution was then poured into excess hot dilute hydrochloric acid and the product was crystallized from acetic acid, giving 2.9 g. of small yellow plates. It began to lose carbon dioxide and change its appearance at 270°; the residue melted at 350–352° without effervescence.

Anal. Calcd. for $C_{16}H_9NO_4$: C, 68.8; H, 3.2. Found: C, 68.6; H, 3.4.

2-Hydroxy[1]benzopyrano[4,2-de]quinoline, VII.—The acid VI (2.9 g.) left a residue of nearly pure decarboxylation product (2.4 g.) when it was heated at 360°. Sublimation gave long yellow needles, m. p. 350–352°.

Anal. Calcd. for $C_{15}H_9NO_2$: C, 76.6; H, 3.9. Found: C, 76.8; H, 3.8.

2-Chloro[1]benzopyrano[4,2-de]quinoline, VIII.—A solution of 2.4 g. of VII in 10 ml. of phosphorus oxychloride was heated on a boiling water-bath for thirty minutes, then cooled and poured on ice. The mixture was neutralized and the product was crystallized from benzene, giving 2.3 g. of yellow crystals, m. p. 179–180°.

Anal. Calcd. for $C_{15}H_8ClNO$: C, 71.0; H, 3.2. Found: C, 70.9; H, 3.2.

[1]Benzopyrano[4,2-de]quinoline, IX.—A solution of 2 g. of VIII and 1 g. of sodium acetate in 100 ml. of acetic acid was shaken with 0.1 g. of platinum oxide and hydrogen at two atmospheres for twenty minutes. Treatment of the product with hydrochloric acid left 0.54 g. of unchanged chloro compound and dissolved the desired dehalogenated substance. The latter formed fine yellow needles (0.5 g.) from ligroin; m. p. 138–140°.

Anal. Calcd. for $C_{15}H_9NO$: C, 82.2; H, 4.1. Found: C, 82.2; H, 4.2.

2-Chloro[1]benzopyrano[4,2-de]quinoline-1-carboxylic Acid, X.—A solution of 0.9 g. of VI in 5 ml. of phosphorus oxychloride was heated for thirty minutes, then poured into water and allowed to stand overnight. The bicarbonate soluble product crystallized from alcohol in the form of a bright yellow powder (0.25 g.), m. p. 221–222° with decomposition.

Anal. Calcd. for $C_{16}H_8ClNO_3$: C, 64.5; H, 2.7. Found: C, 64.6; H, 2.7.

The corresponding **ethyl ester**, yellow crystals from benzene–ligroin, m. p. 177–179°, was obtained in a yield of 80% from 3.3 g. of V, with 10 g. of phosphorus oxychloride.

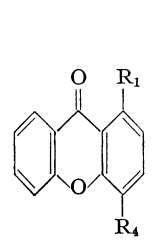
Anal. Calcd. for $C_{18}H_{12}ClNO_3$: C, 66.3; H, 3.7. Found: C, 66.6; H, 3.8.

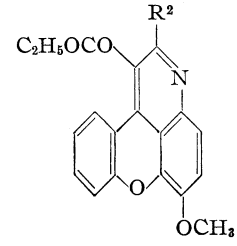
[1]Benzopyrano[4,2-de]quinoline-1-carboxylic Acid, XI.—Dehalogenation of 0.24 g. of X was accomplished by shaking its solution in dilute alkali with Raney nickel and hydrogen at three atmospheres for ninety minutes. The product formed yellow crystals from alcohol, m. p. 265° dec., yield, 0.125 g.

Anal. Calcd. for $C_{16}H_9NO_3$: C, 73.0; H, 3.4. Found: C, 72.8; H, 3.6.

The residue left from the melting of the acid was nearly pure decarboxylation product (IX), yellow needles from alcohol, m. p. 138–139° alone or mixed with the previously described substance.

Preceding the work described above, experiments designed to furnish the 6-methoxy derivative of IX and involving compounds XII–XVI, were undertaken. Because of poor yields of intermediates, the objective was not reached. These experiments are outlined in the following paragraphs.





XII, R_1 = H, R_4 = OH
XIII, R_1 = NH_2, R_4 = OCH_3
XIV, R_1 = $NHCOCH_2COOC_2H_5$, R_4 = OCH_3
XV, R_2 = OH
XVI, R_2 = Cl

4-Hydroxyxanthone, XII.—The Ullmann reaction between guaiacol and *o*-chlorobenzoic acid gave *o*-(*o*-methoxy)-phenoxybenzoic acid in yields of 36% when no solvent was used, and 43% when *n*-amyl alcohol was used.[6] Cyclization by sulfuric acid in acetyl chloride[9] and subsequent demethylation using aluminum chloride[4] in benzene gave nearly quantitative yields.

4-Methoxy-1-xanthonamine, XIII.—4-Hydroxyxanthone (23.4 g.) suspended in cold aqueous soda coupled with diazotized sulfanilic acid to give an azo compound in nearly quantitative yield. This dye was dried and mixed with 100 ml. of methyl sulfate. The mixture was treated with 300 g. of 20% aqueous sodium hydroxide, added with shaking and cooling (70°) during thirty minutes. The resulting material was diluted, treated with more sodium hydroxide and boiled to destroy excess methyl sulfate, and then treated with excess sodium hydrosulfite. The part of the product soluble in hydrochloric acid was crystallized from methanol, giving 14 g. (52%) of yellow prisms, m. p. 169–169.5°. In most preparations the yields were much smaller (5–20%), but the reason was never found.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.7; H, 4.6. Found: C, 69.9; H, 4.4.

The acetyl derivative, from the amine and acetic anhydride in 90% yield, formed yellow crystals from benzene, m. p. 234–234.5°. No pyridone ring closure[8] could be effected using sodium hydroxide in water, or sodium alkoxide in butyl or ethyl alcohol; from these experiments, the acetyl derivative was recovered largely unchanged.

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6. Found: C, 67.8; H, 4.6.

1-(Carbethoxyacetamido)-4-methoxyxanthone, XIV.—From 4 g. of XIII and 100 ml. of malonic ester, there was

(5) Purgotti, *Gazz. chim. ital.*, **44**, i, 641 (1914).

(6) Ulmann and Zickasoff, *Ber.*, **38**, 2111 (1905).

(7) DeTurski, German Patent 287,756; *Frdl.*, **12**, 120 (1914).

(8) Camps reaction: for a summary and references, see Hollins, "The Synthesis of Nitrogen Ring Compounds," E. Benn, Ltd., London, 1924.

(9) Gottesmann, *Ber.*, **66**, 1168 (1933).

obtained 5 g. (85%) of pure product, pale yellow crystals from ethanol, m. p. 154–155°.

Anal. Calcd. for $C_{19}H_{17}NO_6$: C, 64.2; H, 4.8. Found: C, 64.5; H, 4.7.

Ethyl 2-Hydroxy-6-methoxy[1]benzopyrano[4,2-de]-quinoline-1-carboxylate, XV.—From 4 g. of XIV, with 450 ml. of 1% alcoholic sodium ethoxide, there was obtained 3.4 g. (89%) of product, yellow needles from alcohol, m. p. 272–274°.

Anal. Calcd. for $C_{19}H_{15}NO_5$: C, 67.6; H, 4.5. Found: C, 67.5; H, 4.4.

Ethyl 2-Chloro-6-methoxy[1]benzopyrano[4,2-de]-quinoline-1-carboxylate, XVI.—From 2 g. of XIV, treated with 10 ml. of phosphorus oxychloride, there was obtained 1.7 g. of product, yellow crystals from benzene–ligroin, m. p. 161–162°.

Anal. Calcd. for $C_{19}H_{14}ClNO_4$: C, 64.1; H, 4.0. Found: C, 63.8; H, 4.0.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINNESOTA RECEIVED MAY 14, 1949

Chemical Degradation of Isotopic Succinic Acid[1]

BY MORTON KUSHNER AND SIDNEY WEINHOUSE

In connection with biochemical studies it was necessary to determine the distribution of isotopic carbon in samples of succinic acid isolated from biological sources. It has been found that pyrolysis of the barium salt in a high vacuum at 500° results in a satisfactory conversion of the carboxyl carbon of succinic acid to barium carbonate. The course of this reaction is uncertain. In addition to barium carbonate and some carbon, products such as carbon dioxide, carbon monoxide, methane, ethane, ethylene and hydrogen were identified by mass-spectrometric analysis.

The accompanying table, giving the results of the pyrolysis of carboxyl- and methylene-labeled succinates, shows that the barium carbonate satisfactorily represents the carboxyl carbon. Evidently there is some contamination of the carboxyl carbon by methylene carbon, but this is so small as to introduce only a negligible error. This slight enrichment of C^{13} in the non-labeled carboxyl position was not an artifact, since non-isotopic barium succinate invariably yielded barium carbonate with the normal C^{13} abundance. This enrichment may be due to oxidation of the methylene carbon by traces of oxygen; or possibly, to transfer of oxygen between barium carbonate and the accompanying residual carbon.

TABLE I

C^{13} DISTRIBUTION IN SYNTHETIC LABELED SUCCINIC ACIDS

Atom % C^{13} excess

	Over-all	Carboxyl carbon—Calcd.	Carboxyl carbon—Found
Carboxyl-labeled	2.41	4.82	4.80
Methylene-labeled	3.10	0.00	0.04 ± 0.02
Unlabeled	0.00	.00	.00 ± .01

(1) This work was sponsored by the Sun Oil Company and aided by a grant from the National Cancer Institute, U. S. Public Health Service.

Experimental

Preparation of Isotopic Succinic Acids.—Carboxyl-labeled succinic acid was prepared by refluxing ethylene dibromide with isotopic potassium cyanide, according to the procedure of Vanino.[2] The dinitrile was saponified with alkali without isolation, and after removal of neutral substances by extraction with ether, the succinic acid was isolated by acidification and continuous ether extraction. Yields ranged between 85 and 95%.

The methylene-labeled acid was prepared by a 4-step process giving an over-all yield of about 40%. Barium carbonate was reduced to the carbide according to the procedure of Cramer and Kistiakowsky[3] and the acetylene obtained therefrom reduced to ethylene by a modification of the method of Patterson and du Vigneaud.[4] This was converted to ethylene dibromide by addition of bromine and the former converted to succinic acid by the same procedure used for the carboxyl-labeled acid.

Preparation and Pyrolysis of Barium Salts.—About 20 mg. of the acid is dissolved in 1 ml. of water, 1 ml. of 20% barium chloride is added, and the solution brought to neutrality with dilute ammonia. Two volumes of 95% ethanol are added and the precipitated barium salt centrifuged, washed successively with alcohol and ether, and dried thoroughly in a vacuum.

The barium salt is transferred to a small glass tube, which is then sealed to the vacuum line or attached by means of a standard taper joint. After evacuation to a low pressure the salt is heated to 500° in an electric furnace. After about an hour the tube is cooled, the dark-colored residue is treated with dilute sulfuric acid and the evolved carbon dioxide collected for mass-spectrographic analysis.[5] It is important to avoid even traces of oxygen in this degradation since in its presence some of the methylene carbon will be oxidized to carbon dioxide and contaminate the carboxyl carbon.

Acknowledgment.—The authors express their appreciation to the Sun Oil Company for its support and interest, and to Mr. Arthur Kent for the C^{13} analyses.

(2) Vanino, "Handb. d. prep. Chem.," **3**, p. 263.
(3) Cramer and Kistiakowsky, *J. Biol. Chem.*, **137**, 549 (1941).
(4) Patterson and du Vigneaud, *ibid.*, **123**, 327 (1938).
(5) "Preparation and Measurement of Isotopic Tracers," Edwards Brothers, Ann Arbor, Mich., 1946, p. 43.

RESEARCH INSTITUTE AND
DEPARTMENT OF CHEMISTRY
TEMPLE UNIVERSITY
PHILADELPHIA, PA. RECEIVED JUNE 11, 1949

Methoxyacetone

BY RAYMOND P. MARIELLA AND JOHN L. LEECH

In continuing our investigations of unsymmetrical ketones, it became necessary to prepare a large quantity of methoxyacetone.

It was found that the wet oxidation of the inexpensive and easily-available 1-methoxy-2-propanol (Dowanol 33B) with chromic acid at room temperature goes conveniently in one step to give methoxyacetone. The present method is adapted from that of Petrov[1] and gives methoxyacetone in much shorter time than other published methods[2–5] although in a somewhat lower yield.

(1) Petrov, *J. Gen. Chem., U. S. S. R.*, **16**, 1206 (1946); *cf. C. A.*, **41**, 3051 (1947).
(2) Henry, *Ann. chim.*, [8] **16**, 318 (1908).
(3) Henze and Rigler, THIS JOURNAL, **56**, 1350 (1934).
(4) Leonardi and diFranchis, *Gazz. Chim. Ital.*, **33**, I, 319 (1903)
(5) Traetta, Masca and Preti, *ibid.*, **51**, II, 275 (1921).

The dry catalytic dehydrogenation of 1-methoxy-2-propanol was also investigated, but no ketone could be isolated. Various attempts to prepare methoxyacetone from chloroacetone using a non-polar solvent also failed.

Two derivatives of methoxyacetone were easily obtained; the 2,4-dinitrophenylhydrazone and the *p*-nitrophenylhydrazone, but the semicarbazone did not form. Attempts to prepare the semicarbazone gave a very insoluble substance, which was proved to be the disemicarbazone of *pyruvaldehyde*. In addition, the osazone of pyruvaldehyde was prepared from phenylhydrazine and methoxyacetone.

Methoxyacetone gave a positive Benedict test (basic medium),[6] a positive Schiff test (acid medium) and a positive test with Tollens reagent (basic medium). Apparently then, methoxyacetone is not too stable in either acid or basic media in the presence of oxidizing agents. This accounts for the rather low yield (28%) in its preparation from Dowanol 33B.

It is probably the rapidity of the reaction of methoxyacetone with 2,4-dinitrophenylhydrazine and *p*-nitrophenylhydrazine, and the insolubility of the resulting derivatives that make their isolation feasible. It is interesting to note that methoxyacetaldehyde also did not give the expected semicarbazone.[7] The product obtained was probably the disemicarbazone of glyoxal.

The authors wish to express their thanks to the Graduate School for providing some funds, to Misses Guy, Hines and Hobbs, for the microanalyses, and to the Dow Chemical Company for a generous sample of Dowanol 33B.

Experimental

Methoxyacetone from 1-Methoxy-2-propanol.—To a solution of 375 g. of sodium dichromate and 202 g. of 1-methoxy-2-propanol (b. p. 118–120° at 745 mm.) in 200 cc. of water was added dropwise over a period of six hours, a solution of 450 g. of sulfuric acid in 115 g. of water. The reaction mixture was stirred during the addition and the temperature kept between 20–25°. After standing at room temperature all night, the green mixture was extracted four times with 200-cc. portions of ether. The ether extract was dried with anhydrous potassium carbonate, the ether removed, and the product fractionated; b. p. 112–116° at 750 mm.; yield 55.5 g. There was also isolated 10 g. of unreacted alcohol. The ketone was carefully refractionated, and the liquid, b. p. 114.5–115.0° at 756 mm., collected; $n^{20}D$ 1.3982, d^{20}_4 0.9494.

The *p*-nitrophenylhydrazone[5] was isolated as yellow-orange plates from alcohol, m. p. 110–111°.

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: N, 18.9. Found: N, 19.2.

The 2,4-dinitrophenylhydrazone was easily formed as yellow-orange needles from alcohol, m. p. 162.5–163°.

Anal. Calcd. for $C_{10}H_{13}N_4O_5$: N, 20.9. Found: N, 20.6.

When 1.0 g. of methoxyacetone, 1.2 g. of semicarbazide hydrochloride and 0.9 g. of sodium acetate were refluxed in 10 cc. of water for three hours, on cooling, 0.6 g. of a white solid was formed. It was insoluble in all common solvents. A sample was recrystallized with great difficulty from a very large volume of water, m. p. 250–254° (dec.). Wohl and Lange[8] noted the insolubility of the disemicarbazone of pyruvaldehyde, and reported a m. p. of 254°, which was not sharp.

Anal. Calcd. for $C_5H_{11}N_3O_2$ (monosemicarbazone of methoxyacetone): N, 29.2. Calcd. for $C_5H_{10}N_6O_2$ (disemicarbazone of pyruvaldehyde): N, 45.1. Found: N, 45.3.

When 1.0 g. of methoxyacetone, 5.0 g. of phenylhydrazine hydrochloride and 7.0 g. of sodium acetate in 40 cc. of water were refluxed for three hours, on cooling, a very viscous dark liquid was formed. This material was easily separated from the water layer by decantation. Crystallization of this liquid from alcohol–water slowly deposited 0.6 g. of an orange solid. Several recrystallizations produced an orange-brown solid, m. p. 147°.[9]

Anal. Calcd. for $C_{10}H_{14}N_2O$ (phenylhydrazone of methoxyacetone): N, 15.7. Calcd. for $C_{15}H_{16}N_4$ (osazone of pyruvaldehyde): N, 22.2. Found: N, 21.7.

Methoxyacetone turned Benedict solution green in ten minutes and a small red precipitate was visible in one-half hour. When a few drops of methoxyacetone were added to 2 cc. of Schiff reagent, a deep purple color was produced immediately. With Tollens reagent, methoxyacetone developed a faint turbidity at room temperature in fifteen minutes, and gave a visible silver mirror in five minutes when heated on a steam-bath.

Attempted Catalytic Dehydrogenation of 1-Methoxy-2-propanol.—1-Methoxy-2-propanol (110 cc.) was passed over brass turnings at a rate of 1.2 cc. per minute. The gas evolution was almost negligible at 400°, increased slightly at 450°, and at 500° the evolution was rapid at first, but then decreased after the first fifteen minutes. At 500°, for instance, 3100 cc. of gas was collected. The product was fractionated and was for the most part unreacted starting material. No 2,4-dinitrophenylhydrazone of methoxyacetone could be isolated from any of the material.

Reactions with Chloroacetone.—Freshly distilled chloroacetone was added to sodium methoxide in benzene and, in another experiment, sodium methoxide was added to chloroacetone in benzene. In both cases, a brown sticky mass was obtained and no methoxyacetone could be isolated.

(6) This result is similar to that obtained with α,α'-diethoxyacetone, which also gave a positive Fehling test; Grimaux and LeFèvre, *Bull. soc. chim.*, [3] **1**, 12 (1889).

(7) Drake, *et al.*, THIS JOURNAL, **60**, 73 (1938).

(8) Wohl and Lange, *Ber.*, **41**, 3615 (1908).

(9) Knopfer reports a m. p. of 148° for the osazone of pyruvaldehyde [*Monatsh.*, **32**, 767 (1911)].

CHEMICAL LABORATORY
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EVANSTON, ILLINOIS

RECEIVED MAY 26, 1949

The Sulfonation of *m*-Aminophenol

BY ALFRED L. MILLER,[1] HARRY S. MOSHER,[2] F. W. GRAY AND FRANK C. WHITMORE[3]

The sulfonation of *m*-aminophenol has been reported to yield 2-amino-4-hydroxybenzenesulfonic acid by Oehler.[4] The reference to Oehler's work in Beilstein[5] describes the product as the isomeric 4-amino-2-hydroxybenzenesulfonic acid. Other workers[6,7] who have used the Oehler pro-

(1) Present address: Celanese Corp. of Amer., Summit, N. J.

(2) Present address: Department of Chemistry, Stanford Univ., Calif.

(3) Deceased.

(4) Oehler, German Patent 70,788; *Frdl.*, **3**, 59.

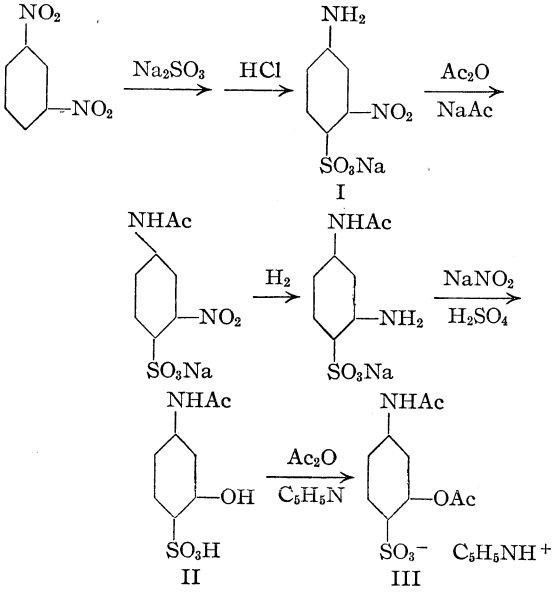
(5) Beilstein, "Handbuch der organischen Chemie," Vol. XIII, 1st ed., Julius Springer, Berlin, 1930, p. 402.

(6) Jacobs, Heidelberger and Rolfe, THIS JOURNAL, **41**, 471 (1919).

(7) Thorpe and Williams, *Biochem. J.*, **35**, 61 (1941).

cedure have reported this latter structure for the product. To the best of our knowledge no structure proof for the product from the sulfonation of *m*-aminophenol has been reported.

In connection with some of our work in the field of synthetic drugs we have determined the structure of this amino-hydroxybenzenesulfonic acid by synthesis through another route as indicated in the series of reactions given. The structure of the intermediate 4-amino-2-nitrobenzenesulfonic acid (I) has been previously established beyond reasonable doubt.[8] Since neither 4-



amino-2-hydroxybenzenesulfonic acid nor the acetyl derivative (II) have definite melting points, comparison was made of the pyridinium-4-acetylamino-2-acetoxybenzenesulfonate (III) derivatives. The products made by the above method and that obtained from the sulfonation of *m*-aminophenol followed by the action of acetic anhydride and pyridine were shown to be identical by a mixed melting point study. This clearly indicates that the structure reported in the Oehler patent is in error and that the stable sulfonation product of *m*-aminophenol is 4-amino-2-hydroxybenzenesulfonic acid as assumed in the other reports.[5,6,7]

Experimental

The Sulfonation of *m*-Aminophenol.—The Oehler procedure[4] consists in heating a solution of one part of *m*-aminophenol in three parts of concentrated sulfuric acid on the water-bath for one hour. The product is obtained by dilution with water. It was converted into the pyridinium acetylaminoacetoxybenzenesulfonate (III) by the method of Thorpe and Williams.[7] After recrystallization from absolute ethanol and ether, it melted at 164–166°.

4-Amino-2-nitrobenzenesulfonic Acid.—A slurry of 86 g. of *m*-dinitrobenzene in 800 ml. of a saturated sodium sulfite solution was prepared and heated until solution was complete. To the hot solution, 250 ml. of concentrated hydrochloric acid was added and the resulting mixture heated at boiling for thirty minutes. The precipitate that formed on cooling was purified by solution and reprecipitation; yellow powder, 50 g.[8,9]

Sodium 4-Acetylamino-2-nitrobenzenesulfonate.—To a slurry of 10.5 g. of 4-amino-2-nitrobenzenesulfonic acid in 30 ml. of glacial acetic acid, sufficient sodium acetate was added to effect solution. After the addition of 30 ml. of acetic anhydride, the acetylation mixture was heated at reflux overnight. One-half of the acetic acid was evaporated and sufficient ether added to cause precipitation. The product was recrystallized from absolute ethanol; 14 g.

Sodium 4-Acetylamino-2-aminobenzenesulfonate.—A solution of 14 g. of sodium 4-acetylamino-2-nitrobenzenesulfonate in 300 ml. of absolute ethanol was shaken with hydrogen in the presence of Adams catalyst at three atmospheres pressure. The reduction was not complete. The precipitate which formed was filtered and purified, 2.5 g. It gave a positive test for an aromatic amine.

4-Acetylamino-2-hydroxybenzenesulfonic Acid.—A solution of 3.5 g. of sodium 4-acetylamino-2-aminobenzenesulfonate in 50 ml. of 3% sulfuric acid was prepared and cooled to 3°. Upon completion of the slow addition of a sodium nitrite solution (1.2 g. of sodium nitrite in 15 ml. of water), 100 ml. of a 1% copper sulfate solution was added and the resulting solution refluxed for one hour. After cooling for several days at 0°, approximately 1 g. of a light brown solid was isolated which gave a negative test for a free amine group and which had no definite melting point.

Pyridinium-4-acetylamino-2-acetoxybenzenesulfonate.—To a pyridine solution of the 1 g. of crude 4-acetylamino-2-hydroxybenzenesulfonic acid was added 1 ml. of acetic anhydride and the resulting precipitate was recrystallized from absolute ethanol and ether, m. p. 164–166°. A mixed melting point with the previously prepared pyridinium salt gave no depression.

We gratefully acknowledge the financial assistance of Parke, Davis and Company in this work.

(8) Nietzke and Helbach, *Ber.*, **29**, 2449 (1896).

(9) Hunter and Sprung, THIS JOURNAL, **53**, 1440 (1931).

SCHOOL OF CHEMISTRY AND PHYSICS
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNSYLVANIA RECEIVED MAY 5, 1949

The Willgerodt Reaction with Acetylphenylacetylene and Benzalacetone

BY DOROTHY NIGHTINGALE AND RICHARD A. CARPENTER[1,2]

The Willgerodt reaction with acetylphenylacetylene and benzalacetone appeared to offer a method for the synthesis of γ-phenylethynylacetic acid and γ-phenylvinylacetic acid. Initial experiments with acetylphenylacetylene and ammonium polysulfide at 190°[3] yielded a product, m. p. 54–56°, containing nitrogen and sulfur which decomposed on standing and was too unstable for consistent analyses. When the reaction was repeated by the procedure of Schwenk and Bloch[4] using morpholine and sulfur, the γ-phenylethynylthioacetomorpholide (I) was obtained in 51% yield. Ozonolysis of (I) followed by oxidative cleavage yielded benzoic acid. All efforts to hydrolyze the thioacetomorpholide to γ-phenylethynylacetic acid were fruitless. Propionylphenylacetylene, morpholine and sulfur yielded an intractable tar.

(1) From the Master's thesis of Richard A. Carpenter.

(2) Present address: Wood River Refinery, Shell Oil Company, Wood River, Illinois.

(3) Wadsworth, Ph.D. Dissertation, University of Missouri (1948).

(4) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

Benzalacetone reacted with morpholine and sulfur under the same conditions to form γ-phenylvinylthioacetomorpholide (II) in 35% yield. Ozonolysis of (II) followed by reductive cleavage yielded benzaldehyde which was identified by its dimethone derivative. Hydrolysis of (II) with alcoholic potassium hydroxide yielded only unchanged starting material, but long refluxing with hydrochloric acid and acetic acid yielded a product (III) melting at 112–114°, soluble in base and containing neither nitrogen halogen nor sulfur. Analyses of (III) approximated an empirical formula of $C_7H_7O_2$, but a neutral equivalent of 189–195 and a mixed melting point indicated that the product was not benzoic acid.

Experimental[5]

γ-Phenylethynylthioacetomorpholide.—Acetylphenylacetylene (29 g., 0.2 mole), 26 g. (0.3 mole) of morpholine and 9.6 g. of sulfur were heated gently for one hour and then refluxed vigorously for three hours more. The reaction mixture was cooled, taken up in 200 cc. of benzene, washed with dilute hydrochloric acid and finally with water. The benzene solution was dried, the benzene removed and the residue recrystallized first from aqueous alcohol and finally from Skellysolve A. The thioacetomorpholide (I) crystallized in pale yellow amorphous knobs, m. p. 79–80°; yield 25 g. (51%).

Anal. Calcd. for $C_{14}H_{15}ONS$: C, 68.53, H, 6.16. Found: C, 68.34; H, 6.52.

Ozonolysis of 0.1 g. of (I) in carbon tetrachloride at 0° followed by oxidative cleavage yielded benzoic acid, melting point and mixed melting point, 121°.

When 2 g. of (I) was refluxed for ten hours with 20% alcoholic potassium hydroxide or with a solution of 2 cc. of concentrated hydrochloric acid in 15 cc. of glacial acetic acid, only starting material was recovered.

γ-Phenylvinylthioacetomorpholide (II).—Benzalacetone (30 g., 0.2 mole), 26 g. (0.3 mole) of morpholine and 9.6 g. (0.3 mole) of sulfur were heated gently for one hour and then refluxed vigorously for four hours. The product was worked up as described above except that the tarry residue was recrystallized from aqueous alcohol and finally treated with boneblack to remove the color. The thioacetomorpholide (II) crystallized in white plates, m. p. 133–134°; yield, 17 g. (35%).

Anal. Calcd. for $C_{14}H_{17}ONS$: C, 67.98; H, 6.93; N, 5.67. Found: C, 67.93; H, 6.57; N, 5.85.

The thioacetomorpholide (II) (80 mg.) dissolved in ethyl bromide was ozonized at 0°. The solvent was removed and the solid ozonide was decomposed reductively in the usual manner. The benzaldehyde was isolated as the dimethone derivative, melting point and mixed melting point 194–195°.

Hydrolysis of (II).—The thioacetomorpholide (II) (2 g.), 2 cc. of hydrochloric acid and 15 cc. of acetic acid were refluxed vigorously for ten hours. The reaction mixture was poured into water and after standing overnight the solution and suspended solid were extracted with ether. The ether extract was dried, the ether removed and the gummy residue was sublimed. A white solid (III) was obtained which melted at 112–114°[6] and contained no nitrogen or sulfur. The product was soluble in base but the melting point of the recovered acid was unchanged. A mixture of benzoic acid and (III) melted at 100–105°.

Anal. Calcd. for γ-phenylvinylacetic acid, $C_{10}H_{10}O_2$: C, 74.04; H, 6.21; neut. equiv., 162. Found: C, 67.10; H, 5.95; neut. equiv., 189, 195.

When (II) was refluxed with 20% alcoholic potassium hydroxide for ten hours, only unchanged starting material was isolated.

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COLUMBIA, MISSOURI

RECEIVED MAY 20, 1949

(5) The semimicro carbon–hydrogen analyses were done by R. A. Carpenter.

(6) The recorded melting point of γ-phenylvinylacetic acid is 86°. Fittig and Jayne, *Ann.*, **216**, 98 (1883).

N-(*p*-Chlorophenyl)-diamidophosphoric Acid

BY KURT RORIG

A compound considered to be N-(*p*-chlorophenyl)-amidophosphoric acid, p-$ClC_6H_4NHPO(OH)_2$, on the basis of an elemental analysis for carbon and hydrogen was first prepared by Otto[1] in 1895. Recently it has been prepared by Otto's method for use as an enzymatic substrate in histochemical experiments.[2]

This compound was also prepared according to Otto in our laboratory and was found to have the melting point reported by him. A complete elemental analysis, however, showed it to be N-(*p*-chlorophenyl)-diamidophosphoric acid, p-$ClC_6H_4NHPO(OH)(NH_2)$, rather than the monoamidophosphoric acid postulated by Otto. In accordance with the diamidophosphoric acid structure, the titration curve of our compound showed only the one break characteristic of a monobasic acid. A mixed melting point determination has shown that Gomori's compound[2] is the same as ours. However, our N-(*p*-chlorophenyl)-diamidophosphoric acid, melting at 156–157°, is insoluble both in hot water and in hot ethanol; whereas Otto reported that his compound, melting at 155°, was soluble in these solvents. Since Otto has also reported the existence of a di-silver salt of his compound, it is prudent to say only that by following his somewhat incomplete instructions as closely as possible, N-(*p*-chlorophenyl)-diamidophosphoric acid was obtained by Gomori and ourselves.

Furthermore, the formation of the diamidophosphoric acid is in harmony with the experience of Caven,[3] who found that anilidophosphoryl-dichloride, when dissolved in aqueous ammonia, formed N-phenyl-diamidophosphoric acid rather than the monoamidophosphoric acid as surmised by Michaelis and Schulze.[4]

Experimental

A mixture of 163.5 g. (1 mole) of *p*-chloroaniline hydrochloride and 307 g. (2 moles) of phosphorus oxychloride was refluxed for two and one-half hours. The cooled, solidified reaction mixture was filtered and washed with petroleum ether (b. p. 60–71°) to give 202 g. of crude *p*-chloroanilidophosphoryl-dichloride, p-$ClC_6H_4NHPOCl_2$, melting at 97–104°. A small sample melted at 105–107° when recrystallized from benzene.

Thirty grams of crude *p*-chloroanilidophosphoryl dichloride was added slowly to 60 ml. of aqueous ammonium hydroxide (28%) while keeping the temperature below 10°. The turbid solution was immediately filtered and acidified with a slight excess of hydrochloric acid to precipitate the

(1) Otto, *Ber.*, **28**, 617 (1895).

(2) Gomori, *Proc. Soc. Exp. Biol. Med.*, **69**, 407 (1948); *ibid.*, **70**, 7 (1949).

(3) Caven, *J. Chem. Soc.*, **81**, 1367 (1902).

(4) Michaelis and Schulze, *Ber.*, **26**, 2939 (1893).

gelatinous N-(*p*-chlorophenyl)-diamidophosphoric acid. This crude product when filtered, washed thoroughly with water and dried, weighed 19.5 g. and melted 143–148°. The crude N-(*p*-chlorophenyl)-diamidophosphoric acid was purified by washing first with boiling water, then with hot ethanol and finally with ether. It then melted at 156–157° and had a neutral equivalent of 203 (calcd. 206.5).

Anal. Calcd. for $C_6H_8ClN_2O_2P$: C, 34.88; H, 3.90; Cl, 17.17; N, 13.56; P, 15.00. Found: C, 34.94; H, 3.77; Cl, 17.20; N, 13.26 (Kjeldahl), 13.29 (Dumas); P, 14.4.

The melting point of the mixture of Gomori's compound (m. p. 153–154°)[5] with ours (m. p. 156–157°) was 154–155.5°.

(5) We wish to thank Dr. Gomori for providing this sample.

RESEARCH LABORATORIES
G. D. SEARLE AND COMPANY
SKOKIE, ILLINOIS

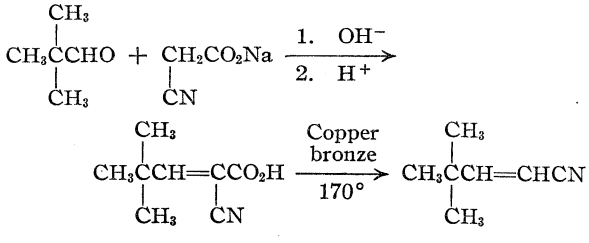
RECEIVED MAY 20, 1949

The Preparation of Some β-Alkylated Acrylonitriles

BY ROBERT M. ROSS[1] AND MARY LOUISE BURNETT

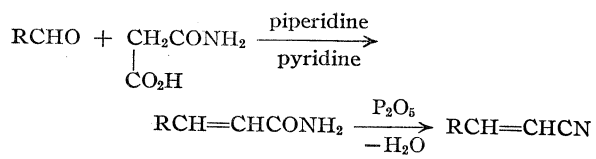
Certain nitriles, namely, β-*t*-butylacrylonitrile, β-isopropylacrylonitrile and β-ethylacrylonitrile were needed for studies which were in progress in this Laboratory. No method for the synthesis of β-*t*-butylacrylonitrile could be found in the literature and, although preparative methods exist for β-isopropylacrylonitrile and β-ethylacrylonitrile,[2] they appeared unnecessarily arduous. Accordingly, new routes for the syntheses of the desired nitriles have been investigated.

β-*t*-Butylacrylonitrile has been prepared by the condensation of pivalaldehyde with sodium cyanoacetate[3] in an aqueous, alkaline medium and subsequent decarboxylation of the cyano acid thus obtained.



The over-all yield for the method is about 45%.

Galat[4] reported a novel synthesis of α,β-unsaturated amides which involved the condensation of aromatic aldehydes with malonmonoamide. We have extended the use of malonmonoamide to include condensations with some aliphatic aldehydes. β-Isopropylacrylamide and β-ethylacrylamide were prepared in this manner. The amides were then dehydrated by the usual method using phosphorus pentoxide.



This synthesis affords over-all yields of about 56 and 20% for the β-isopropyl- and β-ethylacrylonitriles, respectively. A previously reported[2] method for the preparation of these nitriles consisted of a relatively tedious four-step synthesis and furnished β-isopropylacrylonitrile in about 18% yield; no over-all yield was reported for β-ethylacrylonitrile. Thus, the use of malonmonoamide eliminates two reaction steps and affords significantly greater yields at least in the preparation of β-isopropylacrylonitrile.

Experimental

Pivalaldehyde.—Trimethylpyruvic acid[5] was decarboxylated in the presence of diphenylamine to yield pivalaldehyde according to the directions of Trister and Hibbert.[6]

Malonmonoamide.—Galat's[4] procedure for the synthesis was employed.

α-Cyano-β-*t*-butylacrylic Acid.—A mixture of 126 ml. of 2.65 *M* sodium cyanoacetate solution,[7] 1.63 g. of sodium hydroxide pellets and 85 ml. of water were placed in a 500-ml., three-necked, round-bottomed flask equipped with a rubber-sealed Hershberg stirrer, condenser and thermometer. To the contents of the flask was added 19.0 g. (0.24 mole) of pivalaldehyde and vigorous stirring was commenced. The contents of the flask were heated to 50° for fifteen minutes by a warm water-bath. At the end of this time, the bath was removed and stirring was continued for two hours. Then an additional 40 ml. of 2.65 *M* sodium cyanoacetate solution and 0.51 g. of sodium hydroxide pellets were added to the reaction mixture. The contents of the flask were reheated to 50° for fifteen minutes and stirring was continued for three hours longer. At the end of this time, the solution was made neutral to litmus by the careful addition of concentrated hydrochloric acid. A 20-ml. excess of hydrochloric acid was added to the neutral solution. The brown oil which formed was induced to crystallize by scratching the flask sides with a glass rod. After thorough chilling at 0°, the tan-colored crystals of α-cyano-β-*t*-butylacrylic acid were removed by filtration, suction dried on the filter funnel, and washed with 30 ml. of cold benzene. A total of 26 g. (71%) of crude α-cyano-β-*t*-butylacrylic acid was isolated, m. p.[8] 115–119° (dec.). Recrystallization was effected from about 150 ml. of dilute ethanol (10%) with Norit. Long, white needles were obtained, m. p. 123.5–125° (slight dec.).

Anal.[9] Calcd. for $C_8H_{11}O_2N$: C, 62.72; H, 7.24; N, 9.15; neut. equiv., 153. Found: C, 62.70; H, 7.30; N, 8.99; neut. equiv., 157.

β-*t*-Butylacrylonitrile.—In a 50-ml., round-bottomed flask, equipped with mechanical stirrer and condenser, were placed 6.5 g. (0.042 mole) of α-cyano-β-*t*-butylacrylic acid and 1.5 g. of fine copper–bronze powder. The contents of the flask were heated by an electrically controlled oil-bath. The temperature of the oil-bath was raised rapidly to 170°. When the cyano acid melted (about 125°), stirring was started and the evolution of carbon dioxide was noted by leading an exit tube from the condenser top into a test-tube of water. The evolution of carbon dioxide became rapid when the bath temperature was 140°, and at 160°

(1) Preliminary investigations of this work were carried out by one of us (R. M. R.) as the du Pont postdoctoral fellow.

(2) von Auwers, *Ann.*, **432**, 46 (1923).

(3) A similar method was employed in the preparation of α-cyano-β-phenylpyruvic acid; see Lapworth and Baker, "Organic Syntheses," Coll. Vol. I, p. 181.

(4) Galat, THIS JOURNAL, **70**, 2596 (1948).

(5) Richard, *Ann. chim. phys.*, [8] **21**, 360 (1910).

(6) Trister and Hibbert, *Can. J. Research*, **14B**, 415 (1936).

(7) Lapworth and Baker, "Organic Syntheses," Coll. Vol. I, p. 181.

(8) All melting points reported herein are uncorrected.

(9) The analyses reported were done by the Clark Microanalytical Laboratories, Urbana, Illinois.

it was vigorous. After twenty-five minutes of heating at 170°, carbon dioxide was no longer evolved. Heating was stopped and the melt was allowed to cool. The copper–bronze powder was removed by filtration with the aid of a small amount of ether. The powder was washed thoroughly with 25 ml. of ether which was combined with the filtrate. Ether was removed by distillation, and the residue was distilled under reduced pressure. A colorless and pungent smelling liquid, boiling between 59 and 60° (28 mm.) was obtained; $n^{20}D$ 1.4344. The yield was 3.2 g. (70%).

Anal.[9] Calcd. for $C_7H_{11}N$: C, 77.01; H, 10.16. Found: C, 77.16; H, 10.16.

β-Isopropylacrylamide.—In a 100-ml., round-bottomed flask were placed 10.8 g. (0.15 mole) of freshly distilled isobutyraldehyde, 30.9 g. (0.30 mole) of malonmonoamide, 25 ml. of dry pyridine and eight drops of dry piperidine. The mixture was heated under reflux (oil-bath temperature was 82°) for twenty-four hours. At the outset of the heating, there was a vigorous evolution of carbon dioxide, which gradually subsided over the twenty-four-hour period. At the end of this time, the mixture was concentrated to dryness under reduced pressure. The residue was diluted with 10 ml. of water and extracted with 250 ml. of ether in five 50-ml. portions. The ether extract was dried over anhydrous magnesium sulfate. Ether was removed by distillation whereupon the residue solidified. The crude, nearly white β-isopropylacrylamide was dried under a reduced pressure of less than 1 mm. overnight. The yield was 11.9 g. (70%), m. p. 79–84°. Recrystallization from 15 ml. of hot benzene gave 9.0 g. of white crystals which melted between 83 and 86° (lit.[2] 82–86°).

β-Isopropylacrylonitrile.—A mixture of 4.4 g. (0.039 mole) of β-isopropylacrylamide and 6.5 g. of phosphorus pentoxide was placed in a 100-ml., round-bottomed flask. The contents were mixed thoroughly. The flask was equipped with a small take-off head for downward distillation and the contents were heated gradually by an oil-bath. The temperature of the bath was brought to and maintained at 200°. At the end of thirty minutes the system was placed under a reduced pressure of about 50 mm. The distillate was collected in a tube immersed in a Dry Ice–acetone-bath. Heating was continued for about two hours and during this time the pressure was lowered gradually to 15 mm. The black residue frothed considerably during this period. At the end of this time, no further distillation took place and heating was stopped. A total of 3.0 g. of colorless β-isopropylacrylonitrile was obtained; $n^{20}D$ 1.4316. Redistillation yielded a product which possessed the following physical constants: $n^{20}D$ 1.4329, b. p. 68° (34 mm.). Reported[10] values for the *trans* compound are: $n^{20}D$ 1.4342, b. p. 48.5° (13.5 mm.).

β-Ethylacrylamide.—Essentially the same conditions were employed for the preparation of β-ethylacrylamide as those described for β-isopropylacrylamide. Crude β-isopropylacrylamide was isolated in the amount of 7.2 g. from 8.7 g. of freshly distilled propionaldehyde and 30.9 g. of malonmonoamide. Subsequent recrystallization from acetone afforded 3.4 g. of glistening, white needles, m. p. 148–148.5° (lit.[2] 148°).

β-Ethylacrylonitrile.—β-Ethylacrylamide was dehydrated with phosphorus pentoxide under essentially the conditions described for the preparation of β-isopropylacrylonitrile. A mixture of 6.28 g. (0.06 mole) of β-ethylacrylamide and 9.2 g. of phosphorus pentoxide yielded 2.3 g. (45%) of colorless β-ethylacrylonitrile, b. p. 72° (72 mm.), $n^{20}D$ 1.4301 (lit.,[11] b. p. 73° (72 mm.), $n^{20}D$ 1.4298 (for the *trans* compound)).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED JUNE 6, 1949

(10) Bruylants, *Bull. soc. chim. Belg.*, **41**, 309 (1932); *C. A.*, **27**, 267 (1933).

(11) Bruylants and Jmoudsky, *Bull. sci. acad. roy. Belg.*, [5] **17**, 1161 (1931); *C. A.*, **26**, 3232 (1932).

Equilibria of the Boric Acid–Mannitol Complexes

BY SIDNEY D. ROSS AND ARTHUR J. CATOTTI

The recent publication by Deutsch and Osoling[1] on the stoichiometry and equilibria of boric acid–mannitol complexes prompts us to report some related results obtained in these laboratories. We have focused our attention on determining the equilibrium constant for the reaction

$$HB + 2M \rightleftarrows BM_2^- + H^+$$

In determining this constant, we have consciously selected concentrations of both boric acid and mannitol which would permit us to make the simplifying assumption that the concentrations of both B^- and BM^- are negligible in comparison with the concentrations of both H^+ and BM_2^-. For the equilibrium constant, we may write

$$K = \frac{[H^+][BM_2^-]}{[HB][M]^2} \cong \frac{[H^+]^2}{[HB_0 - H^+][M_0 - 2H^+]^2}$$

and K can be calculated from a single pH measurement. The justification for this assumption will be discussed later.

The reagents were C.P. boric acid and mannitol and freshly boiled distilled water. All solutions were thermostatted at 25°, and the ionic strength was kept at 0.10–0.12 M by addition of C.P. potassium chloride. The pH's were measured with a Beckman pH meter. The results are summarized in Table I.

TABLE I

CALCULATED VALUES OF K

[HB]	[M]	[M]/[HB]	[KCl]	pH	$K \times 10^4$
0.0141	0.0534	3.78	0.117	4.20	1.01
.0166	.0985	5.94	.104	3.88	1.09
.0141	.0865	6.16	.117	3.99	0.955
.00532	.0370	6.95	.104	4.56	1.05
.00350	.0257	7.30	.114	4.81	1.05
.00350	.0292	8.30	.114	4.79	0.892
.00851	.0737	8.70	.104	4.17	1.00
.00350	.0374	10.7	.114	4.66	0.990

The average of these values is 1.00×10^{-4} and the maximum deviation from this average value is less than 11%. This agreement is as good as can be expected, since the uncertainty in the pH measurement is 0.02 unit, and a change of 0.02 in pH will change K by as much as 11%.

To check our accuracy, we determined the dissociation constant of boric acid in 0.104 M potassium chloride at 25.0°. The determined values ranged from 6.77×10^{-10} to 8.24×10^{-10}, with the average value being 7.40×10^{-10}. Again, all of the deviations from the average value can be accounted for by an uncertainty of 0.02 unit in the pH measurement. The accepted value for the dissociation constant in pure water is 6.4×10^{-10}, and a higher value is to be expected in our medium of higher ionic strength.[2]

(1) Deutsch and Osoling, THIS JOURNAL, **71**, 1637 (1949).

(2) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 89.

Böeseken, Vermaas and Küchlin[3] have also determined the equilibrium constant for this complex formation from data on the potentiometric titration of boric acid in the presence of mannitol. They do not specify the temperature at which the measurements were made but report a value of 1.7×10^{-4} for K. Neither this result nor the result obtained by us are in agreement with that reported by Deutsch and Osoling.[1] The latter workers have defined K differently, but their K can be made equivalent to ours by multiplying it by the dissociation constant for boric acid. This gives for K, 0.33×10^{-4}, a value only one-third that obtained by us. Part but certainly not all of this difference can be attributed to the fact that our measurements were made in solutions of much higher ionic strength.

In making our calculations we have assumed that both B^- and BM^- are negligible compared to H^+ and BM_2. We have chosen concentrations of both boric acid and mannitol such that the hydrogen ion concentration is in every case at least ten times what it would be in the absence of the mannitol. Moreover, by using our determined value for the dissociation constant of boric acid and the Deutsch and Osoling value for the equilibrium constant, K_1, of the reaction

$$B^- + M \rightleftarrows BM^-$$

we can calculate the concentrations of B^- and BM^- and correct our equilibrium constant accordingly. We have not reported these revised values, since we strongly question the validity of the value of K_1 as determined by Deutsch and Osoling, and since these corrections would change our values by no more than 10% which is within our known experimental uncertainty.

(3) Böeseken, Vermaas and Küchlin, *Rec. Trav. Chim.*, **49**, 711 (1930).

RESEARCH LABORATORIES
THE SPRAGUE ELECTRIC COMPANY
NORTH ADAMS, MASSACHUSETTS RECEIVED JUNE 10, 1949

Boron Trifluoride Catalyzed Esterification of *p*-Aminosalicylic Acid

BY JOSEPH J. SCHAEFER AND LEONARD DOUB

The effectiveness of *p*-aminosalicylic acid (4-amino-2-hydroxybenzoic acid) in experimental tuberculosis chemotherapy[1,2] led us to prepare a number of its esters. These compounds have been prepared by reduction of the corresponding nitro esters,[3] but since *p*-aminosalicylic acid has become commercially available, it was desirable to investigate direct esterification. Conventional methods of esterification under various conditions led to very low yields,[4] the primary product being *m*-aminophenol.

Boron trifluoride as an esterification catalyst, following the work of Sowa and Nieuwland,[5] was tried and found to give excellent results. Approximately 70% yields were obtained with several alcohols. In general we used 4.5 moles of boron trifluoride for each mole of *p*-aminosalicyclic acid. In accord with the procedures of Sowa and Nieuwland, this provides one-half mole excess of boron trifluoride over that necessary for complex formation with the functional groups.

Experimental

Preparation of the Esters of 4-Amino-2-hydroxybenzoic Acid.—To a suspension of 153 g. (1.0 mole) of 4-amino-2-hydroxybenzoic acid in 1000 ml. of the anhydrous alcohol, 565 ml. (4.5 moles) of boron trifluoride–ethyl ether complex was added slowly, keeping below 40°. The resulting clear solution, after standing at room temperature for several days, was evaporated under reduced pressure to a thick slurry, and 500 ml. of water was introduced. Solution was effected by adding 10 *N* sodium hydroxide with cooling until alkaline to phenolphthalein. After charcoaling and filtering, solid carbon dioxide was added with agitation to precipitate the ester. This precipitate was removed by filtration and dissolved in dilute hydrochloric acid, charcoaled and filtered. The filtrate was neutralized with potassium bicarbonate. The ester precipitated, was filtered off and crystallized from ethyl alcohol.

ESTERS OF 4-AMINO-2-HYDROXYBENZOIC ACID

Ester	Reaction time, days	Yield, %	M. p., °C.	Empirical formula	Nitrogen, % Calcd.	Found
Methyl	10	74	121–122[4]	$C_8H_9NO_3$	7.73	7.88
Ethyl	10	71	114–115[3]	$C_9H_{11}NO_3$	8.38	8.27
Isopropyl	30	75	73–75[3]	$C_{10}H_{13}NO_3$	7.18	7.43 7.40

(4) Rosdahl, *Svensk Kem. Tid.*, **60**, 12 (1948), reports the preparation of the methyl ester with sulfuric acid in methyl alcohol. In our hands this procedure gave less than 10% yield.

(5) Sowa and Nieuwland, THIS JOURNAL, **58**, 271 (1936).

RESEARCH LABORATORIES
PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN RECEIVED JULY 1, 1949

The Melting Point of Potassium Hydroxide

BY RALPH P. SEWARD AND KENNETH E. MARTIN

The melting point of potassium hydroxide has been reported as 360° by Hevesy[1] and 380° by Scarpa.[2] A determination of the melting point of potassium hydroxide was suggested by the observation that a sample which had been heated several hours to remove water was found to remain solid above 400°. The observations which are recorded below indicate the melting point to be 410 ± 1°.

The "reagent" quality potassium hydroxide employed, from titration with standard acid, was found to be 86.5% potassium hydroxide and 1.0% potassium carbonate, which agreed with the maker's analysis. On heating to constant weight at a

(1) Lehmann, *Lancet*, **250**, 15 (1946).

(2) Youmans, *Quart. Bull., Northwestern Univ. Med. School*, **20**, 420 (1946).

(3) *Cf., e. g.*, Jensen, Rosdahl and Ingvorsen, *Acta Chir. Scand.*, **2**, 220 (1948).

(1) Hevesy, *Z. physik. Chem.*, **73**, 667 (1910).

(2) Scarpa, *Atti Acad. Lincei*, [5] **24**, 745 (1915); *C. A.*, **9**, 2828 (1915).

dull red heat, a weight loss of 12.5% was found. It was assumed that the only impurity present in significant amount after dehydration was the 1% of carbonate. To estimate the effect of the carbonate, freezing points were determined with known amounts of additional potassium carbonate.

About 50 g. of the hydroxide was melted in a nickel container brought gradually to 475–500°, and kept at this temperature ten to twelve hours to remove water. Further heating did not change the freezing point. The freezing points were obtained from cooling curves. Temperatures were measured with a chromel–alumel thermocouple which was calibrated at the freezing points of tin, lead and zinc, using Bureau of Standards samples. The same freezing point was found with and without a monel metal protecting tube around the couple. When a stream of dry nitrogen was passed over the hydroxide during dehydration and cooling, the freezing point did not differ from the freezing point of the hydroxide in contact with air. The observations are summarized in the accompanying table. The carbonate concentrations are not known with great precision because of the tendency of the molten hydroxide to creep up the walls of the container.

FREEZING POINTS OF KOH–K_2CO_3 MIXTURES

K_2CO_3, wt. %	1.0	4.9	7.0	12.2	16.2
F. p., °C.	408.0	400.0	394.5	384.2	373.5
Eutectic, °C.	358.7	365.0	365.0	366.9	366.5

By extrapolation, the freezing point of potassium hydroxide with no carbonate present was estimated to be 410°. A transition which Hevesy found at 248° and Scarpa at 360° was found at 249°. The heat of fusion calculated from the effect of carbonate on the freezing point was 1830 cal. per mole. Kelley[3] has calculated a value of 1980 cal. per mole from the data of Scarpa on the potassium hydroxide–potassium iodide system.

(3) Kelley, U. S. Bureau of Mines, Bulletin 393 (1936).

STATE COLLEGE, PENNSYLVANIA RECEIVED JUNE 3, 1949

Comparison of Some Properties of Thiolsulfonates and Thiolsulfinates

BY LAVERNE D. SMALL,[1] JOHN HAYS BAILEY AND C. J. CAVALLITO

The thiolsulfinates, R–SO–SR, have been shown to be active antibacterial and antifungal agents.[2] Although these oxides were previously unknown, the dioxides frequently have been described. These are now generally believed to have the thiolsulfonate structure, R–SO_2–SR. No record could be found of antibacterial tests with these compounds and it was of interest to compare the effect of the thiolsulfonate with that of the thiolsulfinate group in this respect.

The compounds used in this comparison were those where R was ethyl in the preceding structures. The thiolsulfonate was only 1.2% soluble in water compared with approximately 11% for the thiolsulfinate. This reduced interest in the higher alkyl thiolsulfonates. Both compounds react quickly with dilute alkalies.

Tests conducted by methods previously described[2] showed that the two thiol esters are of comparable antimicrobial activity, the thiolsulfonate being more effective against *S. aureus* and *K. pneumoniae*.

The antibiotic activity of thiolsulfinates has been attributed to the ability of the compounds to react with biologically essential –SH groups as exemplified by the reaction with cysteine to yield derivatives of type I, R–S–S–CH_2–$CH(NH_2)$–COOH.[3] With the thiolsulfinates one mole of compound yielded, nearly quantitatively, two moles of I. Under similar conditions the thiolsulfonate gave only one equivalent of I and an acid, presumably ethanesulfinic acid. This in harmony with the observations of Smiles and coworkers[4] who found that thiolsulfonates reacted with mercaptans to yield one mole of disulfide and one of the sulfinic acid. The ability of thiolsulfinates to react rapidly with cysteine (thiols) to yield two moles of I is further support of Smiles' evidence that "disulfoxides" have a thiolsulfonate structure. A disulfoxide presumably would yield two moles of sulfenic acid as an intermediate (plus one cystine) and reaction with more cysteine would give two moles of I. As it is, only one mole of I and one of the sulfinic acid are formed under the conditions.

$$R{-}SO_2{-}SR + HS{-}CH_2{-}CH(NH_2){-}COOH \longrightarrow I + RSO_2H$$

$$R{-}SO{-}SR + HS{-}CH_2{-}CH(NH_2){-}COOH \longrightarrow I + RSOH$$

$$RSOH + HS{-}CH_2{-}CH(NH_2){-}COOH \longrightarrow I + H_2O$$

The observation of Toennies and Lavine[5] that cystine "disulfoxide" reacts with cysteine to yield a mole of cystine and one of cysteine sulfinic acid favors the thiolsulfonate structure for this compound. Tests in our Laboratories show that cystine dioxide also is inhibitory to bacterial growth. Such compounds may have an *in vivo* biological growth-control function if oxidation of

TABLE I

ANTIMICROBIAL ACTION OF THE THIOLSULFINATE AND THIOLSULFONATE

Compound	Inhibitory concentration,[a] mg. per cc. *Clostridium perfringens*	*Klebsiella pneumoniae*	*Staphylococcus aureus*	*Escherichia coli*	*Mycobacterium tuberculosis* H37Rv	*Trichophyton mentagrophytes*
$C_2H_5SOSC_2H_5$[b]	0.05	0.05	0.05	0.015	0.005	0.005
$C_2H_5SO_2SC_2H_5$	.05	.015	.005	.01	.005	.005

[a] Concentration producing complete inhibition of growth in serial dilution tests. [b] For preparation see [2].

(1) Present address: University of Nebraska, Lincoln, Nebraska.

(2) Small, Bailey and Cavallito, THIS JOURNAL, **69**, 1710 (1947).

(3) Cavallito, Buck and Suter, *ibid.*, **66**, 1952 (1944).

(4) Smiles and Gibson, *J. Chem. Soc.*, **125**, 176 (1924); Miller and Smiles, *ibid.*, **127**, 224 (1925).

(5) Toennies and Lavine, *J. Biol. Chem.*, **113**, 593 (1936).

–S–S– groups to the mono- or dioxide stage is demonstrated to occur in an organism.

Experimental

Ethyl Ethanethiolsulfonate. Method A.—One liter of ethyl acetate and 24.5 g. (0.2 mole) of ethyl disulfide were placed in a three-liter, three-neck flask. The solution was cooled with an ice-bath and while stirring there was added, during fifteen minutes, a solution of 5 moles of 40% peracetic acid in 500 cc. of ethyl acetate. After stirring and cooling for an additional hour the solution was allowed to stand at room temperature overnight. The reaction mixture was stirred with a solution of 30 g. of ferrous sulfate heptahydrate in 150 cc. of water to decompose excess per-acid. The ethyl acetate layer was separated and shaken with sufficient saturated aqueous sodium bicarbonate solution to remove acids. The ethyl acetate extract was dried over anhydrous sodium sulfate and then evaporated under reduced pressure to remove solvent. The liquid residue was distilled, yielding the thiolsulfonate, b. p. 56° at 0.2 mm.; $n^{25}D$ 1.4972; yield 3.7 g. or 12%.

Anal. Calcd. for $C_4H_{10}O_2S_2$: C, 31.15; H, 6.54. Found: C, 31.42; H, 6.41.

Method B.—Ethyl ethanethiolsulfonate was first prepared by Otto by reaction of an ethyl halide with sodium ethanethiolsulfonate, but few details were given and the compound was poorly characterized.[6,7]

An alcoholic solution of potassium sulfide was prepared by dissolving 0.5 mole of potassium hydroxide in 250 cc. of absolute ethanol, saturating the solution with hydrogen sulfide and adding a second 0.5 mole of alkali to the solution.

Ethanesulfonyl chloride ($n^{25}D$ 1.4515) was prepared by the method of Lee and Dougherty.[8] To the potassium sulfide solution was added dropwise, during four hours of stirring under anhydrous conditions, a solution of 0.5 mole of ethanesulfonyl chloride in 250 cc. of ethanol. The mixture was cooled with an ice-bath during this period. The mixture was then made alkaline to litmus with alcoholic potassium hydroxide and allowed to stand for fifteen hours at 25° and then heated to 50° for ten minutes. The solution was filtered and the filtrate refluxed for four hours with 0.75 mole of ethyl bromide. After cooling, the solution was filtered, the filtrate concentrated under reduced pressure and the residual thiolsulfonate distilled: yield 23.2 g. or 30%.

Anal. Found: C, 31.07; H, 6.23; $n^{25}D$ 1.4977.

Reaction with Cysteine.—Unbuffered aqueous solutions of cysteine hydrochloride and the thiolester adjusted to *p*H 6.5 with sodium hydroxide solution were mixed[3] and within a few seconds there appeared a white crystalline precipitate of I where R is ethyl, m. p. 196° dec. The thiosulfinate yielded nearly two moles of I (compare where R is allyl[3]) with no change in *p*H; the thiolsulfonate gave 90% yield for one mole of I and the *p*H dropped to 3.0.

Anal. Calcd. for I, $C_5H_{11}O_2NS_2$: N, 7.75. Found: N, 7.79.

(6) Otto, *Ber.*, **15**, 122 (1882).

(7) Hilditch, *J. Chem. Soc.*, **97**, 1098 (1910).

(8) Lee and Dougherty, *J. Org. Chem.*, **5**, 83 (1940).

STERLING–WINTHROP RESEARCH INSTITUTE
RENSSELAER, N. Y. RECEIVED MAY 2, 1949

Further Studies on Oxythiamine

BY MORRIS SOODAK[1] AND LEOPOLD R. CERECEDO

The preparation of oxythiamine from thiamine by deamination with gaseous nitrogen oxides has been previously reported from this Laboratory.[2] In the present communication, we wish to report additional information on this compound.

During the course of this work the thiochrome method was used in following the fate of thiamine, and the Prebluda–McCollum reagent as modified by Melnick and Field[3] served in tracing both the thiamine and oxythiamine, since both compounds give a positive reaction with equal color production. We have found that Melnick and Field[3] and also Rosenberg[4] are incorrect in assuming that the amino group in position 4 of the pyrimidine moiety is necessary for the production of color. Todd and Bergel,[5] and Prebluda and McCollum[6] had already shown that the essential features required for the production of color are the β-hydroxyethyl group on position 5 and a free hydrogen on position 2 of the thiazole moiety. In fact, Bergel and Todd[7] were able to synthesize oxythiamine and showed that it gave a positive formaldehyde–azo reaction. Thus, whereas thiamine gives both positive thiochrome and Prebluda–McCollum reactions, oxythiamine reacts only with the Prebluda–McCollum reagent, and the chloroxy- and bromoxythiamine give neither reaction. Our findings, therefore, confirm those of Todd and Bergel.

Oxythiamine is very similar to thiamine in its chemical properties. Both substances form chloride–hydrochloride salts, picrates and picrolonates, and they can be adsorbed on and eluted from Decalso under similar conditions.[8] Neither compound is attacked by sodium in the presence of glacial acetic acid[9] and both are split by the sulfite treatment of Williams.[10] Thus, by treatment of oxythiamine with sulfite, we have obtained 2-methyl-4-oxypyrimidine-5-methylsulfonic acid.

The ultraviolet absorption spectrum of oxythiamine chloride–hydrochloride was determined for aqueous solutions at neutral and acid reactions, by means of a Model DU Beckman spectrophotometer. Oxythiamine shows two maxima at 223 and 266 mμ, respectively, at *p*H 7.2 (phosphate buffer, 0.02 *M*), and at 221.5 and 265 mμ in 0.02 *M* phosphoric acid. The spectrum is very similar to that of oxychlorothiamine.[11]

Experimental[12]

Picrate and Picrolonate of Oxythiamine.—These compounds were prepared in the usual manner. They were recrystallized several times from an ethanol–water (1:1) mixture.

Oxythiamine picrate, m. p. 102–108°. *Anal.* Calcd. for $C_{12}H_{16}O_2N_3S[C_6H_2OH(NO_2)_3]_2$: C, 39.78; H, 3.00. Found: C, 39.46; H, 2.88.

(1) Present address: Biochemical Research Laboratory, Massachusetts General Hospital, Boston, Mass.

(2) Soodak and Cerecedo, THIS JOURNAL, **66**, 1988 (1944).

(3) Melnick and Field, *J. Biol. Chem.*, **127**, 505 (1939).

(4) H. R. Rosenberg, "Chemistry and Physiology of the Vitamins," Interscience Publishers, Inc., New York, N. Y., 1942, p. 129.

(5) Todd and Bergel, *J. Chem. Soc.*, 1559 (1936).

(6) Prebluda and McCollum, *J. Biol. Chem.*, **127**, 495 (1939).

(7) Bergel and Todd, *J. Chem. Soc.*, 1504 (1937).

(8) Cerecedo and Hennessy, THIS JOURNAL, **59**, 1617 (1937).

(9) Tolpin, Foy and Cerecedo, *ibid.*, **63**, 2848 (1941).

(10) Williams, Waterman, Keresztesy and Buchman, *ibid.*, **57**, 536 (1935).

(11) Buchman and Williams, *ibid.*, **57**, 1751 (1935).

(12) All melting points are uncorrected. The analyses were performed by Mr. M. Bier.

Oxythiamine picrolonate, m. p. 130–133°. *Anal.* Calcd. for $C_{12}H_{16}O_2N_3S(C_{10}H_8O_5N_4)_2$: C, 48.36; H, 4.03. Found: C, 48.00; H, 4.15.

2-Methyl-4-oxypyrimidine-5-methylsulfonic Acid.—Oxythiamine hydrochloride was treated with sulfite according to the method of Williams and co-workers.[10] After standing with the sulfite for two days (faint Prebluda–McCollum reaction), the solution was adjusted to *p*H 10, the thiazole fragment removed by extraction with chloroform, and the oxysulfonic acid isolated according to the method used by Cline, *et al.*,[13] in their synthesis of this compound.

Anal. Calcd. for $C_6H_8N_2SO_4$: C, 35.29; H, 3.92. Found: C, 35.70; H, 3.84.

The substance was also prepared as follows: The aminosulfonic acid, obtained by treatment of thiamine with sulfite,[10] was treated with the nitrogen oxide gases. The deamination could be easily followed, since the aminosulfonic acid is insoluble, whereas the oxysulfonic acid is rather soluble. The solution was evaporated to dryness *in vacuo*, and recrystallized by solution in water and precipitation with alcohol.[13]

Anal. Found: C, 35.54; H, 4.03.

Bromoxythiamine Bromide Hydrobromide.—One gram of thiamine hydrochloride was dissolved in 20 ml. of glacial acetic acid saturated with dry hydrogen bromide, and sealed in a bomb tube. The mixture was heated at 150–160° for three hours. After removal from the tube, the solution was concentrated *in vacuo* to dryness. The residue was recrystallized several times by solution in methanol and precipitation with absolute ether.[14] The resulting material was washed with ether and dried. It melted at 206–208° with decomposition. The compound does not form thiochrome and does not react with the Prebluda–McCollum reagent.

Anal. Calcd. for $C_{12}H_{16}N_3SOBr_3$: C, 29.38; H, 3.26; Br, 49.00. Found: C, 29.51; H, 3.87; Br, 49.05.

(13) Cline, Williams, Ruehle and Waterman, THIS JOURNAL, **59**, 530 (1937).

(14) Weil-Malherbe, *Biochem. J.*, **34**, 980 (1940).

THE DEPARTMENT OF BIOCHEMISTRY
FORDHAM UNIVERSITY
NEW YORK, N. Y.

RECEIVED FEBRUARY 8, 1949

Dichlorovinyltrichlorosilanes

BY G. H. WAGNER AND A. N. PINES

In a recent publication,[1] Agre has described the preparation of "α,β-dichlorovinyltrichlorosilane." In the interest of clarifying the structure of his compound, we would like to record the properties and reactions of two dichlorovinyltrichlorosilanes prepared in this Laboratory. Our data indicate that his compound is β,β-dichlorovinyltrichlorosilane. The properties of our dichlorovinyltrichlorosilanes, I and II, are compared below with Agre's compound.

		Compound I	Compound II	Agre's compound
Boiling point	°C.	163.5–164	162.5–163	159
	Mm.	750	750	729
Density, g./cc. at 25°C.		1.56	1.54	....
$n^{20}D$		1.4958	1.4942	1.4942

Compound I on treatment with concentrated potassium hydroxide gave 1,2-dichloroethylene by fission of the carbon–silicon bond similar to that observed[2] for chloromethyl groups attached to silicon. An explosive gas, probably chloroacetylene, was also formed during this treatment. Compound II, which compares well in its properties with Agre's compound, gave 1,1-dichloroethylene on similar treatment with concentrated potassium hydroxide solution. These reactions indicate that compound I is α,β-dichlorovinyltrichlorosilane and compound II is β,β-dichlorovinyltrichlorosilane. Since the properties of these compounds are almost identical, within experimental error, the part of Agre's proof of structure which is based on a comparison of the physical properties of the compounds obtained from the reaction of trichlorosilane with trichloroethylene and with 1,2-dichloroacetylene is questionable.

Experimental

Treatment of Compound I with Concentrated Potassium Hydroxide.—A three-liter flask was fitted with a dropping funnel and a small water condenser. The water condenser was vented to the atmosphere through two traps, one cooled in ice-water and one in Dry Ice and acetone. A solution of 200 g. of potassium hydroxide in 1500 cc. of water was added to the flask. Seventy-seven grams of compound I was added rapidly through the dropping funnel to the potassium hydroxide solution. After heating the mixture for a few minutes at reflux, a water-insoluble liquid formed. This was steam distilled into the traps after shutting off the cooling water to the water condenser. Upon cooling, a violent explosion occurred in the vent lines but 6 g. of material with the following properties was recovered from the traps.

		Unknown	Reported for 1,2-dichloroethylene *cis*	*trans*
Boiling point, °C.		56	48.4	60.3
Density	g./cc.	1.245	1.265	1.29
	°C.	25	15	15
$n^{20}D$		1.4501	1.4490, 15°	1.4519, 15°

Treatment of Compound II with Concentrated Potassium Hydroxide.—Using the same equipment and technique described above, 114 g. of compound II was added to a solution of 300 g. of potassium hydroxide in 700 cc. of water. Upon cooling, a small flash occurred in the vent line; 27.4 g. of material with the following properties was recovered from the traps.

		Unknown	Reported for 1,1-dichloroethylene
Boiling point, °C.		30.5	31.6
Density	g./cc.	1.168	1.218
	°C.	25	20
$n^{20}D$		1.4253	1.4270

The reactions observed here may be formulated in steps as exemplified below for the reaction of β,β-dichlorovinyltrichlorosilane.

$$OH^- + \text{SiCH}{=}CCl_2 \longrightarrow HO\text{Si} + {}^-CH{=}CCl_2 \quad (1)$$

$${}^-CH{=}CCl_2 + H_2O \longrightarrow CH_2{=}CCl_2 + OH^- \quad (2)$$

$${}^-CH{=}CCl_2 \longrightarrow CH{\equiv}CCl + Cl^- \quad (3)$$

The first step is an attack of hydroxyl ion on silicon to give the carbanion, $^-CH{=}CCl_2$, which may stabilize itself by reaction with the solvent, reac-

(1) Agre, THIS JOURNAL, **71**, 300 (1949).

(2) Krieble and Elliott, *ibid.*, **67**, 1810 (1945).

tion (2), or by loss of a chloride ion by reaction (3) to give chloroacetylene.

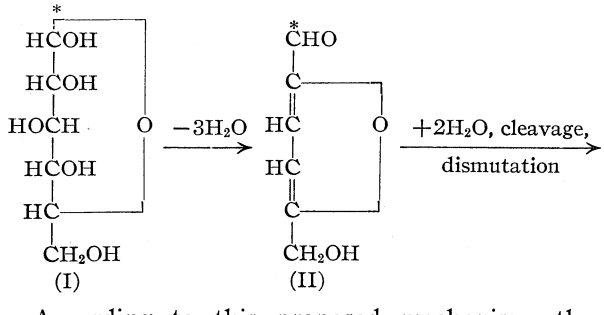
THE LABORATORY OF THE
LINDE AIR PRODUCTS COMPANY
TONAWANDA, NEW YORK RECEIVED JUNE 29, 1949

The Action of Hydrobromic Acid on 1-C^{14}-D-Glucose

BY JOHN C. SOWDEN

The dehydration and cleavage of D-glucose by vigorous treatment with mineral acids was first studied by Grote and Tollens[1] who recognized the principal products of the reaction as levulinic acid and formic acid, which are formed along with varying amounts of highly colored polymeric "humins." Earlier, Mulder[2] had obtained formic acid from the action of sulfuric acid on sucrose and undoubtedly the other product he obtained, "glucinic acid," was in reality levulinic acid, later purified, characterized and renamed by Grote and Tollens.[3]

The mechanism of the reaction remained obscure until comparatively recent times: 5-Hydroxymethyl-2-furaldehyde was recognized as a probable intermediate by Kiermayer[4] and by van Ekenstein and Blanksma.[5] Following a critical study of the reaction, Pummerer and co-workers[6] concluded that 5-hydroxymethyl-2-furaldehyde (II) is first formed from the hexose (I) with the loss of three molecules of water and that this intermediate then undergoes hydration, cleavage and dismutation to produce levulinic and formic acids (III)



According to this proposed mechanism, the aldehyde carbon of the hexose eventually becomes the carbon of the resultant formic acid. This latter assumption has now been substantiated by an examination of the products from 1-C^{14}-D-glucose[7] and hydrobromic acid: The levulinic acid produced was devoid of radioactivity whereas the formic acid showed quantitatively the radioactivity previously possessed by the aldehyde carbon of the glucose.

(1) Grote and Tollens, *Ann.*, **206**, 226 (1880).
(2) Mulder, *J. prakt. Chem.*, **21**, 229 (1840).
(3) Grote and Tollens, *Ber.*, **7**, 1375 (1874).
(4) Kiermayer, *Chem. Z.*, **19**, 1004 (1895).
(5) van Ekenstein and Blanksma, *Ber.*, **43**, 2355 (1910).
(6) Pummerer and Gump, *ibid.*, **56**, 999 (1923); Pummerer, Guyot and Birkofer, *ibid.*, **68**, 480 (1935).
(7) Sowden, *Science*, **109**, 229 (1949).

Experimental

One gram of 1-C^{14}-D-glucose, showing radioactivity of 860 ± 20 c.p.m./mg., was heated with 10.0 cc. of 10% hydrobromic acid in a sealed tube at 130° for twenty-four hours.[8] The resulting slight precipitate of "humins" was filtered off and washed. Sufficient sodium hydroxide solution was then added to the filtrate to exactly neutralize the hydrobromic acid. The resulting solution was distilled to dryness, using an oil-bath, and water was added and the distillation repeated twice.

The residue was extracted with anhydrous ether and the extract concentrated. The residual liquid, on treatment with phenylhydrazine, yielded 0.55 g. (48%) of *non-radioactive* levulinic acid phenylhydrazone, m. p. after recrystallization 109–110°.[9]

The distillate from the reaction mixture was titrated with 0.1 *N* sodium hydroxide solution to neutralize the distilled formic acid, requiring 44.7 cc. (80%) to the methyl red end-point. The resulting sodium formate was converted to *p*-phenylphenacyl formate, m. p. after recrystallization 74–75°.[10] This product when counted in the same manner[7] as the original 1-C^{14}-D-glucose showed radioactivity of 650 ± 20 c.p.m./mg. On the assumption that the formic acid was produced from the aldehyde carbon of the D-glucose the predicted radioactivity was 645 ± 20 c. p. m./mg.

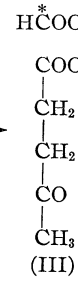
(8) Ploetz, *Naturwiss.*, **29**, 707 (1941).
(9) Fischer, *Ann.*, **236**, 146 (1886).
(10) Drake and Bronitsky, THIS JOURNAL, **52**, 3715 (1930).

RADIOCHEMISTRY LABORATORY
DEPARTMENT OF CHEMISTRY
WASHINGTON UNIVERSITY
SAINT LOUIS, MISSOURI RECEIVED MAY 9, 1949

An Antistine Intermediate

BY ARTHUR J. TOMISEK[1]

This synthesis of (N-phenyl-N-benzylglycyl)-2′-aminoethylamide, $Ph(PhCH_2)NCH_2CONHCH_2CH_2NH_2$, represents an abandoned project in which it was desired to test a synthetic route leading to compounds of antistine-like structure.



Ethyl N-Benzyl-N-phenylglycinate.—Twenty-one and two-tenths grams (0.116 mole) of benzylaniline[2] and 6.42 ml. (0.058 mole) of ethyl bromoacetate in a stoppered flask were heated in a 45° oven for twenty hours. The pasty product was churned for two hours with 585 ml. of 0.3 *N* hydrochloric acid (0.174 mole) in order to extract unreacted benzylaniline. The viscous, semi-crystalline phase was crude ethyl N-benzyl-N-phenylglycinate hydrochloride. This was an unstable product, and was therefore dried in a desiccator and used directly in the next step.

(N-Phenyl-N-benzylglycyl)-2′-aminoethylamide.—The crude ethyl N-phenyl-N-benzylglycinate and 35 ml. of ethylenediamine (95–100%) were refluxed for five hours, cooled and poured into water. The oily phase was extracted with methylene chloride, washed with water and dried over sodium sulfate. Solvent was removed on a steam-bath and the residue was crystallized and recrystallized from anhydrous butanol–ethanol–hydrogen chloride. The white powder separated very slowly. It was characterized by the benzaldehyde odor and the intense red color which result from its contact with strong nitric

(1) Present address: Institute for Enzyme Research, University of Wisconsin, Madison, Wis.
(2) Willson and Wheeler, "Organic Syntheses," Coll. Vol. I, 102 (1941).

acid.[3,4] The yield of crude, pale blue dihydrochloride was 6.8 g. (33% based on ethyl bromoacetate). For purposes of analysis a sample was purified by chromatography of an absolute alcoholic solution over hydrochloric acid-washed alumina. Pure samples of the monohydrochloride were readily obtained by diluting the first few fractions with dry acetone, then adding dry ether to incipient turbidity. The white leaflets melted at 189° (microblock). *Anal.* Calcd. for $C_{17}H_{21}N_3O\cdot HCl$: C, 63.84; H, 6.93; N, 13.14; Cl, 11.09. Found: C, 63.68; H, 6.85; N, 13.13; Cl, 11.17.

(N-Phenyl-N-benzylglycyl)-2′-benzamidoethylamide.—This was prepared in excellent yield from the preceding compound by the Schotten–Baumann method and recrystallized from pyridine–water and from alcohol; m. p. 165–166° (microblock). *Anal.* Calcd. for $C_{24}H_{25}N_3O_2$: C, 74.40; H, 6.50; N, 10.85. Found: C, 74.36; H, 6.65; N, 10.64.

(3) The color test is negative for the ethyl phenylbenzylglycinate.

(4) Bischoff, *Ber.*, **31**, 2675 (1898), reports the benzaldehyde test as characteristic of N-phenyl-N-benzylglycine.

NUTRITION RESEARCH LABORATORIES
CHICAGO 30, ILL.

RECEIVED JUNE 13, 1949

NEW COMPOUNDS

Symmetrical Morpholinium and Thiamorpholinium Alkyl Sulfates[1]

The previously reported studies in "Symmetrical Morpholinium Alkyl Sulfates"[2] dealt with the reaction of dimethyl, diethyl, di-*n*-butyl, di-*n*-hexyl and di-*n*-hexadecyl sulfates with N-*n*-dodecyl, N-*n*-tetradecyl, N-*n*-hexadecyl and N-*n*-octadecyl morpholines. The purpose of the present communication is to report the extension of these reactions to include di-*n*-octyl, di-*n*-decyl and di-*n*-dodecyl sulfates and the reaction of di-*n*-hexadecyl sulfate with the corresponding previously described thiamorpholines, oxides and dioxides.[3]

TABLE I

SYMMETRICAL N,N-DIALKYL MORPHOLINIUM ALKYL SULFATES $O(CH_2CH_2)_2N(R)(R')^+SO_4R'^-$

R	R′	Formula	M. p., °C. (uncor.)	N analyses, % Calcd.	Found
n-Dodecyl	*n*-Octyl	$C_{32}H_{67}O_5NS$	112	2.43	2.46
n-Tetradecyl	*n*-Octyl	$C_{34}H_{71}O_5NS$	122	2.31	2.37
n-Hexadecyl	*n*-Octyl	$C_{36}H_{75}O_5NS$	132	2.21	2.27
Methyl	*n*-Decyl	$C_{25}H_{53}O_5NS$	99	2.92	2.99
n-Dodecyl	*n*-Decyl	$C_{36}H_{75}O_5NS$	81	2.21	2.26
n-Tetradecyl	*n*-Decyl	$C_{38}H_{79}O_5NS$	79	2.10	2.11
n-Hexadecyl	*n*-Decyl	$C_{40}H_{83}O_5NS$	82	2.03	2.03
Methyl	*n*-Dodecyl	$C_{29}H_{61}O_5NS$	87	2.60	2.57
n-Dodecyl	*n*-Dodecyl	$C_{40}H_{83}O_5NS$	53	2.03	2.06
n-Tetradecyl	*n*-Dodecyl	$C_{42}H_{87}O_5NS$	63	1.95	1.93
n-Hexadecyl	*n*-Dodecyl[a]	$C_{44}H_{91}O_5NS$	93	1.88	1.85
Methyl	*n*-Hexadecyl[b]	$C_{37}H_{77}O_5NS$	99.5	2.16	2.11

[a] Calculated: C, 70.81; H, 12.29. Found: C, 70.88; H, 12.08. [b] Calculated: C, 68.57; H, 11.97; S, 4.93. Found: C, 68.91; H, 11.63; S, 4.84.

(1) Abstracted in part from the thesis presented by C. T. Camilli to the Graduate School of St. John's University in partial fulfillment of the requirements for the degree of Master of Science, April, 1948.

(2) J. B. Niederl and co-workers, THIS JOURNAL, **70**, 618 (1948).

(3) W. F. Hart and J. B. Niederl, *ibid.*, **66**, 1610 (1944); **68**, 714 (1946).

Dialkyl sulfates were prepared by the method of Barkenbus and Owen.[4]

N-Alkyl thiamorpholines, oxides and dioxides were prepared by the methods previously described.[3]

TABLE II

SYMMETRICAL N,N-DIALKYL THIAMORPHOLINIUM ALKYL SULFATES

R	R′	Formula	M. p., °C. (uncor.)	N analyses, % Calcd.	Found
Thiamorpholium $S(CH_2CH_2)_2N(R)(R')^+SO_4R'^-$					
n-Dodecyl	*n*-Hexadecyl	$C_{48}H_{99}O_4NS_2$	160	1.71	1.70
n-Tetradecyl	*n*-Hexadecyl	$C_{50}H_{103}O_4NS_2$	127	1.65	1.59
n-Hexadecyl	*n*-Hexadecyl	$C_{52}H_{107}O_4NS_2$	84	1.60	1.63
n-Octadecyl	*n*-Hexadecyl[a]	$C_{54}H_{111}O_4NS_2$	86	1.55	1.57
Thiamorpholinium-1-oxide $OS(CH_2CH_2)_2N(R)(R')^+SO_4R'^-$					
n-Dodecyl	*n*-Hexadecyl	$C_{48}H_{99}O_5NS_2$	124	1.67	1.71
n-Tetradecyl	*n*-Hexadecyl	$C_{50}H_{103}O_5NS_2$	121	1.62	1.64
n-Hexadecyl	*n*-Hexadecyl	$C_{52}H_{107}O_5NS_2$	126	1.57	1.60
n-Octadecyl	*n*-Hexadecyl[b]	$C_{54}H_{111}O_5NS_2$	92	1.52	1.54
Thiamorpholinium-1-dioxide $O_2S(CH_2CH_2)_2N(R)(R')^+SO_4R'^-$					
n-Dodecyl	*n*-Hexadecyl	$C_{48}H_{99}O_6NS_2$	71	1.64	1.68
n-Tetradecyl	*n*-Hexadecyl	$C_{50}H_{103}O_6NS_2$	78	1.60	1.61
n-Hexadecyl	*n*-Hexadecyl	$C_{52}H_{107}O_6NS_2$	117	1.54	1.55
n-Octadecyl	*n*-Hexadecyl[c]	$C_{54}H_{111}O_6NS_2$	116	1.49	1.48

[a] Calculated: C, 71.85; H, 12.39. Found: C, 71.65; H, 12.33. [b] Calculated: C, 70.60; H, 12.18. Found: C, 70.42; H, 12.07. [c] Calculated: C, 69.39; H, 11.97. Found: C, 69.45; H, 11.74.

N,N-Dialkylmorpholinium alkyl sulfates were obtained by the reaction of equimolecular quantities (approximately 0.003 mole) of the N-alkylmorpholine and the appropriate dialkyl sulfate in a tightly stoppered Pyrex test-tube. The reaction mixture was heated to 115° (external temperature) by means of an oil-bath, held at this temperature for six hours and then allowed to remain at room temperature overnight. The reactions employing di-*n*-dodecyl and di-*n*-hexadecyl sulfates were heated at 150° for five hours. The resultant products were washed with 3 cc. of ether at 33°, cooled and centrifuged. The ether layer containing the more soluble unreacted starting materials was decanted. The washed products were crystallized three times from ethyl acetate and dried on a porous tile. Yields by this method varied from 25 to 47%, in most cases from 40 to 45%.

It was found that carrying out the reaction by refluxing the reactants in toluene for eight hours gave somewhat lower yields.

N,N-Dialkylthiamorpholinium Alkyl Sulfates.—Equimolecular quantities (approximately 0.003 mole) of the N-alkylthiamorpholine, oxide or dioxide and di-*n*-hexadecyl sulfate were added to 5 cc. of toluene which had been dried over sodium. The solution was refluxed for four hours, using an oil-bath, with an external temperature of 160–170°. Lower temperatures were found to give incomplete reaction. The toluene was distilled off *in vacuo* a little alcohol was added and distilled *in vacuo* to remove the last traces of toluene. The residue was taken up in ethyl acetate and crystallized from this solvent. In cases where decolorization was necessary, this was done with Darco in alcohol solution. The compounds were recrystallized three times from ethyl acetate or from ethyl acetate containing a little ethyl alcohol.

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CONCETTO F. CAMILLI

RECEIVED JUNE 14, 1949[5]

(4) Barkenbus and Owen, *ibid.*, **56**, 1204 (1934).

(5) Original manuscript received January 17, 1949.

Some New Chalcones[1]

In connection with the study of the antifungal activity of organic compounds, we have prepared fourteen new chalcones. Except as noted, these were made by the condensation of substituted benzaldehydes and acetophenones at 0–10° in ethanol–water mixture using sodium hydroxide as a catalyst,[2] the duration of the reaction being about eighteen hours.

CHALCONES

Substituents	M. p., °C.[a]	Formula	Analyses,[b] % Calculated C	Calculated H	Found C	Found H
2,3-Dimethoxy[c]	.....[d]	$C_{17}H_{16}O_3$	76.10	6.01	75.95	5.59
2,4'-Dichloro[e]	82–83	$C_{15}H_{10}OCl_2$	65.00	3.64	64.83	3.74
3,4-Diethoxy	128	$C_{19}H_{20}O_3$	77.00	6.80	76.64	6.55
3,4-Dichloro	112–113[f]	$C_{15}H_{10}OCl_2$	65.00	3.64	64.64	3.58
4-Methoxy-2'-chloro	80–81	$C_{16}H_{13}O_2Cl$	70.46	4.80	70.37	4.72
4-Isopropyl-4'-methoxy	69–70[g]	$C_{19}H_{20}O_2$	81.40	7.19	81.08	7.35
2,4,2'-Trichloro[e]	109–110	$C_{15}H_9OCl_3$	75.82	2.91	57.90	3.06
2,4-Dichloro-4'-methoxy	134	$C_{16}H_{12}O_2Cl_2$	62.56	3.94	62.61	4.18
3,4'-Dimethoxy-4-hydroxy[h]	158–159[i]	$C_{17}H_{16}O_4$	71.81	5.67	71.81	5.79
3-Methoxy-4-hydroxy-4'-chloro	101[i]	$C_{16}H_{13}O_3Cl$	66.56	4.54	66.56	4.46
3,4-Diethoxy-4'-methoxy-[j]	72–74[k]	$C_{20}H_{22}O_4$	73.60	6.80	73.35	6.83
3,4-Diethoxy-4'-methyl	96	$C_{20}H_{22}O_3$	77.39	7.15	77.65	7.29
3,4-Methylenedioxy-2'-chloro	97–98[k]	$C_{16}H_{11}O_3Cl$	67.02	3.87	67.20	4.09
3,4-Methylenedioxy-2'-hydroxy-5'-chloro	145–146[l]	$C_{16}H_{11}O_4Cl$	63.48	3.66	63.35[m]	3.70

[a] Except as noted, all compounds were crystallized from ethanol. [b] Except as noted, all analyses are by the Clark Microanalytical Laboratory. [c] Chemical Abstracts numbering. [d] Yellow liquid, b. p. 198–199° (2 mm.). [e] Reaction time four hours. [f] Recrystallized from acetone–ethanol. [g] Recrystallized from ethanol–benzene. [h] Reaction time three hours. [i] Reaction temperature 20–30°. [j] Reaction time two weeks. [k] Recrystallized from methanol. [l] Reaction temperature 30–40°. [m] Analysis by Micro-Tech Laboratories.

The results of the biological tests will be reported elsewhere.

(1) This paper consists of a report of work done under contract with the Medical Division, Chemical Corps, U. S. Army.

(2) *Cf.* "Organic Syntheses," John Wiley & Sons, Inc., New York, N. Y., Coll. Vol. I, p. 78.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA
CHARLES K. BRADSHER
FRANCES C. BROWN
WILLIS B. BLUE

RECEIVED JUNE 2, 1949

Mercaptomethylthiazole Derivatives

2-Methyl-4-mercaptomethylthiazole.—In a 250-ml. three-neck flask fitted with a sealed stirrer, reflux condenser and drying tube, and dropping funnel was placed 16 g. (0.11 mole) of 2-methyl-4-chloromethylthiazole,[1] 10.5 g. (0.14 mole) of thiourea and 32 ml. of anhydrous ethanol. The solution was refluxed with stirring for two hours, cooled, treated with a solution of 8 g. (0.2 mole) of sodium hydroxide in 75 ml. of water and refluxed for an additional hour. To the cooled mixture was added enough 10% hydrochloric acid to show slight acidity to litmus and then 10% sodium carbonate solution to slight basicity. The mixture was extracted four times with 100 ml. of ether, and the solvent phase was dried with anhydrous calcium sulfate. The desiccant was removed by filtration, the volatiles removed from the filtrate by distillation, finally at reduced pressure and the residue distilled at 89–91° (3 mm.) to give 10.3 g. (64% yield) of a colorless oil.

Anal.[2] Calcd. for $C_5H_7NS_2$: N, 9.64. Found: N, 9.34.

2-Methyl-4-benzylthiomethylthiazole.—In a 250-ml. three-neck flask fitted with a sealed stirrer, reflux condenser and drying tube, dropping funnel and thermometer, was placed 4.6 g. (0.08 mole) of potassium hydroxide and 100 ml. of anhydrous ethanol. Stirring and refluxing was initiated and continued until solution was complete, after which time the heater was replaced by an ice-bath until the temperature dropped to 5°, when 8.7 g. (0.07 mole) of benzyl mercaptan in 20 ml. of absolute ethanol was added dropwise (fifteen minutes) at that temperature. At the end of that time, 10 g. (0.07 mole) of freshly prepared 2-methyl-4-chloromethylthiazole in 20 ml. of ethanol was added during ten minutes, causing an immediate precipitation of potassium chloride. The mixture was stirred and refluxed for one hour, cooled, diluted with 700 ml. of water and extracted four times with 200 ml. of ether. The ethereal solution was washed with a total of 200 ml. of water and then dried with calcium sulfate. After separation of the desiccant, the solvent was removed by distillation and the residue distilled at 131–135° (0.75 mm.) to give 12.1 g. (75% yield) of a colorless oil.

Anal. Calcd. for $C_{12}H_{13}NS_2$: N, 5.86. Found: N, 5.35.

(1) Hooper and Johnson, THIS JOURNAL, **56**, 470 (1934).

(2) Analyses by Mr. H. Soloway of this Laboratory.

RESEARCH LABORATORIES
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RECEIVED MAY 26, 1949

(3) Present address: Oxford Products, Inc., Cleveland, Ohio.

Thiol Esters

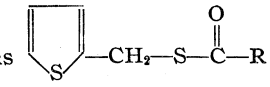
During work on compounds containing the thiophene-2-methyl group, it became desirable to prepare a series of thiol esters derived from thiophene-2-methyl mercaptan.[1] It was found that the mercaptan reacted in the usual manner with acyl halides and with acid anhydrides to give the desired esters in acceptable yields. The new products and their properties are tabulated in Table I.

Experimental

All of the compounds were prepared by the interaction of molar quantities of the appropriate acyl halide or anhydride with the mercaptan in excess pyridine, and worked up in the usual manner.

(1) Prepared *via* the isothiouronium salt from thienyl chloride.

TABLE I

THIOPHENE-2-METHYL THIOL ESTERS 

R	B. p.,[a] °C.	Mm.	Yield, %	Formula	Analyses,[b] % Calculated C	Calculated H	Found C	Found H
CH_3	56–60	2	80	$C_7H_8OS_2$	48.80	4.68	49.06	4.92
C_2H_5	79–83	2	53	$C_8H_{10}OS_2$	51.58	5.41	51.68	5.74
C_6H_5	155	2.5	81	$C_{12}H_{10}OS_2$	61.50	4.30	62.17	4.50
C_4H_3O (furyl)	[c]		78.5	$C_{10}H_8O_2S_2$	53.55	3.59	52.93	3.91

[a] Boiling points are uncorrected. [b] Analyses by Oakwold Laboratories, Alexandria, Virginia. [c] M. p. 55°, recrystallized from aqueous methanol.

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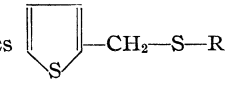
2-Thenyl Sulfides

During work on compounds containing the 2-thenyl grouping, it became desirable to prepare a series of sulfides bearing that loading. Certain of these compounds were obtained in good yields from the interaction of 2-thenyl chloride and the appropriate potassium mercaptide, while 2-(2′-thenylmercapto)-ethyl cyanide and the corresponding mercaptopropionic ester were synthesized by the addition of 2-thenyl mercaptan to the respective acylic compounds in the presence of a trace of alkaline catalyst.[1] The new compounds are listed in Table I.

TABLE I

2-THENYL SULFIDES 

R	Yield, %	B. p., °C.[a]	Mm.	Formula	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Calcd.	Sulfur Found
C_2H_5–	76	66–69	3	$C_7H_{10}S_2$	53.12	53.35	6.37	6.71	40.52	39.75
i-C_4H_9–	70	89–91	3.5	$C_9H_{14}S_2$	58.01	57.43	7.57	7.59	34.41	34.92
n-C_6H_{13}–	65.5	106–109	2	$C_{11}H_{18}S_2$	61.62	61.09	8.46	8.17	29.91	30.19
$C_6H_5CH_2$–	79.5	120–121	1.5	$C_{12}H_{12}S_2$	65.41	65.34	5.49	5.70	29.10	29.21
$C_4H_3SCH_2$–[c]	78	129–131	1.5	$C_{10}H_{10}S_3$	53.06	52.91	4.45	4.49	42.49	42.98
C_2H_5OCO–$(CH_2)_2$–	40	126	1	$C_9H_{12}O_2S_2$					29.64	29.79
NC–$(CH_2)_2$–	47	127–130	2.5	$C_8H_9NS_2$					34.99	34.27

[a] Boiling points are uncorrected. [b] Analyses by Oakwold Laboratories, Alexandria, Virginia. [c] Thiophene-2-methyl.

***i*-Butyl-2-thenyl Sulfide.**—In a 250-ml. 3-neck flask fitted with a sealed Hershberg stirrer, reflux condenser, thermometer and dropping funnel, was dissolved 6.6 g. (0.1 mole) of 85% potassium hydroxide in 100 ml. of absolute ethanol with stirring and heating. After solution was complete, the temperature was allowed to drop to about 25° and 10 g. (0.11 mole) of *i*-butyl mercaptan was added from the dropping funnel during ten minutes, the temperature being maintained constant. At the end of this time, 13.2 g. (0.1 mole) of 2-thenyl chloride[2] was added dropwise at the same temperature (fifteen minutes). The precipitation of potassium chloride began almost immediately, and the mixture was stirred and refluxed for three hours, after which time further heating did not increase the yield. The cooled mixture was poured into 900 ml. of water, causing separation of an oil which was removed by extraction with a total of 400 ml. of ether. The solvent layer was dried with calcium sulfate, filtered from the desiccant, stripped (finally at reduced pressure) and then fractionated through a 30-cm. Vigreux column to give 13 g. (70% yield) of a colorless oil boiling at 89–91° (3.5 mm.).

2-(2′-Thenylmercapto)-ethyl Cyanide.—In a 250-ml. 3-neck flask fitted as above was placed 26 g. (0.2 mole) of 2-thenyl mercaptan,[3] 0.05 g. (0.0022 mole) of sodium and 100 ml. of anhydrous benzene. The mixture was stirred and refluxed until the sodium had reacted completely. The mixture was cooled to 5° and 11.1 g. (0.21 mole) of freshly distilled acrylonitrile in 50 ml. of benzene was added dropwise during five minutes, the temperature rising to 40°.[4] The solution was refluxed for one hour, cooled, acidified with glacial acetic acid and the volatiles removed from the steam-bath at reduced pressure. The residue was fractionated at 127–130° (2.5 mm.) to give 17.3 g. (47% yield) of a colorless oil.

The thenylmercaptopropionic ester was prepared in a similar manner using methyl acrylate instead of acrylonitrile.

RESEARCH LABORATORIES
AMERICAN HOME FOODS, INC.
MORRIS PLAINS, NEW JERSEY
FRANK KIPNIS[5]
JOHN ORNFELT

RECEIVED MAY 26, 1949

(1) Rapoport, Smith and Newman, THIS JOURNAL, **69**, 693 (1947); Gershbein and Hurd, *ibid.*, **69**, 241 (1947); Hurd and Gershbein, *ibid.*, **69**, 2328 (1947).

(2) Blicke and Leonard, *ibid.*, **68**, 1934 (1946).

(3) From 2-thenyl chloride and thiourea, followed by treatment of the isothiouronium salt with alkali.

(4) The reaction could be performed in the absence of solvent, but it proceeded with almost explosive violence.

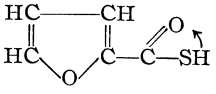
(5) Present address: Oxford Products, Inc., Cleveland, Ohio.

Thiofuroic Acid

Sixteen and four-tenths grams of furoyl chloride was added with agitation to 75 ml. of 10% aqueous sodium hydrosulfide. The reaction proceeded smoothly in the cold (4°). The reaction mixture was acidified to liberate the thioacid and then extracted with ether. The ether solution was dried with anhydrous sodium sulfate and the solvent

removed by distillation. Vacuum distillation of the residue yielded 10.4 g. of a yellow oil boiling 101–103° at 16 mm. *Anal.* Calcd. for $C_5H_4O_2S$: C, 46.9; H, 3.1; S, 25.4. Found: C, 46.5; H, 3.1; S, 23.9. This oil upon hydrolysis with dilute alkali yielded furoic acid and hydrogen sulfide.

Some of the physical and chemical characteristics of this compound are as follows: m. p. −9°; $n^{24}D$ 1.589; it has a disagreeable sulfide-like odor; it is heavier than and insoluble in water, miscible with alcohol and ether; its sodium salt is yellow and water soluble; it gives a green-yellow precipitate with dilute copper sulfate solution and no color reaction with sodium nitroprusside. Earlier attempts to distil the compound at atmospheric pressure were unsuccessful. On standing, the thioacid gives rise to colorless needles m. p. 107–108° which have been identified as difuroyl disulfide (see below). The following structure seems indicated for thiofuroic acid.



A by-product was isolated from the distillation residue, as colorless needles, m. p. 107–108°, by recrystallization from an acetone–water mixture. Hydrolysis of this compound with dilute alkali yielded furoic acid and hydrogen sulfide. A mixed melting point with difuroyl disulfide prepared by Frank, *et al.*,[1] showed no depression (106–108°). *Anal.* Calcd. for $C_{10}H_6O_4S_2$: C, 47.2; H, 2.4; S, 25.2. Found: C, 47.1; H, 2.8; S, 25.6.

The disulfide has a disagreeable odor resembling that of biphenyl. It is insoluble in water and dilute alkali, soluble in alcohol and ether.

The reaction, used in these experiments to synthesize thiofuroic acid, appears to be virtually quantitative when the yield of disulfide is also considered.

The author is indebted to A. P. Dunlop of the Quaker Oats Co. for helpful suggestions concerning this research.

(1) R. L. Frank, J. R. Blegen and Deutschman, *J. Polymer Sci.*, **3** [1], 58-65 (1948).

DEPARTMENT OF DAIRY HUSBANDRY
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNSYLVANIA S. PATTON

RECEIVED JUNE 13, 1949

Alkyl Quinolyl Sulfides

The formation of the hydrochlorides of several aromatic quinolyl sulfides[1] took place readily when 4-chloroquinoline was refluxed with the mercaptan in a solvent such as chloroform. However, when certain aliphatic sulfides of quinoline were desired, reaction failed to take place even at a higher reflux temperature. Alkyl quinoline sulfides were prepared from 2- and 4-chloroquinolines by refluxing with the mercaptan in alcohol in the presence of sodium ethylate, as reported by Clinton and Suter,[2] and as described by Hannan, *et al.*[3]

6-Methoxy-4-*n*-butylthio-2-methylquinoline.—A 0.05-mole run was refluxed in 8 volumes of absolute ethanol for six hours. Sodium chloride separated in the theoretical yield and alcohol was removed under reduced pressure. A chloroform solution of the crude product was washed with normal sodium hydroxide. The oily solid recovered from chloroform was suspended in hexane, filtered, and crystallized from 1.5 volumes of ligroin (90–100°); yield, about 50% of theory. Three crystallizations from ligroin gave a colorless solid melting at 67.3–68°. This sulfide was slightly soluble in pentane and readily soluble in benzene, acetone, methanol and ethanol. *Anal.* Calcd. for $C_{15}H_{19}ONS$: N, 5.36; S, 12.26. Found: N, 5.34; S, 12.33.

6-Methoxy-4-*n*-tetradecylthio-2-methylquinoline.—The alcoholic solution of sodium ethylate, tetradecylthiol[4] (myristyl mercaptan) and 6-methoxy-4-chloro-2-methylquinoline was refluxed for fifteen hours. After treatment with chloroform and alkali, the colorless sulfide was crystallized from 1.2 and from 6 volumes of acetone, m. p. 64–64.5°. Little loss occurred in recrystallizing this product from 10 volumes of methanol; the sulfide is fairly soluble in benzene. *Anal.* Calcd. for $C_{25}H_{39}ONS$: N, 3.49; S, 7.98. Found: N, 3.40; S, 8.16.

(1) Renfrew, THIS JOURNAL, **68**, 1433 (1946).
(2) Clinton and Suter, *ibid.*, **70**, 491 (1948).
(3) Hannan, *et al.*, *ibid.*, **71**, Nov. (1949).

(4) We are indebted to Dr. B. J. Humphrey of the Connecticut Hard Rubber Company of New Haven Connecticut, for the tetradecylthiol.

DEPARTMENT OF RESEARCH IN
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RECEIVED JULY 5, 1949

4-Chloro-4′-*t*-butylbenzophenone and 4-Chloro-4′-*t*-butyldiphenylmethane

4-Chloro-4′-*t*-butyl-benzophenone.—A mixture of 20.4 g. of *t*-butylbenzene, 29.1 g. of *p*-chlorobenzoyl chloride and 115 ml. of anhydrous nitrobenzene was cooled to about 5°. The mixture was stirred and 22.3 g. of powdered aluminum chloride was added slowly. After all the aluminum chloride had been added, the ice-bath was removed and the mixture was stirred overnight at room temperature. The mixture was now cooled to about 5° and small pieces of ice were dropped in. The decomposition was completed with concentrated sulfuric acid. The nitrobenzene was removed by steam distillation and the residue was taken up in ether, washed with water and dried over "Drierite." When the ether was distilled off, the residue crystallized. Recrystallization from 95% ethanol gave white crystals, m. p. 79–81°; yield 34 g. (82%).

Anal. Calcd. for $C_{17}H_{17}OCl$: C, 74.85; H, 6.28; Cl, 13.00. Found: C, 75.11; H, 6.40; Cl, 13.41.

4-Chloro-4′-*t*-butyldiphenylmethane.—A mixture of 50 g. of the above ketone, 50 g. of 47% hydriodic acid and 50 g. of red phosphorus was refluxed for forty hours with mechanical stirring. The mixture was cooled and made basic with 10% sodium hydroxide solution. The mixture was then extracted with ether, the red phosphorus was filtered off, and the ethereal solution was washed with 10% sodium hydroxide solution and then with water. Finally the ethereal solution was dried over "Drierite" and concentrated. The residue was fractionated under reduced pressure. The entire residue distilled at 176–177° (5 mm.), yield 39.5 g. (84%).

Anal. Calcd. for $C_{17}H_{19}Cl$: C, 78.90; H, 7.40. Found: C, 79.05; H, 7.45.

DEPARTMENT OF CHEMISTRY
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DEPARTMENT OF CHEMISTRY
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DURHAM, NORTH CAROLINA CHARLES K. BRADSHER

RECEIVED JULY 2, 1949

COMMUNICATIONS TO THE EDITOR

THE SOLUBILITY OF HYDROGEN CHLORIDE AT LOW TEMPERATURES—A MEASURE OF THE BASIC PROPERTIES OF AROMATIC NUCLEI

Sir:

There is now considerable evidence that aromatic nuclei possess basic properties. Klatt[1] observed that aromatic compounds dissolve in liquid hydrogen fluoride, whereas saturated hydrocarbons do not. Winstein and Lucas[2] and, more recently, Keefer and Andrews[3] attribute complex formation between silver ion and aromatic hydrocarbons to the basic properties of the aromatic nuclei. Fairbrother[4] correlated changes in the apparent dipole moments of iodine in several hydrocarbon solvents with changes in the probable donor character of the π electrons in the hydrocarbon. Finally, the absorption spectra of solutions of iodine in aromatic hydrocarbons show changes which can also be correlated with the basic properties of the solvent.[5]

In the course of studies of the action of the catalyst couple, aluminum chloride–hydrogen chloride, on aromatic hydrocarbons at low temperatures, we have observed that the solubility of hydrogen chloride varies considerably with different aromatic hydrocarbons. The variation in solubility cannot be correlated with any of the usual physical properties of the solvent, but it can be correlated with the predicted variation in the basic properties of the compounds.

In order to investigate this phenomenon more carefully, we developed a method for measuring Henry's law constant with a precision of approximately 1 part in 500. Toluene is used as solvent. A solution of 10 moles of toluene and 1 mole of aromatic hydrocarbon is prepared. The solution is maintained at $-78.51°$ and small quantities of hydrogen chloride are introduced. Henry's law is followed over a wide range of concentration. From the observed pressures, the constant is calculated from the usual expression, $p = kx$, where p is the pressure of hydrogen chloride, x is its mole fraction and k is the desired constant.

The following values for k (in mm.) have been obtained: (1) trifluoromethylbenzene, 332; (2) chlorobenzene, 318; (3) benzene, 308; (4) toluene, 299; (5) *p*-xylene, 294; (6) *o*-xylene, 286; (7) *m*-xylene, 278; (8) pseudocumene, 272; (9) hemimellitene, 265; (10) mesitylene, 254.

It is apparent that the order of increasing solubility is identical with the order of increasing reactivity toward the usual electrophilic substituting agents. Therefore, Henry's law constant may be taken as a measure of the relative basicity of the ring. It is particularly interesting that the method is sufficiently sensitive to differentiate between the isomeric xylenes and trimethylbenzenes.

We are now applying the procedure to other benzenoid derivatives, polynuclear hydrocarbons, heterocyclics and olefins. The data should be useful in giving a quantitative measure of the effect of structure on the relative basicities of these compounds.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

HERBERT C. BROWN
JAMES BRADY

RECEIVED JULY 28, 1949

(1) Klatt, *Z. anorg. allgem. Chem.*, **234**, 189 (1937); Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 293–294.

(2) Winstein and Lucas, THIS JOURNAL, **60**, 836 (1938).

(3) Abstracts of Papers Presented to the Division of Organic Chemistry at the 115th Meeting of the American Chemical Society, San Francisco, 1949, p. 47.

(4) Fairbrother, *J. Chem. Soc.*, 1051 (1948).

(5) Benesi and Hildebrand, THIS JOURNAL, **70**, 2832 (1948); **71**, 2703 (1949).

PROPARGYLGLYCINE: AN ACETYLENIC AMINO ACID ANTAGONIST[1,2]

Sir:

As part of a research program designed to get information concerning the basis for the preparation of specific metabolite antagonists, we prepared and studied the vinylene-type unsaturated amino acids, allylglycine, methallylglycine, crotylglycine and 2-amino-5-heptenoic acid.[3] Since allylglycine was a potent inhibitor of the growth of bacteria and yeast, we deemed it desirable to prepare the corresponding acetylenic amino acid, propargylglycine. In this communication we wish to report the synthesis and preliminary microbial-growth inhibitory properties of propargylglycine.

Diethyl Propargylformamidomalonate.—To a solution containing 0.92 g. (0.04 g. atom) of sodium dissolved in 75 ml. of absolute alcohol was added 8.12 g. (0.04 mole) of diethyl formamidomalonate.[4] Five grams (0.042 mole) of propargyl bromide[5] in 20 ml. of ethanol was added and refluxed for eighteen hours. After concentration to dryness, the residue was taken up in a mixture of chloroform and water. The residue from the chloroform was recrystallized from water. The diethyl propargylformamidomalonate melted at 69–70°, and the yield was 90%. An analytical sample was obtained from di-*n*-butyl ether, m. p. 71–72°.

Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.22; N, 5.81. Found: C, 54.85; H, 6.34; N, 5.59.

(1) This work was supported in part by a research contract with the Office of Naval Research.

(2) The authors gratefully acknowledge the technical assistance of Mrs. Ann E. Johnson and Mr. Robert P. Martin.

(3) (a) Dittmer, Goering, Goodman and Cristol, THIS JOURNAL, **70**, 2499 (1948); (b) Goering, Cristol and Dittmer, *ibid.*, **70**, 3310, 3314 (1948).

(4) A. Galat, *ibid.*, **69**, 965 (1947).

(5) A. Kirrmann, *Bull. soc. chim.*, IV, **39**, 698 (1926).

Propargylglycine.—The diethyl propargylformamidomalonate was hydrolyzed by refluxing 2.4 g. (0.01 mole) of the ester with 24 ml. of 8% sodium hydroxide for four hours. The mixture was diluted to 100 ml. with water and passed through a column of Duolite C-10H which removed all the base. The effluent was subsequently passed through a column of Duolite A-2 which removed the formic acid produced. The resulting solution was concentrated *in vacuo*, decolorized with Darco G-60, and on addition of acetone, the amino acid crystallized. The yield was 88.5%. An analytical sample of propargylglycine was obtained from water and acetone, m. p. 243° with decomposition.

Anal. Calcd. for $C_5H_7O_2N$: C, 53.09; H, 6.24; N, 12.39. Found: C, 53.24; H, 6.20; N, 12.47.

Norvaline.—Hydrogenation of 113 mg. (0.001 mole) of propargylglycine in the presence of Adams catalyst, at 28° and 1 atmosphere, required 0.00207 mole (104% of theoretical) of hydrogen and produced 100 mg. of norvaline, which melted with decomposition at 297° in a sealed tube; the benzoyl derivative prepared as above, m. p. 150–151°.

Microbiological Tests.—Propargylglycine was tested as an inhibitor of the growth of *Escherichia coli*, strain 9723 and *Saccharomyces cerevisiae*, strain 139.[6] To inhibit the growth of these microörganisms, to 50% of normal growth, required 4 micrograms per 7.5 ml. of medium for *S. cerevisiae* and 65 micrograms for *E. coli*. According to these data propargylglycine is more active than allylglycine for yeast but less active for the inhibition of *E. coli*.

(6) The methods employed and the test organisms were the same as those previously described.[3a]

DEPARTMENT OF CHEMISTRY
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HERMAN GERSHON
JOHN S. MEEK
KARL DITTMER

RECEIVED AUGUST 5, 1949

N^{10}-NITROSOPTEROYLGLUTAMIC ACID

Sir:

The action of nitrous acid upon 2-aminopteridines has led to destruction of the ring system,[1] desamination in the 2-position,[2] and simultaneous desamination of the 2-position and nitrosation on the nitrogen atom in the 10-position of pteroic acid.[3] "Folic acid" concentrates from natural sources[4] were inactivated by nitrous acid under the conditions of the Van Slyke determination.[5] These experiments involved the use of excess nitrous acid and temperatures ranging from "room temperature" to 100° or higher.

We wish to report that pteroylglutamic acid in cold hydrochloric acid solution reacts quantitatively with one mole of nitrous acid to form N^{10}-nitrosopteroylglutamic acid, which precipitates from the reaction mixture as a white solid.

N^{10}-Nitrosopteroylglutamic acid gives a positive Liebermann nitroso reaction. The nitroso group can be removed by treatment with phenol and hydrochloric acid, and pteroylglutamic acid thus regenerated.

Under substantially the same conditions, the following give N^{10}-nitroso compounds: pteroyl-α-glutamylglutamic acid[6]; pteroyl-γ-glutamyl-γ-glutamylglutamic acid,[7] 9-methylpteroylglutamic acid,[8] 4-aminopteroylglutamic acid,[9] 2-dimethylaminopteroylglutamic acid,[10] and 4-(1-piperidyl)-pteroylglutamic acid.[10]

Neither 2-amino-4-hydroxy-6-methylpteridine,[11] 2,4-diamino-6-methylpteridine,[9b] nor N^{10}-methylpteroylglutamic acid[12] react appreciably with nitrous acid under these conditions.

In a typical experiment, 4.4 g. of pteroylglutamic acid (90% purity,[13] 0.5% *p*-aminobenzoylglutamic acid, 8% H_2O) was dissolved in 50 ml. of concentrated hydrochloric acid, and cooled to 5–10° by the addition of ice. Then 0.7 g. of sodium nitrite dissolved in a little water was added slowly. A white precipitate formed, which was filtered, washed, and dried to give 3.2 g. of N^{10}-nitrosopteroylglutamic acid. One gram of this dissolved in 25 ml. of 5 *N* sodium hydroxide was clarified with activated charcoal. On standing the sodium salt crystallized. It was collected, dissolved in water and precipitated with acid, filtered, washed, and dried two hours at 100° (2 mm.). *Anal.* Calcd. for $C_{19}H_{18}N_8O_7$: C, 48.5; H, 3.83; N, 23.8. Found: C, 48.9; H, 4.77; N, 24.05 (corrected for 3.8% ash).

Through the courtesy of our colleagues, Dr. B. L. Hutchings, and Dr. J. J. Oleson, of the Lederle Laboratories Division, American Cyanamid Company, N^{10}-nitrosopteroylglutamic acid has been tested in a preliminary way in the nutrition of *S. faecalis* R and the chick, and in both cases appears to be equivalent to pteroylglutamic acid.

(1) Schopf and Kottler, *Ann.*, **539**, 134 (1939).
(2) Wieland, *et al.*, *ibid.*, **507**, 245 (1933); Wittle, *et al.*, THIS JOURNAL, **69**, 1780 (1947); Taylor and Cain, *ibid.*, **71**, 2538 (1949).
(3) Wolf, *et al.*, *ibid.*, **69**, 2758 (1947).
(4) Mitchell and Williams, *ibid.*, **66**, 272 (1944).
(5) Van Slyke, *J. Biol. Chem.*, **16**, 121 (1913).
(6) Mowat, *et al.*, THIS JOURNAL, **70**, 1096 (1948).
(7) Boothe, *et al.*, *ibid.*, **70** 1099 (1948).
(8) Hultquist, *et al.*, *ibid.*, **71**, 619 (1949).
(9) (a) Seeger, Smith and Hultquist, *ibid.*, **69**, 2567 (1947) (b) Seeger, *et al.*, *ibid.*, **71**, 1753 (1949).
(10) Roth, Smith and Hultquist, in press.
(11) Mowat, *et al.*, THIS JOURNAL, **70**, 17 (1948).
(12) Cosulich and Smith, *ibid.*, **70**, 1922 (1948).
(13) Hutchings, *et al.*, *J. Biol. Chem.*, **168**, 705 (1947).

CALCO CHEMICAL DIVISION
AMERICAN CYANAMID COMPANY
BOUND BROOK, NEW JERSEY
DONNA B. COSULICH
JAMES M. SMITH, JR.

RECEIVED AUG. 15, 1949

STEROLS. VIII.[1] 17α-HYDROXYPROGESTERONE AND 17α-HYDROXY-11-DESOXYCORTICOSTERONE

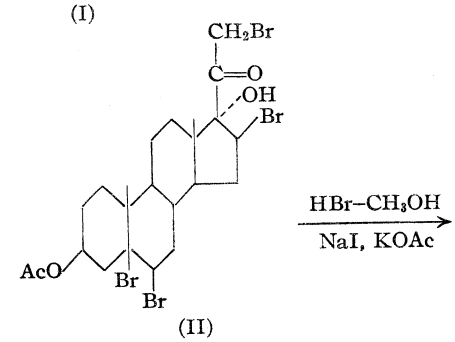
Sir:

Recently we reported[1] the facile preparation of 16,17-oxidoprogesterone from 16,17-oxido-5-pregnene-3β-ol-20-one acetate (I). We now wish to record the use of I as an intermediate for a new and very simple partial synthesis of both 17α-hydroxyprogesterone and 17α-hydroxy-11-desoxycorticosterone acetate (V) (acetate of Reichstein's Compound S). The reactions as applied to the latter are schematically presented by formulas I → V. A treatment of 16,17-oxidoprogesterone

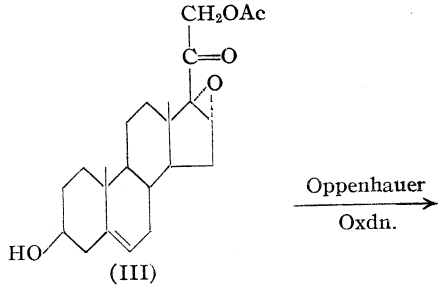
(1) For paper VII in this series see THIS JOURNAL, **71**, 756 (1949)

similar to that given IV produced 17α-hydroxyprogesterone.

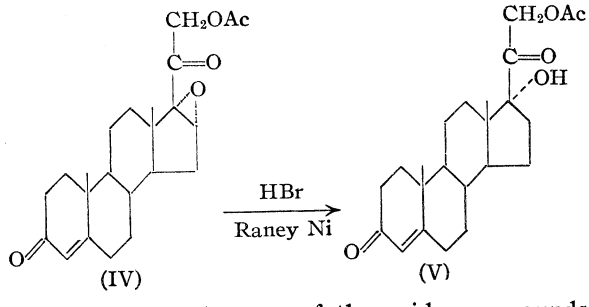
16,17-Oxido-5-pregnene-3β-ol-20-one acetate (I) (I) —Br_2, HBr / Br_2→



(II) —HBr–CH_3OH / NaI, KOAc→



(III) —Oppenhauer Oxdn.→



(IV) —HBr / Raney Ni→ (V)

The smooth cleavage of the oxido compounds by hydrogen bromide, the clean reductive removal of bromine from the resulting bromohydrins by Raney nickel, and the good yields encountered at every step make these hitherto difficultly accessible cortical hormones readily available.

16,17-Oxido-5-pregnene-3β,21-diol-20-one 21-Acetate (III).—From 16,17-oxido-5-pregnene-3β-ol-20-one acetate by treating first with one molar equivalent of bromine in acetic acid–carbon tetrachloride, then with hydrogen bromide in acetic acid followed by a second molar equivalent of bromine. Then hydrolysis with hydrogen bromide in methanol–benzene, treatment with sodium iodide in benzene–ethanol and finally with potassium acetate in acetone gave needles from acetone–petroleum ether, m. p. 190–192°; $[\alpha]^{24}D$ +15° (chloroform). *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 70.86; H, 8.33.

16,17-Oxido-4-pregnene-21-ol-3,20-dione Acetate (IV).—By the Oppenauer oxidation of III; prisms from ether–petroleum ether, m. p. 170–172°; $[\alpha]^{25}D$ +167° (chloroform). *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.82; H, 8.23.

17α-Hydroxy-11-desoxycorticosterone Acetate (V).—From IV with hydrogen bromide in acetic acid, followed by reduction with Raney nickel in ethanol; needles from methanol, m. p. 235–238° (sinters 230°), no depression with material isolated from a natural source[2]; $[\alpha]^{24}D$ +114° (acetone). *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 70.94; H, 8.28.

(2) We are indebted to Dr. Marvin H. Kuizenga of The Upjohn Laboratories for a sample of this material.

THE GLIDDEN COMPANY
RESEARCH LABORATORIES
SOYA PRODUCTS DIVISION
CHICAGO 39, ILLINOIS

PERCY L. JULIAN
EDWIN W. MEYER
WILLIAM J. KARPEL
ISABELLE RYDEN

RECEIVED AUGUST 22, 1949

ELECTRON DEFICIENT COMPOUNDS. IV. THE STRUCTURE OF HEXAMETHYLDIPLATINUM

Sir:

The reaction $(CH_3)_3PtI + K$ was presumed to yield $(CH_3)_3Pt—Pt(CH_3)_3$.[1] A recent explanation of electron deficient bonding[2] suggests that since Pt^{IV} has six low energy orbitals, d^2sp^3, the configuration about platinum should be octahedral, requiring polymerization through electron deficient bonds.

"Hexamethyldiplatinum" is monoclinic, $a_0 = 17.35$, $b_0 = 18.99$, $c_0 = 17.79$ kX., $\beta = 116°$, space group from Weissenberg diagrams, $P2_1/c$. The observed density, 3.65, requires 48 $Pt(CH_3)_3$ per unit cell. There can be only 2 or 4 crystallographically equivalent atomic aggregates per unit cell. In molecular crystals these aggregates are almost invariably the molecules, so that the unit cell and density data indicate a minimum molecular size of $[(CH_3)_3Pt]_{12}$. Our data do not exclude continuous chains.

Patterson functions, $P(x,z)$ and $P(x,y)$, have been calculated, each involving about 125 reflections. All important peaks of $P(x,z)$ (Fig. 1) are interpreted, even as to heights, in terms of 16 platinum positions. Since h is even except for 13 weak reflections, there is a pseudo eightfold set of positions: x,z; $\bar{x},\bar{z}$; $x,{}^1/_2+z$; $\bar{x},{}^1/_2-z$; ${}^1/_2+x,z$; ${}^1/_2-x,\bar{z}$; ${}^1/_2+x,{}^1/_2+z$; ${}^1/_2-x,{}^1/_2-$

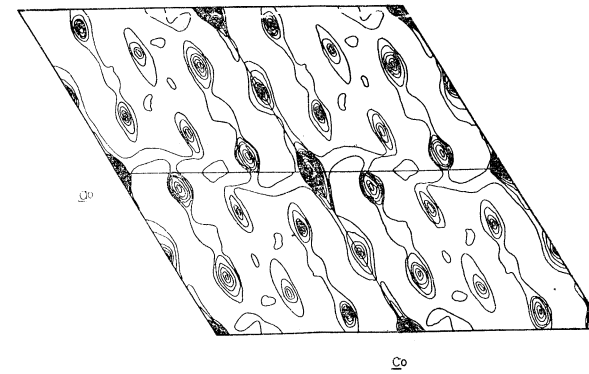


Fig. 1.—Patterson projection, $P(xz)$ for "Hexamethyldiplatinum."

(1) H. Gilman and W. Lichtenwalter, THIS JOURNAL, **61**, 957 (1939).

(2) R. Rundle, *ibid.*, **69**, 1327 (1947); *J. Chem. Phys.*, **17**, 671 (1949).

z. There are two such sets with $x_1 = 0.313$, $z_1 = 0.125$; $x_2 = 0.138$, $z_2 = 0.008$. These parameters lead to satisfactory ($h0l$) intensities.

The sixteen platinum positions projected onto (010) form four, well-separated squares per unit with Pt–Pt = 2.84 kX. Each point must represent three platinum atoms. $P(xy)$ gives 2.82 kX. for one important Pt–Pt distance along b_0. There are four molecules, or possibly four continuous chains, per unit cell. The square projection on $P(x,z)$ suggests that platinum is octahedral, as expected. The complete structure has not yet been determined.

"Hexamethyldiplatinum" is quite soluble in benzene, but negligibly soluble in non-aromatic hydrocarbons. The pronounced difference suggests that benzene may depolymerize the molecule. It is noteworthy that benzene leaves the tetramethylplatinum tetramer unaltered.[3]

Thanks are due Prof. Henry Gilman for advice and encouragement.

(3) R. E. Rundle and E. J. Holman, THIS JOURNAL, **71**, 3264 (1949).

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA
GABRIELLO ILLUMINATI
R. E. RUNDLE

RECEIVED AUGUST 15, 1949

NEW BOOKS

Aquametry. Application of the Karl Fischer Reagent to Quantitative Analyses Involving Water. By JOHN MITCHELL, JR., M.S., and DONALD MILTON SMITH, Ph.D., Ammonia Department, E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware. (Chemical Analysis. Vol. V. A Series of Monographs on Analytical Chemistry and Its Applications. Editors: Beverly L. Clarke and I. M. Kolthoff) Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y. 1948. xi + 444 pp. 51 figures. 15.5 × 23.5 cm. Price, $8.00.

The monograph "Aquametry" by John Mitchell, Jr., and Donald Milton Smith is the fifth of a series dealing with topics in Analytical Chemistry. The present work is primarily concerned with "the application of the Karl Fischer reagent to quantitative analyses involving water" but the authors have done much more than is indicated in this sub-title. The book is written in two parts; the first and longer section deals with considerations of a general nature as well as with specific quantitative determinations using the Karl Fischer reagent; the latter part deals with the determination of organic functional groups.

Contained in the first part is a brief survey of the classical methods used for the determination of water. It is shown later that in most cases the Karl Fischer Reagent yields better results and for this reason the older methods are not discussed in detail. There follows a chapter which presents almost in outline form a summary of the most important procedures which utilize the Karl Fischer Reagent. The presentation of this laboratory manual so early in the running text is a departure from the usual practise. It is placed in its particular position so that persons who have studied the pertinent portions of the book will be able to work in the laboratory more efficiently. The authors then present a discussion of possible alternative compositions of the reagent and give what they consider to be the best of those studied. After an investigation of the stoichiometry of the reactions involved, there is given a series of general discussions which deal with the determination of water on the macro and micro scales. This includes an excellent review of the important instrumental as well as the usual visual methods. Then actual working procedures are given for many common organic and inorganic materials. In each of these latter cases there are outlined alternative methods when such exist but these are necessarily brief. Extensive references are given in all cases. The first section is closed with examples of reactions with inorganic compounds which lead to apparent anomalies. These include redox couples which react with the iodine liberated in the titration to give false end-points. The second part of the book will probably be of great use to organic chemists. In this section there are detailed instructions for the determination of various functional groups such as the alcoholic hydroxyl, the amino and the carbonyl radicals. These are not direct titration methods but include some intermediate water producing step. The frequent reference to interfering substances will be of great help to future workers. The book closes with a chapter on work which is as yet not done.

The volume as a whole is formulated in a concise, accurate and readable manner. The lack of serious errors is commendable and is probably due in large part to the care with which practically every entry was checked in the laboratory of the authors. If all future volumes in the Analytical Chemistry series are up to the standards set by Mitchell and Smith, one can easily visualize a set of these treatises in every complete chemical library.

EDWARD H. DE BUTTS

Natural Products Related to Phenanthrene. By LOUIS F. FIESER and MARY FIESER, Department of Chemistry, Harvard University. Third Edition of the Monograph Previously Entitled "Chemistry of Natural Products Related to Phenanthrene" by L. F. Fieser. A. C. S. Monograph No. 70. Reinhold Publishing Corporation, 330 West 42nd Street, New York 18, N. Y., 1949. xii + 704 pp. Price, $10.00.

More than a decade has passed since the scientific world greeted with unanimous acclaim the first edition of Fieser's treatise which Butenandt has called a model *par excellence* for chemical monographs. The first edition arrived at a time when steroid chemistry had just firmly established itself as a special branch of organic chemistry, when most of the important hormones and related products had been discovered and the rough outlines of their structures had been drawn. Since then, in a bewildering multitude of papers, the more intimate structural details have been furnished with which to complete the picture. Once again Fieser, now in coöperation with Mrs. Fieser and Dr. Turner, has summarized the significant developments and has presented them in an eminently lucid and readable manner. The book is much more than a mere review of the subject. It abounds in original ideas concerning the revision of nomenclature, the relations between physical properties and structure of steroids, the course of certain

reactions and other points, ideas which might well have been the subject of separate publications. Like its predecessor the present edition is bound to become the most significant treatise, the standard reference book on the subject.

It appears futile to the reviewer to recommend this volume to the specialists in the field. They have been waiting impatiently for its appearance and they have probably enjoyed reading it by the time this review is published. The reviewer strongly recommends study of this book to organic chemists in general and to graduate students in particular. Not only does it present a very important subject in a most captivating manner, but it also acquaints the reader with a multitude of reactions and syntheses, and with the significance of physical properties in form of a story rather than as isolated facts. In short, the monograph is recommended as an outstanding, advanced textbook of organic chemistry.

WERNER BERGMANN

The Theory of Solutions of High Polymers. By A. R. MILLER, Imperial Chemical Industries, Research Fellow at the Royal Society Mond Laboratory in the University of Cambridge. Oxford University Press, 114 Fifth Avenue, New York 11, N. Y., 1949. vi + 117 pp. Illustrated. 14.5 × 23 cm. Price, $3.25.

The aim of this brief monograph is "to give an account of the [recent] mathematical advances in the treatment of solutions of high polymers," a subject to which its author has made significant contributions. The introductory chapter discusses models for solutions of simple molecules and the formulation of partition functions for them. The extension of the quasi-lattice model to polymer solutions is dealt with briefly in the second chapter. Chapter III begins with an account of Bethe's method and its grand partition function analog presents the fairly obvious extension to monomer-dimer mixtures and ultimately leads to the formulation of a partition function for monomer-polymer systems of zero mixing energy. The comparison of the theory with experiment in Chapter IV is partially satisfactory, but a rather large discrepancy occurs in dilute solutions. The refinement of the theory (Chapter V), after the manner of the late Dr. W. J. C. Orr, to allow for non-randomness brought about by non-zero energies of mixing fails to remove the discrepancy. The final chapter (VI) presents a non-mathematical discussion of limitations of the theory and concludes with a statement to which this reviewer subscribes completely: "Further advances . . . are probably to be sought in a physical model which represents an actual liquid more faithfully than does the quasi-crystalline model, rather than in refinements of the mathematical and statistical techniques."

The subject is approached primarily from the viewpoint of the contributions of its author supplemented in part by those of Guggenheim and of Orr. This preference is excusable and may in part be justified, but the casual disposal of the alternate method of direct evaluation of the combinatory factor because it "introduces unwanted algebraic complications" is not realistic and may be quite misleading. The emphasis on mathematical rigor is commendable, but it is disappointing to see that it carries one substantially no further than the obviously simpler procedures. In the opinion of this reviewer, the book's most serious weakness occurs in the discussion of the failure of the theory as applied to dilute solutions. This failure has been shown to result from the certain inapplicability of the assumption of randomness in dilute solutions, and separate theories have been advanced which are successful at sufficient dilutions. These are either misrepresented or ignored altogher. The author prefers to attribute the state of affairs in dilute solutions to aggregation of molecules which in some unexplained fashion is favored by dilution!

The book contains a number of minor errors, few of which are troublesome. It is disconcerting to see Raoult's law misstated on p. 3 and again in the figures appearing on pp. 70, 71 and 72, where the activity is equated to volume fraction in the name of Raoult. Research workers interested in polymers or in the statistical mechanics of solutions will welcome this monograph. It will not be digested easily, however, without a well developed feeling for the methods of statistical mechanics.

P. J. FLORY

The Basis of Chemotherapy. By THOMAS S. WORK B.Sc., Ph.D., Research Staff, National Institute for Medical Research, London, and ELIZABETH WORK, B.A., Ph.D., Research Staff, Department of Chemical Pathology, University College Hospital Medical School, London. Interscience Publishers, Inc., 215 Fourth Ave., New York, N. Y., 1948. xx + 435 pp. 14.5 × 22.5 cm. Price, $6.50.

The authors present the subject of the drug therapy of infectious diseases from the point of view of the biochemist and microbiologist. Principal exposition is given to bacterial and protozoal diseases, less attention (due no doubt to our lesser knowledge) to virus infections, and scanty attention to parasitic and mycotic diseases. Throughout the book is emphasized the place of enzyme inhibition and metabolite antagonism in mechanisms of drug action. The first half of the book consists of an orientation in these subjects through excellent chapters on cell metabolism, essential metabolites, and enzyme inhibition, along with a historical introduction as fascinating as some popular expositions, but far more penetrating. The second half of the book consists of chapters on "Drug Antagonism," covering substances that diminish or modify the action of drugs, "Drug Resistance," or the tendencies toward adaptation or selection of resistant strains of organisms, and a brief chapter on "The Relation of Structure to Activity." This arrangement may inconvenience somewhat readers seeking information on particular groups of drugs or organisms, but serves well the authors' purpose of seeking logical bases for chemotherapeutic action. The book shows strongly the influence of Wood, Fildes, Woolley, Lwoff, and Sevag.

The book seems to be addressed mainly to advanced students of chemistry, microbiology and medicine; it should be extremely useful to these groups. More advanced research workers may also find in it convenient summaries of work in fields related to their specialties, and references that might otherwise be overlooked. The style is direct and readable, the explanations usually clear, printing legible, and formulas carefully drawn.

WALTON B. GEIGER

Fourier Technique in X-Ray Organic Structure Analysis. By A. D. BOOTH, PH.D., Fellow and Lecturer at Birkbeck College, London. (The Cambridge Series of Physical Chemistry. General Editor, E. K. Rideal.) Cambridge University Press, The Macmillan Company, 60 Fifth Avenue, New York 11, N. Y., 1948. vii + 106 pp. Illustrated. 14.5 × 22 cm. Price, $2.75.

This little book comprises an extremely condensed, but rather complete, presentation of the methods currently being used to discover the atomic arrangements in complex crystals. As the author writes in his preface, this subject is developing so rapidly that one or two important methods inevitably were not included, because they had not been discovered when the book was written two years ago. This detracts in no way from the book's value.

There are seven concise chapters, entitled, respectively: I. The interaction of X-rays with matter; II. The representation of electron density by Fourier series; III. Methods of obtaining approximate structures; IV. The refinement of atomic coördinates; V. Methods of computation; VI. Mechanical computation; VII. The results of Fourier synthesis. These titles show the scope and character of the book: it is intended as a handbook for those actively engaged in the determination of crystal structures. Such workers will find here many valuable de-

tails not conveniently available elsewhere. In particular, the author has included many of his own important contributions to the art of crystal structure analysis by means of Fourier series. For beginning students of X-ray diffraction methods, however, this book may well prove too concise.

DAVID HARKER

Rhenium. DVI-Manganese. The Element of Atomic Number 75. By J. G. F. DRUCE, M.A., M.Sc. (Lond.) R.Nat.Dr.(Prague), F.R.I.C., Fellow of the Chemical Society, Member of the Masaryk Academy of Work, Corresponding Member of the Royal Bohemian Scientific Society, Member of the Netherlands Chemical Society, etc. Cambridge University Press, The Macmillan Company, 60 Fifth Avenue, New York 11, New York. 1948. viii + 89 pp. 14.5 × 22 cm. Price, $2.50.

This book is the first published summary of the studies of rhenium since the appearance of "Das Rhenium" by I. and W. Noddack in 1933. In the fifteen-year interval between the writing of these two books knowledge concerning rhenium has increased materially through the efforts of numerous investigators in many countries. These advances are briefly and clearly reviewed in this newest publication, and the present status of the element is shown in concise manner.

The subject matter is divided into eight chapters. In the Introduction there is a brief and impartial summary of the search for both eka-manganese and dvi-manganese. This is followed by chapters devoted to (2) The Isolation and Properties of Rhenium, (3) The Oxides of Rhenium, (4) Perrhenic Acid and Its Salts, (5) The Halogen Compounds of Rhenium, (6) The Sulfides, Selenides and Thio-Salts of Rhenium, (7) Some Organic Rhenium Derivatives, and (8) Applications and Patents Related to Rhenium. Possibly the most valuable feature of the book is the complete and useful bibliography, of which there are over 300 references, arranged both topically and chronologically.

That the author is eminently qualified to give authoritative information about rhenium is indicated by the fact that at least 36 of these references are to his own articles, those of his late colleague, F. H. Loring, and their collaborators. Few first edition errors are apparent. There is an adequate index.

In this book Dr. Druce has made an outstanding contribution to the literature of the less familiar elements. It will be welcomed by all who are interested in rhenium.

B. S. HOPKINS

Radioactive Measurements with Nuclear Emulsions. By HERMAN YAGODA, Senior Physical Chemist, National Institute of Health. John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y., 1949. ix + 356 pp. 75 figs. 22 × 14 cm. Price, $5.00.

The first phenomenon utilized for the detection of radioactivity was the fogging of photographic emulsions. Methods based on the use of sensitized halide emulsions were quickly supplanted by procedures based on ionization measurements. In the last few years, however, emulsions have been staging a strong comeback, owing particularly to the development of thick, fine-grained emulsions astonishingly well suited to the study of densely ionizing particles. These emulsions may be designated as "nuclear" to distinguish them from ordinary photographic emulsions. Studies such as the now classic researches of Powell and his collaborators on the detection of meson components in cosmic radiation illustrate the refinements in techniques employing nuclear emulsions which have reached a point hardly conceivable ten years ago. No comprehensive treatment of radioactive measurements using nuclear emulsions appears to have been available until the publication of this book.

It has been the author's purpose to present a volume which provides sufficient coverage of the field so that "any scientist who owns a microscope can make quantitative measurements." There seems to be little doubt that this objective has been achieved remarkably well and that the reader will find a well integrated description of theory and practice in the use of nuclear emulsions. The material is organized into 12 chapters, the first two of which afford a succinct account of basic principles. Probably one of the most useful sections is the third chapter on laboratory manipulations in which the reader will find a number of recipes for the preparation of various types of samples as well as useful material on exposure and processing of emulsions. In other chapters there are included numerous instances of applications to radiochemistry, biology, crystallography, metallurgy and nuclear physics. A bibliography containing some 700 references is included.

The text is enlivened by many historical references and quotations. Some readers will be interested in the author's use of the word "serendipical." This is an adjectival construction from the word "serendipity" coined by Walpole in the 18th century to indicate the gift of finding agreeable or valuable things not sought for. It is to be hoped that this word comes into more common use because it is a convenient descriptive term for one of the most characteristic aspects of scientific research.

The format employed is one with small margins on a convenient page size. However, the glossy finish renders the print somewhat less legible than would have been the case on a rougher stock.

MARTIN D. KAMEN

Silicones and Other Organic Silicon Compounds. By HOWARD W. POST, Department of Chemistry, University of Buffalo. Reinhold Publishing Corporation, 330 West 42nd St., New York 18, N. Y., 1949. 230 pp. 15.5 × 23.5 cm. Price, $5.00.

The author has set himself the task of abstracting every published article on organosilicon compounds. He has succeeded in making a complete search of the literature through 1947—no small achievement in view of his bibliography of over 700 references. The present extent of organosilicon chemistry has created a need for a handy, up-to-date reference book on the subject. This book could have admirably filled that need, but it has several faults which have somewhat reduced its usefulness.

In the first place the organization of the book is on a historical rather than a chemical basis, which makes it difficult to look up material under a given subject. The first two chapters are introductory, and deal with the inorganic chemistry of silicon. Chapter 3 covers the work of Kipping and others prior to about 1935. Kipping's work is taken up in a more or less chronological order, rather than subject by subject; as it is all in one place, however, it is easy to look through it. Chapter 4 covers the more recent scientific literature on the preparation of organosilicon compounds at moderate temperatures and Chapter 5 covers the patent literature on the same subject. Included here are preparations involving Grignard reagents, hydrolysis, dehydration and other metathetical reactions. The accompanying tables of compounds classified according to the method of preparation may be of value. The physical chemistry of organosilicon compounds is given a rather inadequate treatment, 35 articles being abstracted in 30 sentences near the end of Chapter 4.

Chapter 6 covers reactions carried out at temperatures over about 250°. This includes some of the interesting new industrial methods. Chapter 7, "The Uses of Polymerized Oxosilanes," would have been more valuable if the distinction between silicone resins, oils, rubbers and other products had been made clear. It does, however, give a good idea of the extraordinary versatility of the silicones. Chapter 8 purports to be an extension of the author's previous book, "The Chemistry of the Aliphatic Orthoesters." It is actually a jumble of unrelated material on alkoxy and amino silanes and other derivatives, many of which have no carbon–silicon bonds and are therefore not true organosilicon compounds.

In Chapter 9 on nomenclature Dr. Post has reprinted articles by Sauer and by the A. C. S. Committee on Nomenclature in their entirety. He has thus done justice to the present rules of nomenclature, but he does not follow them himself. Thus the silyl radical is frequently called "silicyl," a term which he also uses for multivalent radicals as in "dichlorosilicyl diisocyanate." His resurrection of the "oxosilanes" seems unnecessary. The strange combination of Greek and Latin roots as in "quadradecamethylhexasiloxane" is not in accord with general usage.

Chapter 10 consists of a table of physical properties of compounds. It appears to be reasonably complete, although there are a few omissions, pentamethylphenyldisiloxane, for instance. The boiling point given for tetraphenylsilane is low by 68°.

The haste with which this book has apparently been prepared is regrettable. The organization within each chapter is generally bad. There are innumerable misprints and misspelled words and some of the tables appear without proper explanation or reference in the text.

The serious student will find "Silicones" of some value, despite its shortcomings; he will have to search a little for his information, but it is all here.

RICHARD N. LEWIS

Elsevier's Encyclopedia of Organic Chemistry, Volume 13A, Bicyclic Compounds (Except Naphthalene) Series III, Carboisocyclic Condensed Compounds. E. JOSEPHY AND F. RADT, Editors. Elsevier Publishing Company, Inc., 215 Fourth Avenue, New York 3, N. Y., 1948. xxvii + 1262 pp. 17.5 × 26 cm. Subscription Price, $78.00; Serial Price, $91.00; Single Volume Price, $104.00.

The general remarks on this new encyclopedia made by L. F. Fieser (THIS JOURNAL, **70**, 1294, (1948)) are equally pertinent to the volume here under consideration; these remarks have the whole-hearted approval of the present reviewer. Although the work may eventually assume something of the function of Beilstein, the two should be considered supplementary. Because of different publishing schedules, Elsevier will dominate certain fields and Beilstein others.

Elsevier is in clear English. It has the advantage of a viewpoint some forty years more mature than Beilstein. The wide use of the charts and tables is not only superb from the encyclopedic standpoint, but also makes the work of greater utility as a general reference. Because of these charts the advanced student can study from Elsevier, something which could hardly be done from Beilstein. There is a general criticalness in Elsevier which is lacking in Beilstein, but it is not used to obscure or to evade references, but rather to point out the existence of doubts and controversies.

Specifically, Volume 12 A contains bicyclic compounds, except naphthalene and its derivatives. The bicyclic terpenes, bicyclic sesquiterpenes, indene and its derivatives make up most of the book. The literature has been covered completely through 1941 and references bearing on structure through 1947. No errors of omission were apparent in the terpene fields, and there are surprisingly few typographical errors. The lack of patent references is not a serious handicap in the chemistry here covered; however, this may prove a serious objection in fields of greater industrial activity.

From the standpoint of topography, system, indices and binding, the volume is indeed of very high standard.

Larger libraries should maintain both Beilstein's Handbuch and Elsevier's Encyclopedia. Collections operating on smaller budgets will probably find Beilstein more essential because of its present completeness in the organic field in comparison with Elsevier. Single volumes of Elsevier should certainly find their way into specialized collections and to the desks of practicing chemists, especially those working in fields which have been very active in the last thirty years.

We American organic chemists must be eternally appreciative of our foreign colleagues who undertake these monumental tasks so successfully.

W. A. MOSHER

Fundamental Processes of Dye Chemistry. By HANS EDUARD FIERZ-DAVID AND LOUIS BLANGEY, Eidgenössische Technische Hochschule, Zürich. Translated from the Fifth Austrian Edition by Paul W. Vittum, Eastman Kodak Company, Rochester, New York. Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y., 1949. xxix + 479 pp. 57 figs. 15.5 × 23.5 cm. Price $9.50.

This book is an excellent translation of the fifth Austrian edition of "Grundlegende Operationen der Farbenchemie" (1943) which constitutes a revision and extension of the earlier Austrian editions. Its primary object, as stated by the authors, is to teach the fundamental principles of dye chemistry to the student and to serve primarily as a laboratory manual; they point out specifically that this book is not intended to compete with the more comprehensive books such as that of P. H. Groggins, "Unit Processes in Organic Synthesis" (1947). To this end, the material has been presented in a most successful manner so that it may be employed either as a text for systematic reading or as a laboratory reference manual.

The major portion of the book (279 of the 479 pages) is devoted to detailed procedures with discussion for the laboratory preparation of dye intermediates and the finished dyes. Many of the examples are taken from industrial practice and much of the descriptive material will be of immediate value not only to the student of dye chemistry but to those chemists interested in unit operations. This includes a discussion, with examples, of the numerous available methods for introducing into the aromatic nucleus the sulfonic acid, nitro, hydroxyl, amino, alkoxy and halogen groups; also a brief treatment of oxidation and reduction reactions with procedures. It provides the student with an excellent appreciation of the many possible routes leading to a single dye intermediate, and furthermore alerts him to the fact that the most direct or the least expensive process from the chemical standpoint is often not the best one when all factors are taken into consideration. The established process may, for example, employ less direct methods in order to avoid producing isomeric or other undesirable products; or excessive corrosion or expensive equipment may rule out what otherwise might be considered a good laboratory process. In this respect the authors are very prone to weigh and compare the laboratory procedures with the industrial operations, and, in fact, one complete chapter (III) is devoted to technical details covering such subjects as vacuum distillation in the laboratory and in the plant, the construction and use of autoclaves, factory management and methods for computing cost calculations for production of a simple dyestuff.

The analytical section provides a treatment of methods employed in dye chemistry and is followed by a most instructive discussion dealing with the determination of the constitution of unknown commercial dyes; also references to published works which have become accepted as basic standards in the dye industry.

One of the main features of this book is the schematic arrangement of approximately six hundred compounds in twenty-one tables. A genetic system is used and clearly presents the general steps involved for the production of dyes and their intermediates from the basic coal tar products. The usefulness of these tables is further increased by cross references to one another and to details of the reactions described in the text, and in some instances to the original literature. In the reviewer's opinion the scope of the book would have been increased appreciably had many more references, especially to patents, been included.

Chapter VI dealing with light fastness of dyes is not so thoroughly treated as the other sections of the book. It seems unfortunate also that less than two pages are devoted to the phthalocyanin class of dyes which have proved so valuable because of their excellent stability to light and

washing. However, the broad scope of the book and the clear manner in which the material is presented makes it most valuable to the beginner whose primary concern is that of learning the basic principles of dye chemistry.

WILLARD D. PETERSON

Colloid Science. Volumes I and II. By A. E. ALEXANDER AND P. JOHNSON. Oxford University Press, 114 Fifth Avenue, New York 11, N. Y. (Oxford at the Clarendon Press.) April 14, 1949. xx and viii + 837 pp. Illustrated. 15.5 × 24.5 cm. Price, $15.00 the set.

This book aims to be intermediate in level between the elementary textbook and the specialized monograph and to give especially the newer methods. A review of the topics discussed will indicate what the book is about and what two young workers in one of the most active centers of colloid research think colloid science is now and is about to become.

The book is divided into three parts. Part I gives in five chapters a general survey with a history of colloids, a review of the present status, thermodynamics with some applications to colloid problems, and the theory of the electrostatic interaction of ions. In Part II, fourteen chapters are devoted to experimental methods: determination of composition and solvation in particular, osmotic equilibria, sedimentation equilibria, translational diffusion, sedimentation, velocity, electrophoresis, viscosity, rotational diffusion, scattering of light, X-rays and electrons, plasticity and elasticity, insoluble monolayers, adsorbed films at fluid interfaces and liquid–solid interfaces. Part III, with nine chapters in a separate volume, discusses the specific colloidal systems: dilute suspensions and sols, gels and pastes, foams, emulsions, colloidal electrolytes, clays and zeolites, proteins, polymers, and membranes.

The index at the end of Volume II is only a third as long as the Table of Contents at the beginning of Volume I. References are given at the end of each chapter. There are about seven hundred, but many of these are duplications, especially among the forty references to books.

As a result of this division and of the disregard of any shortage of paper, a topic may be discussed in any part or in all three of them, and the index is quite inadequate to follow the discussion. For example, the Flory–Huggins theory comes up under thermodynamics, osmotic pressure and high polymers, but I could not find it in the index.

Very few errors have caught my eye, none of them typographical. One glaring error is in equations 4.81 to 4.83 which appear to violate the law of conservation of mass as well as those of thermodynamics.

The use of this book for teaching will be greatly restricted by the authors' decision to pass lightly over surface chemistry since it is well treated elsewhere. There are other omissions which seem important to this reviewer. The treatment of adsorption stops before Brunauer–Emmett–Teller. The discussion of X-rays gives most space to single crystals although they are not of great importance to colloid science. The treatment of the osmotic pressure of proteins overemphasizes the importance of membrane potential at the expense of both the empirical extrapolation of P/C as for non-aqueous solutions and the exact thermodynamic treatment. The electrostatic treatment makes no mention of Kirkwood's treatment of ions which lack spherical symmetry.

One of the important contributions of a book of this kind is to consider many diverse phenomena from a uniform and consistent point of view. In this book we find none of the occultism or of the inferiority complex of many of the older colloidal chemists. Colloid Science does not claim to be an isolated system, but is a branch of Physical Chemistry which merges gradually with the many other branches.

The authors have not always succeeded in carrying their treatment back to fundamentals. For example, there is no indication in the electrostatic theory that the treatment is limited to spherical symmetry; and the treatment of surface omits the fundamental relation upon which the measurement of surface tension depends. However, it is clear that the authors have tried hard to unify Colloid Science as a true science, and they have succeeded much better than most writers on colloids. The book will be a very useful addition to any reference shelf.

GEORGE SCATCHARD

The Chemical Arts of Old China. By LI CH'IAOP'ING. Professor of Chemistry, National Northeastern University, Mukden, China, with a Foreword by Tenney L. Davis. Published by Journal of Chemical Education, Easton, Pennsylvania, 1948. viii + 215 pp. Illustrated. 15.5 × 23.5 cm. Price, $5.00.

It is probably safe to say that the knowledge of the average American chemist of the chemical arts of China is limited to the discovery of gunpowder and the manufacture of porcelain. It is therefore of especial interest to find so extended and detailed a record of the Chemical Arts of Old China as recorded by the author in this book.

Following quite an extended account of the alchemy of ancient China wherein the desire to acquire the "Elixir of Life" or Immortality seemed to predominate over the desire to produce gold and silver, called the "Art of Yellow and White," the author reviews the following topics: METALS AND ALLOYS.—Here is discussed the smelting and refining of silver, copper, zinc, iron, including steel, tin and lead. SALT.—The driving of wells, the evaporation of the recovered brines and that of sea-water. CERAMICS.—The author naturally gives much space to the description of the porcelains of the various Dynasties, and to the reviewer, unacquainted with the different porcelains of old China, this chapter makes most interesting reading. The porcelains of the Sung Dynasty (960–1126) and the Ming Dynasty (1368–1544) seem to be regarded as outstanding. LACQUER AND LACQUERING.—This work is done with the sap of *Rhus vernicifera*. The processes of both the flat and carved work is described. GUNPOWDER.—The author makes out a good case for China as the originator of gunpowder and places it at the time of the Sung Dynasty (960–1126). Still earlier in various internal revolutions fire weapons called "thunder caps," "fire-arrows" and "fire-balls" had been used. The author states that the gunpowder used at the battle of Crëcy (1346) and Augsburg (1353) were later than the time of the Chinese invention in the 12th century. COLORS AND DYES.—This chapter includes the processes of making Chinese ink, lamp-black, vermilon, white and red-lead, stamp-ink, indigo and sufflower. VEGETABLE OILS AND FATS.—The author tells of methods of extraction of essential oils, the production of rouge and face-powders dating back to 1100 B. C.! Other chapters discuss Sugar, Paper, Leather and Glue, Soybean Products and Alcoholic Beverages and Vinegar.

The book is illustrated by many fine line drawings in the Chinese style depicting the processes described; it is unique in subject and style, well printed and will be an addition to the History of Chemistry.

H. MONMOUTH SMITH

The Problem of Reducing Vulnerability to Atomic Bombs. (A Report Prepared for the Committee on the Social and Economic Aspects of Atomic Energy of the Social Science Research Council.) By ANSLEY J. COALE. Princeton University Press, Princeton, N. J., 1947. 116 pp. 14 × 21 cm. Price, $2.00.

In the present plethora of works on the atomic bomb, this sound and solid study of the Committee amounts to a valuable touchstone with which may be tested the validity of many of the statements now being made and the speculations offered as to the employment of the bomb. Often

it seems to elude writers that proposing defenses against the hurtful effects of nuclear fission is analogous to proposing defenses against the operation of gravity. The bomb admits of no genuine defense and restricts all such efforts to what Mr. Coale calls "the problem of reducing vulnerability." Under this proper description, Mr. Coale, with the collaboration of Committee members, canvasses the possibilities of political agreement and of attack prevention. He discusses measures which may be taken before and after bombs are exploded. In extremely small compass this book covers a vast range of material. Its striking and useful purpose lies in its careful organization. It raises far more questions than it offers to solve and in so doing makes clear that all glib and over-simplified atomic bomb "defense" proposals must be regarded with high suspicion.

RUSS SYMONTOWNE

Surface Active Agents. Their Chemistry and Technology. By ANTHONY M. SCHWARTZ, Harris Research Laboratories, Washington, D. C., and JAMES W. PERRY, Massachusetts Institute of Technology, Cambridge, Massachusetts. Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, New York. 1949. xi + 579 pp. Illustrated. 15.5 × 23.5 cm. Price, $10.00.

Surface active (S. A.) agents are those which, in the authors' words, "have the startling property of altering the surface energy of their solvents to an extreme degree," even when present at low concentrations. The oldest, most familiar and still the most important is soap, but many hundreds of synthetic S.A. compounds have been described within the past twenty years and, to the reviewer's knowledge, this is the first book adequately to cover the subject. The authors have done a splendid job with a difficult assignment.

This book has been limited in scope to S.A. compounds other than soap (soap is discussed very briefly) and their behavior in dilute solutions. Aqueous solutions are, naturally, emphasized almost to the exclusion of others. The book is divided into an introduction and three major parts which cover, respectively, general considerations and classification, synthesis and manufacture, physical properties of solutions and industrial applications.

In the introductory part (18 pp.), S.A. compounds are classified as far as possible on the basis of the ionic character of the hydrophylic group, which leads to the three familiar and logical designations of anionic, cationic and non-ionic compounds. In addition, the authors have quite logically put ampholytes in a fourth class and have included two others which do not fit into the general scheme: water-insoluble emulsifiers (*e. g.*, monoglycerides) and compounds useful in non-aqueous systems (*e. g.*, lubricant additives). Further breakdown is, first, on the basis of the "connecting link," *i. e.*, the atom or group(s) which connect the hydrophylic to the lipophylic portion of the molecule. For example, we have: I. Anionics, B. Sulfuric Esters (Sulfates). 1. Sulfate joined direct to hydrophobic group, a (Simple types such as alkyl sulfates).

Part I (212 pp.) covers the organic chemistry of S.A. compounds—preparation, properties and manufacture—the discussion being arranged as far as practicable to conform to the order of the classification outline in the introduction. Coverage is adequate and complete, and is conspicuously well done when one considers that, except for patents, there is next to nothing in the way of pertinent original literature. In such a situation, it is almost impossible to avoid endowing some types, which have been described but never used, with unwarranted importance, but on the whole the commercially successful types have been singled out for especial mention and others thereby relegated to their proper perspective. For example, the table on page 126 lists 15 aromatic nuclei and 23 alkyl side-chain sources without pointing out that the keryl and tetrapropenyl benzenes probably account for more production than all the rest put together. On the other hand, the inclusion in the text of trade names and their identification for the most part with the proper active ingredient types (Oronite detergent, p. 123 is one conspicuous exception) tends to emphasize the commercially important compounds and to make the discussion correspondingly more useful. Other features of this section illustrate the careful job the authors have done. For example (p. 153), it is emphasized that cationics have been developed largely for applications where their surface activity is of only secondary importance. Again, description of the important fatty monoglyceride sulfate manufacturing process (p. 71) serves to emphasize this ingenious procedure over the usual sulfation methods theoretically applicable to monoglycerides.

Part II (153 pp.) deals with the physical chemistry of aqueous solutions of S.A. compounds in discussions which are lucid and readable. Here the authors have access to a considerable body of original literature and their coverage is remarkably complete. The collection and coördination of published work on detergency, foaming and other interfacial effects serves a very useful purpose, especially since it is handled in such a realistic manner. For instance, it is repeatedly emphasized that, even though our knowledge of S.A. solution properties has increased enormously in recent years, our understanding of the many complex factors involved in detergency is still far too limited to allow us to make useful performance tests out of any measurements short of actual washing experiments.

Part III (120 pp.) is an interesting discourse on industrial applications of S.A. agents. By the authors' own statement, application patents are not covered completely, but this is a recommendation rather than a criticism and the section is on the whole well done.

Even with the authors' careful handling of their material, some inaccuracies have inevitably crept in, but for the most part they are of minor importance. Mono- and diethanolamines are said to give predominantly amides in reacting with F.A. (p. 182); actually their behavior should be contrasted, since diethanolamine gives mostly ester. The statement that soap shampoos are still the most widely used (p. 444) is misleading, since certainly of products sold as shampoos, synthetic-base products make up the large volume. This reviewer will emphatically take issue with the statement (p. 444) that ". . .such irritating effect (of coconut oil soap) has been traced, *with a high degree of certainty*, to the presence of C_8 and C_{10} fatty acids. . . ." Nonyl naphthalene sulfonate (p. 124) is hardly in a class with the good alkyl benzene sulfonates as a detergent. Isobutene polymers have not proved very suitable for alkylating benzene (p. 125) to form good surface-active compounds. On the other hand, certain other reports from the literature are handled with discrimination. For instance (p. 373) "rosin soap is by itself a poor detergent, but up to 50% can be incorporated into fatty acid soaps without seriously impairing the detergency of the latter"—a very good summary of the situation.

The book as a whole is well set-up, printing is good and no typographical errors have been noted. Indexing is good, which enhances the volume's value as a reference. In short, it is a pleasure to recommend this volume to anyone interested in the subject.

N. B. TUCKER

The Structure of Matter. By FRANCIS OWEN RICE, Professor of Chemistry, The Catholic University of America, and EDWARD TELLER, Professor of Physics, The University of Chicago. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. (Chapman and Hall, Ltd., London) 1949. xiii + 361 pp. 15.5 × 23.5 cm. Price, $5.00.

In this book the distinguished authors have boldly attempted to describe in words a very extensive range of applications of quantum mechanics with only the barest recourse to mathematics. The topics covered include atomic structure, chemical binding, the solid state, mag-

netic and dielectric properties of matter, molecular vibrations, electronic spectra, nuclear chemistry and even the state of matter in stars. All of these topics are treated in a very original manner, using qualitative statements based on various quantum-mechanical generalizations.

This reviewer found the book profitable reading and believes that there are few who would not likewise at least acquire useful new viewpoints from it. The attack on the subject is tremendously ambitious and the scope covered is very great.

Nevertheless, it is a little difficult to decide upon a class of reader for whom it can be recommended without qualification. It is obviously intended for readers not prepared to undertake the study of the mathematical basis of quantum mechanics. This is a hard task and one should not expect perfection in any such enterprise. It must be reluctantly confessed, however, that this reviewer does not like the general approach which was used. It seems too dogmatic, too ready to jump into rather glib word-explanations of complicated phenomena without a proper discussion of fundamentals, too lacking in clear definitions of concepts or precise statements of basic hypotheses. The reader is not, for the most part, presented with evidence in support of statements made. Although it is not always feasible to present a clean-cut mathematical derivation from definitely stated hypothesis to carefully worded conclusions, it would seem that the basic hypotheses, the results and the experimental comparisons should be given.

It appears doubtful that the reader who cannot even be exposed to the Schrödinger equation is going to be able to grasp the concepts of "coulomb and exchange integrals" introduced on p. 73 without any real explanation, to pick just one example. These are likely to remain mere words, perhaps memorized and repeated back to the teacher, but carrying no useful meaning.

It can be argued that the proper way to introduce the non-mathematical reader to the results of quantum mechanics is the conventional one of using the experimental approach. The observed facts of electron diffraction, spectroscopy, chemical valence, etc., provide a credible framework upon which to hang underived statements of the results of quantum mechanical calculations, but even then much discussion of the nature of the fundamental postulates is desirable and a very definite distinction between those conclusions which follow rigorously from the postulates and those which involve approximations of untested validity.

It is unfortunate that these criticisms seem necessary, because the authors have carried out a really remarkable translation of a vast variety of deductions into word pictures. It is certainly highly desirable for theoretical scientists to uncover the physical meaning of each stage of their mathematical derivations.

In summary, it may well be that this book will be most useful for those who have previously been exposed to some mathematical treatment of quantum mechanics and can, therefore, view the word pictures in the proper perspective. Such readers are sure to learn something new from this challenging work.

E. BRIGHT WILSON, JR.

BOOKS RECEIVED

August 10, 1949–September 10, 1949

WALTER CRAFTS AND JOHN L. LAMONT. "Hardenability and Steel Selection. Theories, Calculations, Properties, Test Methods." (Pitman Metallurgy Series.) Pitman Publishing Corporation, 2 West 45th Street, New York, N. Y. 1949. 279 pp. $5.50.

TENNEY L. DAVIS, Editor-in-Chief. "Chymia." Annual Studies in the History of Chemistry. Vol. II. University of Pennsylvania Press, 3446 Walnut Street, Philadelphia 4, Pennsylvania. 1949. 143 pp. $4.00.

G. H. DIEKE AND A. B. F. DUNCAN. "Spectroscopic Properties of Uranium Compounds." (National Nuclear Energy Series. Manhattan Project Technical Section. Division III-Vol. II.) McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 18, N. Y. 1949. 290 pp. $2.75.

JAMES ENGLISH, JR., AND HAROLD G. CASSIDY. "Principles of Organic Chemistry." (International Chemical Series.) First Edition. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 18, N. Y. 1949. 512 pp. $4.50.

MAX JAKOB. "Heat Transfer." Vol. I. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1949. 758 pp. $12.00.

J. MURRAY LUCK, Editor, *et al.* "Annual Review of Biochemistry." Vol. XVIII. Annual Reviews, Inc., Stanford, California. 1949. 739 pp. $6.00.

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"Bibliography of Research on Heavy Hydrogen Compounds." (National Nuclear Energy Series. Manhattan Project Technical Section. Division III-Vol. 4 C.) Compiled by Alice H. Kimball. Edited by Harold C. Urey and Isidor Kirshenbaum. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 18, N. Y. 1949. 350 pp. $3.25.

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"Transactions of The Electrochemical Society." Vol. XCII. 1947. Published by The Electrochemical Society, Inc., 235 West 102nd Street, New York 25, N. Y. 1948. 595 pp.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY]

The Low Temperature Heat Capacity of Columbium Nitride[1,2]

BY GEORGE T. ARMSTRONG[3]

Measurements of the thermodynamic properties of superconducting materials and of the effect of magnetic field upon them have provided a valuable tool for the study of the nature of the superconducting state. Heat capacity measurements have previously been made at low temperatures on the elements tin,[4] thallium[5] and tantalum,[6] alloys of tin with bismuth,[7] lead with bismuth[8] and of lead with thallium.[9] No measurements have been reported on any superconducting compound. The existence of columbium nitride with a transition temperature near 15°K. provides an opportunity for the study of the heat capacity of such a compound in a region which can be reached with liquid hydrogen. The only previous heat capacity measurements on this substance were reported by Sato and Sogabe[10] above 0°. On the basis of their work Milton[11] estimated the low temperature heat capacity. This is a report of the measurement of the heat capacity of columbium nitride between 11 and 21°K. in the absence of magnetic fields and in the presence of fields up to 1000 gausses.

(1) The major part of this paper is from a dissertation submitted by G. T. Armstrong to the Board of University Studies of the Johns Hopkins University in conformity with the requirement for the degree of Doctor of Philosophy, June 1948.

(2) This work was supported by funds from the Office of Naval Research, Physics Division, U. S. Navy.

(3) Present address: Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut.

(4) Keesom and Kok, Leiden Comm. 221e.

(5) Keesom and Kok, Leiden Comm. 230c.

(6) Keesom and Desirant, Leiden Comm. 257b.

(7) Mendelssohn, *Proc. Roy. Soc.* (*London*), **152**, 34 (1935).

(8) Shubnikov and Chotkevitch, *Physik. Z. Sowjetunion*, **6**, 605 (1934).

(9) Mendelssohn and Moore, *Proc. Roy. Soc.* (*London*), **151**, 334 (1935).

(10) Sato and Sogabe, *Sci. Papers Inst. Phys. Chem. Research* (*Tokyo*), **38**, 174 (1941).

(11) Milton, *Chem. Revs.*, **39**, 419 (1946).

Materials

The columbium nitride, CbN, which was used in the measurements was prepared by roasting columbium metal powder of 400-mesh size or finer in an atmosphere of nitrogen for twelve hours at 1300°. The time was somewhat longer than that used by Horn and Ziegler[12] and this may account for the fact that the product has a somewhat higher nitrogen content than was reported by them. The columbium metal was obtained from the Fansteel Metallurgical Corporation and was reported to have impurities present only as traces of less than 0.1%. The nitrogen used was a prepurified grade containing not more than 0.002% each of oxygen and hydrogen. The product of the reaction was gray with a distinct yellowish tinge. X-Ray examination showed only the sodium chloride lattice, with no evidence of any other structure. The gain in weight in preparation indicated 48.1 mole per cent. nitrogen, while an analysis by the Dumas method performed by a commercial analyst indicated 49.1 mole per cent. nitrogen.

Apparatus and Methods

The Cryostat.—The general plan of the cryostat is conventional in most respects. The calorimeter is shielded from the influences of room temperature by being immersed in a liquid hydrogen-bath which in turn is contained in a dewar of nitrogen. Figure 1 shows a cross section view of the hydrogen chamber and its contents and the location of the magnetic field solenoid (j). The hydrogen can (e) is suspended from a circular brass plate bolted to the lid of the german silver nitrogen dewar. It consists of a supernickel tube two inches in diameter fitted with spun metal top and bottom. Supernickel tubes from above are hard soldered to the top. These tubes are: (a) a half-inch filling tube, which is also the pump line for reducing the pressure of hydrogen vapor, (b) a quarter-inch tube which goes through the top and extends to the calorimeter shield below, used for high vacuum pumping, (c) an eighth-inch tube extending to the manometer for

(12) Horn and Ziegler, THIS JOURNAL, **69**, 2762 (1947).

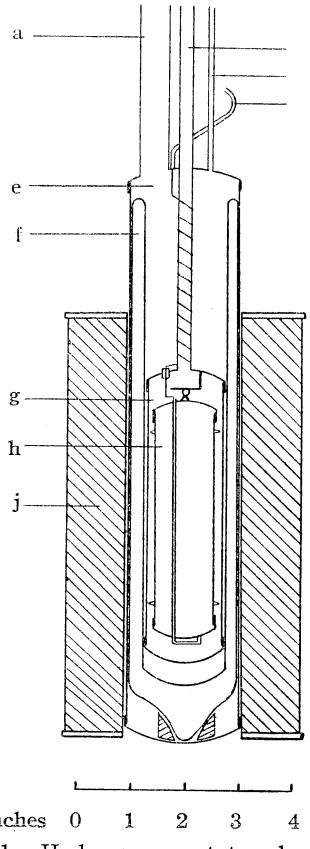


Fig. 1.—Hydrogen cryostat and solenoid.

hydrogen vapor pressure measurement, (d) a sixteenth-inch tube carrying six no. 40 copper wires for the calorimeter. The cover with its attached tubes is removable to permit access to the calorimeter.

Inside the hydrogen can is the glass hydrogen dewar (f). Its diameters are such that there is little clearance between it and the can outside or the calorimeter chamber inside. The dewar contains about sixty cubic centimeters of hydrogen above the calorimeter chamber and this is sufficient to permit operation for approximately four hours before refilling is required. The only advantage of the small volume is that it permits rapid passage through the triple point of hydrogen.

Suspended from the hydrogen can cover by the quarter-inch supernickel tube is the calorimeter chamber (g). This is of 1.25-inch supernickel tubing with spun covers. Access to the interior is obtained by unsoldering the upper cover, to which all attachments are made. To prevent radiation leakage from above striking the calorimeter inside, a baffle of copper is placed so as to cover the opening of the high vacuum line. This baffle provides a convenient point from which to suspend the calorimeter (h). Because the calorimeter chamber must be capable of evacuation to 10^{-6} mm. of mercury, all necessary precautions must be taken to ensure tightness when it is assembled. The electrical leads are brought in through glass buttons sealed in kovar and having a kovar center conductor. The tube carrying the wires ends at the top of the hydrogen can, and the wires are then wrapped on the high vacuum tube to provide additional length in the hydrogen-bath before passing into the calorimeter chamber.

The Calorimeter.—The calorimeter consists of a tube of supernickel of 0.020-inch wall thickness, one inch in diameter and four inches long, with top and bottom spun from sheet metal. The top is silver-soldered in place, but the bottom is soft soldered and is removable. The calorimeter is wound non-inductively with 300 feet of no. 38 gold wire lacquered carefully in place, which is used both as a resistance thermometer and as a heater. Two copper leads are soldered to each end of the resistance element. In order to get increased length in spite of the very small space available, the wires are led once around the long dimension of the calorimeter before going to the glass insulators. In circling the calorimeter the wires are contained in a very thin wall capillary tube of glass to prevent them from touching either calorimeter or shield. The glass is mounted on small drops of a cement made of water glass and talc. Additional tiny pyramids of this same cement are used as spacers to keep the calorimeter from touching the shield. As a result of the precautions described here, the heat leak into the calorimeter was found to be approximately 0.004 calorie per minute per degree difference in temperature. The completed calorimeter weighs 58 g. and has a volume of 50.5 cc.

The choice of supernickel for construction of the calorimeter was in part suggested by factors of convenience and compactness of assembly made possible by its use. It should be noted that although supernickel is not ferromagnetic, its composition is rather close to that for which ferromagnetism occurs among copper nickel alloys at low temperature, and so it should be used with caution where small magnetic effects are to be observed. This fact does not appear to have had any effect upon the present work, but should be borne in mind in considering other applications of the material.

Temperature Control and Measurement.—For control of the hydrogen-bath temperature a Cenco Megavac pump is used, the pumping speed being regulated by means of valves. Approximately constant hydrogen pressure is secured by the use of a regulator similar in design to one described by O'Gorman.[13] This does not provide absolutely constant pressure, nor does it have sufficient flexibility to permit control at all hydrogen pressures, so that other valves must be used with it. The pressure regulation is sufficiently good to permit heat capacity measurements for periods up to an hour without adjustment.

The vapor pressure of the hydrogen-bath was used as the temperature standard. The vapor pressure equation of Simon[14] was used for temperatures below the triple point and that of Henning and Otto[15] was used from the triple point to 21 °K. The vapor pressure was calculated from these equations for every tenth of a degree and observed temperatures were calculated from observed pressures by linear interpolation between these values. For the purpose of calibration of the gold resistance thermometer the hydrogen vapor pressure is indicated by a large bore manometer from which a small tube runs directly to the hydrogen chamber. The absence of any pumped gases in this line ensures that there is no pressure gradient due to flow of hydrogen. A value of $g = 980.103$ cm. sec.$^{-2}$ for Baltimore was used and corrections were made for temperature changes in the glass and the brass scale in all measurements of pressure. The calibration data of the resistance thermometer was smoothed according to well-known procedures and the value of dR/dT was evaluated at intervals of one-tenth degree by numerical differentiation of the smoothed data. Values of T and dR/dT corresponding to observed values of resistance were obtained by linear interpolation between the tabulated values.

Measurements of thermometer resistance were made using the White potentiometer arrangement described by Ahlberg, Blanchard and Lundberg.[16] The thermometer resistance is 18.084 ohms at 20.40 ° and 15.667 ohms at 11.00 °K. The value of dR/dT is 0.450 ohm deg.$^{-1}$ at 20.40 ° and diminishes nearly linearly to 0.0800 ohm deg.$^{-1}$ at 11.00 °K. Although no special calibration of the resistance thermometer was made in magnetic field, sufficient evidence is contained in the original measurements to show

(13) O'Gorman, *Ind. Eng. Chem., Anal. Ed.*, **19**, 506 (1947).

(14) Simon, *Z. Physik*, **15**, 307 (1923).

(15) Henning and Otto, *ibid.*, **37**, 639 (1936).

(16) Ahlberg, Blanchard and Lundberg, *J. Chem. Phys.*, **5**, 539 (1937).

that any change produced by a field of 1000 gausses is not larger than the order of magnitude of 0.01°K.; so that there is little possibility that an appreciable error has resulted from this source.

Time Measurement.—In order to minimize the number of operations to be performed in each experimental heat capacity determination, so that one person could handle them all, and to increase the accuracy of time measurement, the heating intervals were mechanically controlled. The time standard was a General Radio precision 100 cycle per second tuning fork, the output of which was used to activate a two-decade electronic counter. The electronic counter operated a stepping relay at one-second intervals. The stepping relay was connected to the heating circuit in such a way that it would close the heating circuit on one count and open it an integral number of seconds later. The length of the heating period could be adjusted to multiples of 10 seconds, with an error not greater than 0.01 second.

Magnetic Field.—The magnetic field was generated by a solenoid in which size and weight were reduced to a minimum by designing it to fit in the annular space around the hydrogen can, within the nitrogen chamber. In order to give a reasonably uniform field over the length of the calorimeter the solenoid was made nearly twice the length of the calorimeter. Twenty thousand turns of no. 25 B. and S. gage enamelled wire were used. The resistance was 640 ohms at room temperature, but diminished to 80 ohms when cooled in nitrogen. A field of 1000 gausses could be achieved with a power dissipation of 50 watts which resulted in the boiling away of nitrogen at the rate of about a liter per hour. The strength of the field was measured with a search coil calibrated by the U. S. Bureau of Standards. Calibration of the field strength was made under conditions as nearly resembling the actual experimental conditions as possible. Because of the possibility of ferromagnetism at low temperatures in the copper–nickel alloys used in the construction of the cryostat, the field was measured with the search coil enclosed within two supernickel cans at 11°K. The calibration under these conditions was the same as in the absence of any supernickel containers, so it may be concluded that the materials used in the cryostat do not shield the contents of the calorimeter from the magnetic field. The uniformity of the field was such that at the ends of the calorimeter the field was 5% less than at the center. The values of magnetic field listed in the experimental work are those measured at the center of the calorimeter.

Heat Capacity Measurement.—A heat-capacity determination was made in the following way. The temperature of the calorimeter was recorded at one-minute intervals during a fore-period of about six minutes to determine its rate of drift. The heating period was then begun and amounted generally to one hundred and fifty seconds. After the heating current was shut off the temperature drift of the calorimeter was observed during an after-period of eight or ten minutes. The time elapsed between the last point of the fore-period and the first point of the after-period was three minutes. The resistances during the fore- and after-periods were extrapolated to the center of the heating period. The change in temperature caused by the heating was taken from the difference between the resistances at this point, and the heat input was computed using their mean value as the resistance of the heater.

For measurement of the heat capacity of the columbium nitride, the calorimeter was filled with 182.21 g. of material. In order to secure rapid thermal equilibrium throughout the sample, the interstices were filled with helium gas to a pressure of one atmosphere at room temperature. A small correction was added to the heat capacity of the calorimeter because of the heat capacity of this gas.

Experimental Results

The heat capacity of columbium nitride in the absence of magnetic fields was determined principally on two different days. Table I shows smoothed values for this data at intervals of 1°K. Measurements in magnetic fields were made with slight variations in procedure during different runs. The first series was made in the following way. The calorimeter was brought to the desired temperature and then the field was applied only during the course of the measurements. In this way one set of measurements was made in which the temperature was varied but the magnetic field was 500 gausses for each point. Another set of measurements was made in which for each of several magnetic fields the initial temperature of the calorimeter was the same or nearly so. A group of measurements of this type was made at a number of temperatures both below and above the superconducting transition temperature, including magnetic fields of 250, 750 and 1000 gausses. In some cases a point at 0 field and at 500 gausses was taken to provide a check on the consistency of data taken on different days. The purpose of taking measurements in this way was to provide information about the behavior of the heat capacity at constant temperature as a function of magnetic field strength. One particularly complete group of measurements of this type was made near 11° including ten values of the field between 0 and 1200 gausses.

TABLE I

HEAT CAPACITY OF COLUMBIUM NITRIDE IN THE ABSENCE OF MAGNETIC FIELDS

T, °K.	C_p (cal. deg.$^{-1}$ mole^{-1})	T, °K.	C_p (cal. deg.$^{-1}$ mole^{-1})
11.00	0.0390	16.00	0.0848
12.00	.0468	17.00	.0983
13.00	.0612	18.00	.1123
14.00	.0791	19.00	.1300
15.00	.0874	20.00	.1535

In order to satisfy certain questions concerning the interpretation of the data obtained in the presence of a magnetic field, an additional series of measurements was made on July 9 in a field of 1000 gausses, in which the field was applied before the calorimeter was cooled below the transition temperature. The field was not turned off during the whole series of measurements.

Discussion of the Results

The experimental data are plotted in Fig. 2. A smooth curve has been drawn through the points determined in the absence of magnetic fields. These points have a mean deviation of 0.7% from the curve. This curve shows an anomaly between 14.7 and 15.3°K., in which the heat capacity decreases as the temperature rises. This anomaly is in the region in which the transition to superconductivity of columbium nitride is commonly found. Although all previous work on the heat capacities of superconductors has shown a sharp discontinuity at the transition temperature, the present work indicates that the anomaly of columbium nitride is spread over a range of 0.6° and is a smoothly rounded hump. It has been observed

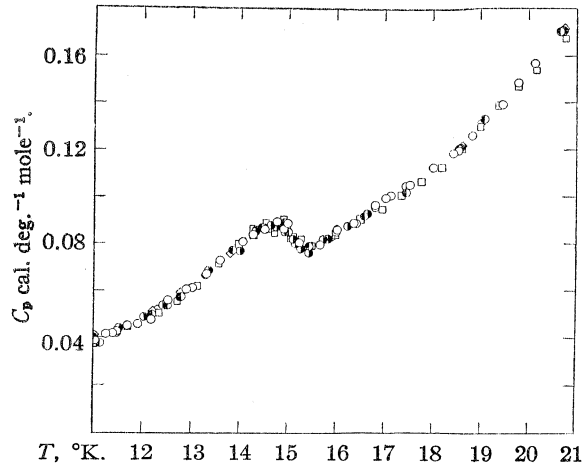


Fig. 2.—Field 0, ○; 250, ◐; 500, □; 750, ◇; 1000, ◑.

in this Laboratory that powdered samples of columbium nitride prepared in different batches show slightly different transition temperatures, and that for a single batch the transition studied by an induction method occupies several tenths of a degree. A reasonable explanation of the rounding of the anomaly and its width is a variation of transition temperature in various parts of the sample; the possibility that the width of the anomaly would be characteristic of even the most homogeneous sample may not be completely ignored.

If the curves above and below the anomaly are extrapolated to 15°K., their difference at this point is 0.023 cal. mole^{-1}. If this difference be interpreted in terms of the Rutgers formula

$$\Delta C = (VT/4\pi)(dH/dT)^2$$

a value of the slope (dH/dT), of the critical magnetic field needed for quenching superconductivity is found to be 257 gausses per degree.

No true measurements of the critical magnetic field have been reported for columbium nitride.[17] The only comparison which can be made is with some unpublished data of S. J. Socolar which merely indicates that fields less than 300 gausses per degree below the transition temperature were insufficient to produce resistance in a superconducting ribbon. The near agreement of these two figures appears to be quite accidental on the basis of the measurements of heat capacity in the presence of a magnetic field.

A graph of C_p/T *versus* T^2 for points below the transition temperature in the absence of fields gives a straight line passing through the origin, (Fig. 3), from which the Debye θ may be calculated to be 253° from the approximate equation

$$C_p/T = 464T^2/\theta^3$$

(17) It has just come to the writer's attention that Ascherman, Friedrich, Justi and Kramer [*Physik. Z.*, **42**, 349 (1941)], measured the magnetic threshold field slope for restoration of resistance of columbium nitride to be approximately 6500 gausses per degree, near the normal transition temperature. This value is not inconsistent with the calorimetrically observed changes in transition temperature herein reported.

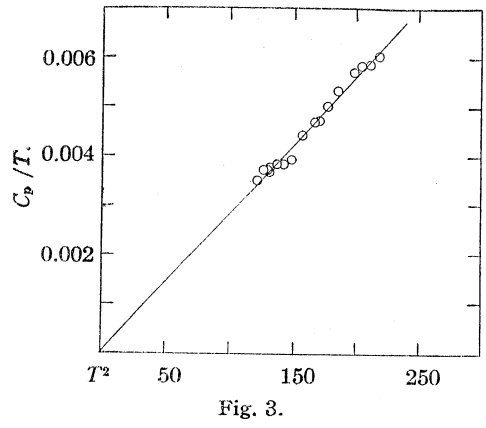


Fig. 3.

The striking fact about the measurements in magnetic fields is the close similarity of the data in every case. The changes in heat capacity either above or below the anomaly are so small that one cannot with certainty say they are greater than would be produced by experimental errors. A graph (Fig. 4) of the data in Table II for 11° shows a slight trend of the heat capacity upward with increasing magnetic field. The change in heat

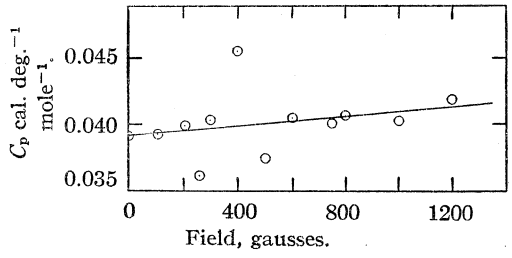


Fig. 4.

capacity between 0 and 1200 gausses is less than the fluctuations between separate points, so that only a qualitative statement of the direction of the change is justified.

TABLE II

HEAT CAPACITY AT 11 °K.

H (gausses)	C_p (cal. deg.$^{-1}$ mole^{-1})	H (gausses)	C_p (cal. deg.$^{-1}$ mole^{-1})
0	0.0391	500	0.0374
100	.0392	600	.0405
200	.0399	750	.0400
250	.0361	800	.0406
300	.0403	1000	.0398
400	.0455	1200	.0418

The temperature of the anomaly is only slightly shifted, although according to the simple thermodynamic treatment of the transition in superconductors one would expect from the magnitude of the anomaly that the transition would be about 4° lower in a field of 1000 gausses. The observed change in the transition temperature appears not to exceed 0.20°, corresponding to a critical magnetic field slope of 5000 gausses per degree. This should be considered only as an order of magnitude in view of the fact that the experimental er-

ror in the points near the transition, as indicated by their spread, is not much smaller in magnitude than the change described.

No positive indication of any latent heat of transition in the magnetic field was found. An irregularity in the data in a field of 500 gausses might be attributed to this source, but since it does not appear again at higher fields, the possibility diminishes that it is evidence of a latent heat.

Investigations of tin[4] and thallium[5] bear out the validity of Rutgers' formula for predicting the discontinuity of specific heat of soft superconductors, for which the magnetic field which first penetrates the body of the material also restores the resistance. Studies of metals for which penetration begins at a much lower field than that required to restore resistance have also been made. Mendelssohn and Moore[9] observed that the heat capacity of an alloy of lead and thallium does not show such a large jump as that predicted on the basis of the field needed to restore resistance. Their measurements were not precise enough to indicate whether a smaller discontinuity existed. Shubnikov and Chotkevitch[8] made a similar observation on an alloy of lead and bismuth. Keesom and Desirant[6] observed that the change in heat capacity of tantalum at its transition temperature corresponds to a much lower critical field slope than is indicated by the depression of the temperature of the calorimetrically observed transition in a magnetic field. They found that the calculated dH/dT corresponds nearly to the threshold field which first penetrates the specimen, while the temperature of the anomaly is more nearly that at which resistance is restored by a given magnetic field.

The powdered columbium nitride used in these measurements has a behavior similar to tantalum in that the lowering of the transition temperature in magnetic field cannot be predicted from the magnitude of the anomaly. Unfortunately, the strength of magnetic field necessary to penetrate CbN has not been measured as a function of temperature, so that it is not possible to compare the slope of this function with that calculated from the calorimetric data by Rutgers' equation.

Because of the resemblance of the thermal properties of CbN to those of alloys and of tantalum, the possibility was considered that some hysteresis phenomenon might cause a difference in the heat capacity observed when the sample is cooled through the transition in the presence of a magnetic field from that observed when the field is applied only below the transition temperature. The data of July 9 were taken with this in mind. No difference is observable in the heat capacity measurements using the different procedure.

In view of the lack of data on the penetration of columbium nitride and the restoration of its resistance by magnetic fields, it is not possible to say whether this compound may behave in other ways like a hard superconductor or an alloy. In any attempt to account for its observed behavior it is reasonable to question whether this behavior is due to the lack of stoichiometric proportions in the sample of the compound used here, or to the small size and irregular shape of the particles, or whether the observed behavior is characteristic of the pure compound in bulk.

Summary

The heat capacity of columbium nitride has been determined in the temperature range from 11 to 21°K. An anomaly of 0.023 cal. mole^{-1} occurs at 15°K., and may be associated with the transition to superconductivity. The effect of magnetic fields of 250, 500, 750 and 1000 gausses is very small both on the magnitude of the heat capacity and the change in temperature of the anomaly. No latent heat of transition was observed.

NEW HAVEN, CONN. RECEIVED MARCH 8, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, WASHINGTON SQUARE COLLEGE, NEW YORK UNIVERSITY]

Kinetics of the Decomposition of Ethyl Xanthic Acid

BY ALFRED CHATENEVER AND CECIL V. KING

The rate of decomposition of various xanthic acids was first studied in detail by V. Halban and Kirsch,[1] who tried to correlate the rates with dielectric constant and other properties of the solvents used. Later V. Halban and Hecht[2] studied the decomposition rates of potassium methyl and ethyl xanthates in aqueous hydrochloric acid at 0°. They found that these xanthic acids are not fully ionized, and assumed the reaction to be a unimolecular decomposition of the undissociated acid, though recognizing this to be kinetically identical with a bimolecular reaction between hydrogen and xanthate ions.

The decomposition of ethyl xanthic acid in dilute aqueous buffers has been studied by King and Dublon.[3] It was shown that there is little or no salt effect on the rate in acetic acid–sodium acetate buffers of low ionic strength, since primary and secondary effects cancel; in aniline–anilinium ion buffers, on the other hand, there is a large primary salt effect.

The rate of decomposition of various xanthic acids in non-aqueous solvents has been studied in

(1) V. Halban and Kirsch, *Z. physik. Chem.*, **82**, 325 (1913).

(2) V. Halban and Hecht, *Z. Elektrochem.*, **24**, 65 (1918).

(3) King and Dublon, THIS JOURNAL, **54**, 2177 (1932).

this Laboratory by F. M. Lewis.[4] Free ethyl xanthic acid is quite stable in anhydrous benzene, and the catalytic effect of added substances is roughly proportional to their strength as bases.

In the present work the decomposition rate was studied with potassium ethyl xanthate in dilute acetic acid–sodium acetate buffers, with added dioxane from 0 to 60% by volume, at temperatures from 15 to 35°. The purpose of the work was to obtain the energy and other thermodynamic quantities of activation, to attempt to learn more about the mechanism of the reaction, and to test the applicability of the theories dealing with electrostatic effects on ionic reaction rates.

Experimental

In all the experiments reported here small weighed samples of solid potassium ethyl xanthate were dissolved in 60 ml. of solution containing 0.0848 *M* acetic acid and 0.0106 *M* sodium acetate. Rates were measured by following the evolution of carbon disulfide in an apparatus similar to that used previously.[3] Ground caps with mercury seals and no lubrication were used on the flasks, and a solenoid release mechanism served to drop glass capsules containing the xanthate. Measurements were made at 15, 20, 25, 30 and 35°, and the thermostat temperature was maintained constant to ±0.02°. The thermometer used was compared, at each temperature, with one calibrated at the Bureau of Standards.

Potassium ethyl xanthate was prepared by recrystallizing a commercial sample from alcohol until an aqueous solution of the dried salt was neutral to litmus. A sample synthesized in the laboratory gave identical rates.

Acetic Acid.—Sodium acetate buffers were made by partial neutralization of an appropriate solution of the acid with carbonate-free sodium hydroxide (standardized with potassium acid phthalate). The mixture was then diluted to volume with water or dioxane and water.

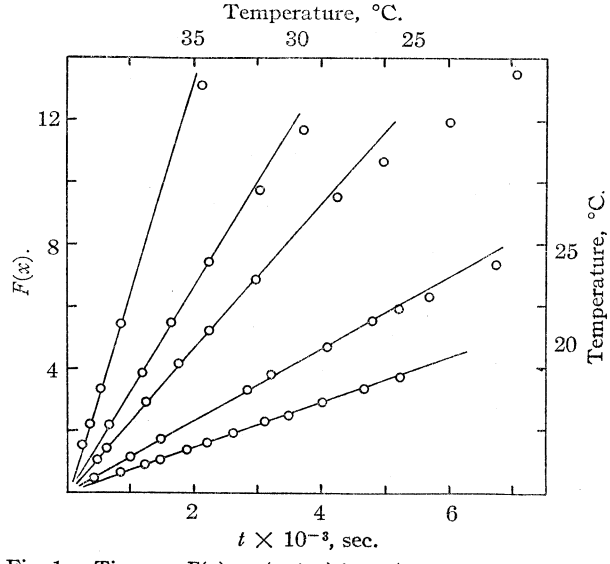


Fig. 1.—Time *vs.* $F(x) = (a + c) \log a/a - x - (b + c) \log b/b - x$; solvent 30% dioxane by volume.

(4) Lewis, Dissertation, New York University, 1947.

Dioxane (**dioxane-1,4**) was purified by refluxing a commercial product with sodium until a fresh surface of the metal remained untarnished for several hours; a portion was then distilled just prior to use. The boiling point was 101.2°, in agreement with the data of Kraus and Vingee.[5] Some determinations were made using dioxane prepared by the more exacting method of Harned and Morrison,[6] with no appreciable difference in rate. Solutions were made with 10, 20, 30, 40, 50 and 60 ml. of dioxane per 100 ml. of solution, and weight per cent. values were obtained by interpolation using densities in the literature.[7]

Specific Rate Constants.—In acetic acid buffers the over-all reaction is essentially

$$\left[S{=}C\begin{matrix}OC_2H_5\\ S\end{matrix}\right]^- + HAc \longrightarrow CS_2 + C_2H_5OH + Ac^- \quad (1)$$

and the rate equation derived previously[3] may be written

$$k(\text{expt.}) = kK_0 = \frac{2.3}{(b-a)t}\left[(a+c)\log\frac{a}{a-x} - (b+c)\log\frac{b}{b-x}\right] \quad (2)$$

In this equation a, b and c are the initial molar concentrations of xanthate ion, acetic acid and acetate ion, respectively; $a - x$ and $b - x$ are values at the time t (in minutes), and the value of K_0 depends on the mechanism of the reaction (see below). The quantity in brackets (called $F(x)$ in Fig. 1) was plotted *vs.* time for each experiment and k(expt.) was evaluated from the slope. Typical plots are shown in Fig. 1, and while it is seen that there is some deviation as the reaction progresses, the linear relation is satisfactory over about 70% of the reaction.

Up to 30% dioxane the precision of k(expt.) is about ±3%. At higher dioxane concentrations the solubility of carbon disulfide increases, the pressure rise in each experiment becomes less, and the possible error in k becomes as high as ±10% in 60% dioxane. The concentration of potassium xanthate varied from one experiment to another, averaging about 0.009 *M*. Limitations of the apparatus made it difficult to use higher concentrations in order to increase the pressure rise in the apparatus.

The rate constants are summarized in Table I, each value being the average from two or more experiments. The dielectric constants D were interpolated from large plots of the data of Åkerlöf and Short.[8] The columns headed K_0 and k will be referred to later.

(5) Kraus and Vingee, THIS JOURNAL, **56**, 511 (1934).
(6) Harned and Morrison, *Am. J. Sci.*, **33**, 161 (1937).
(7) Hovorka, Schaefer and Dreisbach, THIS JOURNAL, **58**, 2264 (1936); Harned and Calmon, *ibid.*, **60**, 334 (1938).
(8) Åkerlöf and Short, *ibid.*, **58**, 1241 (1936).

Several experiments were carried out with the addition of 0.025 *M* and 0.05 *M* sodium chloride to the solutions. Only at the highest dioxane concentrations was the effect on the rate greater than 3%, and it may be concluded that the constants given in Table I are essentially valid for zero ionic strength.

TABLE I

THE RATE CONSTANTS IN DIOXANE–WATER MIXTURES

t, °C.	Volume % dioxane	*D*	k (expt.) $\times 10^3$ min.$^{-1}$	log $K_0 + 8$	log k
15.00	0	82.3	1.39	3.24	1.90[a]
	10	73.0	1.33	2.99	2.13
	20	63.7	1.29	2.70	2.41
	30	54.5	1.34	2.35	2.77
	40	45.5	1.37	1.95	3.19
	50	36.4	1.23	1.42	3.74
	60	27.7	1.14	0.73	4.33
20.00	0	80.4	2.29	3.24	2.12
	10	71.2	2.24	3.00	2.35
	20	62.1	2.31	2.70	2.66
	30	53.0	2.22	2.36	2.99
25.00	0	78.6	4.17	3.24	2.38
	10	69.5	4.17	3.00	2.62
	20	60.5	4.04	2.70	2.90
	30	51.7	4.31	2.36	3.27
	40	42.9	4.56	1.95	3.71
	50	34.4	4.56	1.42	4.24
	60	26.2	3.80	0.72	4.86
30.00	0	76.7	6.59	3.24	2.58
	10	67.7	6.25	2.99	2.80
	20	58.9	6.33	2.70	3.10
	30	60.3	6.61	2.36	3.46
35.00	0	74.9	10.9	3.24	2.80
	10	66.1	11.5	2.98	3.08
	20	57.5	12.4	2.69	3.40
	30	49.0	12.4	2.35	3.75
	40	40.6	11.5	1.93	4.13
	50	32.5	12.1	1.40	4.69
	60	24.7	11.2	0.69	5.36

[a] k in (moles/liter)$^{-1}$ (min.)$^{-1}$

Analysis of Results.—As seen in Table I, the addition of dioxane, changing the dielectric constant as much as from 82 to 28, has very little effect on the observed rate or on values of k (expt.). While the variation at each temperature is outside the precision of individual experiments, it is probably within the over-all experimental error, at least to 50% dioxane. The small effect of changing the solvent is not unexpected if activity coefficients involved in the rate expression cancel, although the dielectric constant effect on a reaction between an ion and a neutral molecule is probably usually somewhat greater.

Average values of k(expt.) at each temperature, up to 40% dioxane, may be expressed with a maximum deviation of about 5% by the equation

$$\log k(\text{expt.}) = 11.56 - 19{,}050/2.3RT \qquad (3)$$

where 11.56 is the Arrhenius frequency factor and 19,050 cal. is the activation energy.

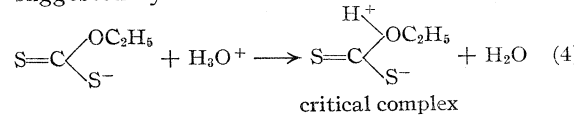
Mechanism of Reaction.—While the stoichiometric reaction is closely approximated by equation (1), it is evident that the rate-determining step is not between xanthate ion and molecular acetic acid, which would not be in accord with the rate equation (2). As postulated by V. Halban, the reaction could be a unimolecular decomposition of undissociated xanthic acid or a bimolecular reaction with hydrogen ion. In the first case K_0 of equation (2) would be the equilibrium constant of the reaction

$$X^- + HAc \rightleftarrows HX + Ac^-$$

where X^- indicates the xanthate ion; then $K_0 = K_{HAc}/K_{HX}$, the ratio of the two ionization constants.

This mechanism does not appear plausible for two reasons: since molecular xanthic acid is stable in aprotic solvents, there is no reason why it should decompose spontaneously in water; such decomposition would have to be pseudo-unimolecular, actually reaction with some basic component of the solution, as water or acetate ion, and this has not been detected.

The rate-determining step must then be a bimolecular reaction with hydrogen ion, but this could not be the rapid equilibrium reaction which maintains a very small concentration of undissociated xanthic acid. It is probably an attack on the oxygen bridge in the xanthate molecule, as suggested by Lewis[4]



critical complex

In this case K_0 in equation (2) is the ionization constant of acetic acid, at zero ionic strength in each solvent and at each temperature; and k is the constant for the bimolecular, rate-determining step.

Evaluation and Analysis of the Rate Constant k.—Since accurate values of K_0 for the ionization of acetic acid in the solutions used are available, it is possible to evaluate $k = k(\text{expt.})/K_0$ on the assumption that the mechanism is correct. The ionization constant of acetic acid has been measured in dioxane–water mixtures over a wide temperature range by Harned and Kazanjian,[9] and Harned and Fallon[10] have shown that accurate interpolation is possible. Values of log K_0 and log k are given in Table I for each experimental condition.

The rate constants for a reaction between two ions are related with dielectric constant, ionic strength and size of the interacting ions by the Christiansen–Scatchard equation.[11] In the absence of salt effects this equation becomes

$$\log k = \log k_\infty - \frac{Z_A Z_B \epsilon^2 N}{2.3DRT} \frac{1}{r_A + r_B} \qquad (5)$$

(9) Harned and Kazanjian, THIS JOURNAL, **58**, 1912 (1936).

(10) Harned and Fallon, *ibid.*, **61**, 2377 (1939).

(11) Scatchard, *ibid.*, **52**, 52 (1930); *Chem. Revs.*, **10**, 229 (1932).

In this expression k_∞ refers to the rate constant extrapolated to infinite dielectric constant ($D = \infty$), where coulombic forces between ions should vanish. A plot of log k *vs.* $1/D$ at constant temperature should give a straight line from whose slope the sum of the radii of the interacting ions ($r_A + r_B$), or the radius of the critical complex, may be calculated. Figure 2 gives such a plot for the five temperatures used. Values of ($r_A + r_B$) obtained from the slopes of the linear portions of these curves vary between 1.77 and 1.81 Å., with an average of 1.79 Å. Points at lower dielectric constants deviate from the linear relation, as has often been found in similar cases.[12,13,14]

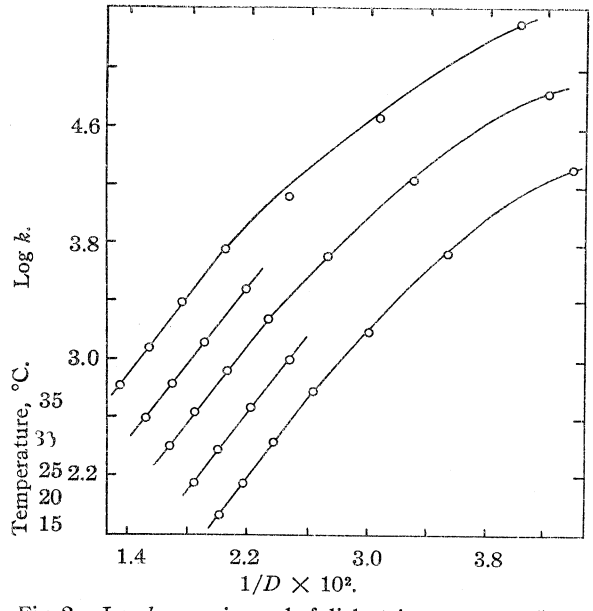


Fig. 2.—Log k *vs.* reciprocal of dielectric constant. Subtract 0.02 from abscissa values for 30°, 0.04 for 25°, etc.

The Arrhenius frequency factor (log A) and activation energy (E) were calculated by the method of least squares and are given in Table II. The equations implied fit the data of Table I with a maximum deviation of 0.05 log unit and an average deviation of <0.02 log unit. The "maximum error" of E is then about ±400 calories, the "probable error" about ±250 cal. There is no indication of variation of E with temperature over this short range.

TABLE II

EXPERIMENTAL ENERGY, FREE ENERGY AND ENTROPY OF ACTIVATION

Dioxane, %	log A	E	ΔF^*, 25°	ΔS^*, 25°
0	15.83	18380	16640	3.76
10	16.60	19100	16310	7.28
20	17.31	19670	15930	10.56
30	17.73	19750	15420	12.45
40	17.72	19150	14820	12.41
50	17.08	17530	14100	9.48
60	20.22	20960	13250	23.86

(12) Amis and LaMer, THIS JOURNAL, **61**, 905 (1939).
(13) Davis and LaMer, *J. Chem. Phys.*, **10**, 585 (1942).
(14) King and Josephs, THIS JOURNAL, **66**, 767 (1944).

The free energy and entropy of activation were calculated using the equations[15]

$$\Delta F^* = 2.3RT\ (\log RT/Nh - \log k) \quad (6)$$
$$\Delta S^* = 2.3R\ (\log A - \log eRT/Nh) \quad (7)$$

These values are given in Table II.[16] Since log A, E, ΔF^* and ΔS^* vary considerably with dielectric constant, they cannot be compared directly with similar quantities for a reaction in an ideal (gaseous) state. It was suggested by Svirbely and Warner[17] that rate constants obtained in mixed, iso-dielectric media (as temperature is varied), would be more nearly comparable to rate constants for ideal gas reactions. While this method frees ΔS^* from electrostatic effects, it still leaves log A, E and ΔF^* as variables with dielectric constant.

Probably a more satisfactory treatment is to calculate log k_∞, E_0, ΔF_0^* and ΔS_0^*, values of these quantities at infinite dielectric constant. Following the suggestion of LaMer,[18] equation (5) may be written as

$$\Delta F^* = \Delta F_0^* + \Delta F_D^* \quad (8)$$

Analogous equations for energy and entropy are $E = E_0 - E_D$ and $\Delta S^* = \Delta S_0^* - \Delta S_D^*$. The dielectric contributions are given by

$$\Delta F_D^* = \frac{Z_A Z_B \epsilon^2 N}{D(r_A + r_B)} \quad (9)$$

$$E_D = \Delta F_D^* + T\ \Delta S_D^* + RT \quad (10)$$

$$\Delta S_D^* = \frac{\Delta F_D^*}{D} \cdot \frac{\partial D}{\partial T} \quad (11)$$

The values of E_0, ΔF_0^* and ΔS_0^* should be independent of solution composition in the range of validity of equation (5), and ΔS_0^* should be the same as ΔS^* obtained from isodielectric media.

These quantities are given in Table III up to 30% dioxane, and are seen to be constant within the experimental error. The calculation is useless when D <50, since equation (5) is not valid, as shown by Fig. 2.

TABLE III

ACTIVATION ENERGY AND ENTROPY AT $D = \infty$, 25°

% Dioxane	ΔF_0^*	E_0	ΔS_0^*
0	19000	16840	−7.4
10	18970	17180	−6.1
20	19000	17310	−5.7
30	19010	17000	−7.0

Comparison with the Collision Theory.—The fundamental collision theory equation, applied

(15) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, pp. 195–199.
(16) The Arrhenius or experimental energy of activation is designated as E and differs by RT from the internal energy of activation ΔE^*.
(17) Svirbely and Warner, THIS JOURNAL, **57**, 1883 (1935); Warner, *Ann. N. Y. Acad. Sci.*, **39**, 345 (1940).
(18) LaMer, *J. Franklin Inst.*, **225**, 709 (1938).

to an ionic reaction, may take the form

$$k_\infty = Z_0 e^{-E_0/RT} \quad (12)$$

Use of k_∞ and E_0 should be most nearly comparable with a reaction between uncharged gas molecules, if calculation of the collision frequency is to take the simplest form. This frequency, Z_0, in terms of moles, liters and minutes, is given by

$$Z_0 = \frac{60N}{1000}\sigma^2\left[\frac{8\pi RT}{\mu}\right]^{1/2} \quad (13)$$

where σ is the average collision diameter and μ is the reduced molecular weight, taken in this case to equal $19 \times 121/140$.

On combining equations (12) and (13) there is obtained

$$\log \sigma = {}^1/_2 \log k_\infty - 13.92 + E_0/2730 \quad (14)$$

Table IV gives log k_∞ (equation (5), using $(r_A + r_B) = 1.79$ Å.) and the corresponding values of σ. It is evident that there is reasonable agreement with the collision theory in its simplest form.

TABLE IV

COLLISION DIAMETERS FOR $D = \infty$, 25°

% Dioxane	log k_∞	σ, Å.
0	0.65	3.72
10	.63	2.09
20	.65	1.66
30	.64	1.25

Similar calculations were made by Amis and LaMer[12] for the reaction of brom phenol blue and hydroxyl ion, and similar results were obtained.

Summary

The rate of reaction of potassium ethyl xanthate in dilute acetic acid–sodium acetate buffers has been measured, at five temperatures from 15 to 35°, in dioxane–water mixtures from 0 to 60% dioxane. The effect of added dioxane, or changed dielectric constant, on the over-all reaction, has been shown to be small. Also, in agreement with previous work, the effect of low concentrations of inert salt has been found negligibly small.

The possible mechanism of the reaction has been discussed, and the formation of a critical complex by bimolecular reaction of xanthate and hydrogen ions has been proposed as most probable. Since the ionization constant of acetic acid in dioxane–water mixtures is known, it was possible to calculate the bimolecular rate constants for the postulated rate determining step.

The variation of rate constants with dielectric constant was found to follow the predictions of electrostatic theory (the Christiansen–Scatchard equation) over the range found usable in other cases (D = 80 to 50), and reasonable values for the radius of the critical complex or $(r_A + r_B)$ were obtained.

The experimental energy, free energy and entropy of activation have been calculated, and the electrostatic contribution to these quantities has been evaluated. Constancy of the values calculated for $D = \infty$ has been found satisfactory.

It has been shown that reasonably good agreement with the simple collision theory is obtained when rate constants and activation energies extrapolated to $D = \infty$ are used in the calculations.

It is believed that these factors support the suggested reaction mechanism.

NEW YORK, N. Y. RECEIVED JUNE 11, 1949

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Molecular Freedom and Proton Transfer in Solid Long-Chain Amines[1]

BY JOHN D. HOFFMAN AND CHARLES P. SMYTH

In the course of investigations of solid long-chain alcohols[1a] a direct current conductivity effect probably attributable to proton transfer[2] was found almost uniquely associated with the solid rotator state, often called the "α phase." The term "rotator" was not meant to imply actual dynamic rotation of all the molecules, but merely their possession of sufficient energy of rotational vibration to permit of frequent passage over restricting potential barriers. The effect also appeared to a smaller extent below the transition point. No such phenomenon appeared in long-chain bromides,[3] ketones[4] or esters.[5] It was thus thought advisable to look for proton transfer and transitions in the amines. If the molecules rotated about their long axes, direct current proton transfer conductivity giving rise to Maxwell–Wagner polarization would be expected to appear.

Purification of Substances

The samples of *n*-dodecyl, *n*-tetradecyl, *n*-hexadecyl and *n*-octadecyl amines obtained from the Paragon Chemical Company were purified by a single vacuum distillation.

TABLE I

Amine	M. p., °C.	F. p., °C.	n_D
n-Octyl	0.0		
n-Dodecyl	27.5	28[6] 28.32[7]	1.4377 (30°)
n-Tetradecyl	37.6	37[6] 38.19[7]	1.4382 (40°)
n-Hexadecyl	45.6	46.77[7]	1.4389 (50°)
n-Octadecyl	52.2	53.06[7]	

(1) This research was carried out with the support of the Office of Naval Research.

(1a) Hoffman and Smyth, THIS JOURNAL, **71**, 431 (1949).

(2) Stearn and Eyring, *J. Chem. Phys.*, **5**, 113 (1937); Bernal and Fowler, *ibid.*, **1**, 515 (1933).

(3) Hoffman and Smyth, to be published.

(4) Müller, *Proc. Roy. Soc.* (*London*), **A158**, 403 (1937).

(5) Baker and Smyth, THIS JOURNAL, **60**, 122 (1938).

(6) "International Critical Tables."

(7) Ralston, Hoerr, Pool and Harwood, *J. Org. Chem.*, **9**, 102 (1944).

n-Octylamine, also from Paragon, was distilled at atmospheric pressure, b. p. 179°. Carbon dioxide, which forms the carbamates, was carefully excluded in the distillations and handling. The melting points of the purified compounds are given in the second column of Table I with literature values for comparison. Refractive indices for the D sodium line are given in the last column.

Experimental Results

The experimental method used to make dielectric constant–temperature runs at 0.5, 5.0 and 50 kc. has been described previously.[1a] In addition to the usual precautions regarding moisture entering the dielectric cell, a tube containing Ascarite was attached to the air vent on the cell to prevent contamination by carbon dioxide. The dielectric constants for the amines studied are given in Table II as a function of temperature. Only the cooling curves are given since the warming curves were very similar. The melting points were higher than the freezing points by 0.2 to 1.3°. The dielectric data are plotted in Figs. 1–5. *n*-Dodecylamine was cooled from 100 to 0° as rapidly as possible in the dielectric cell, and the dielectric constant at 0.5, 5.0 and 50 kc. plotted as a

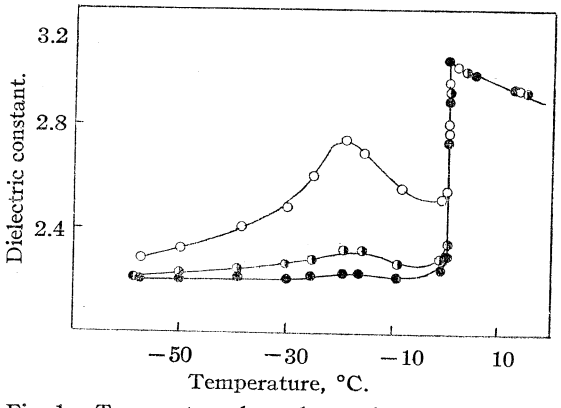


Fig. 1.—Temperature dependence of dielectric constant of *n*-octylamine. Hollow circles represent values at 0.5 kc., half-filled circles values at 5.0 kc., and filled circles values at 50 kc.

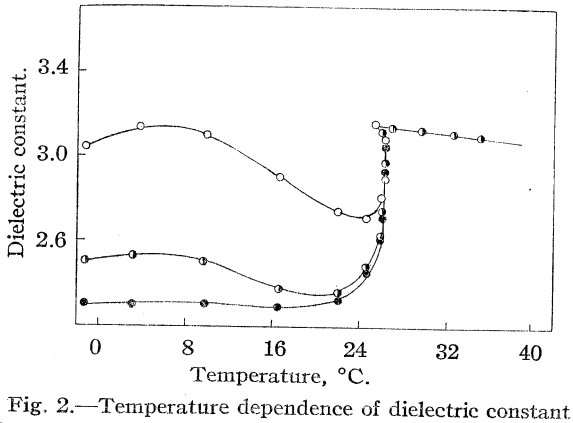


Fig. 2.—Temperature dependence of dielectric constant of *n*-dodecylamine. Hollow circles represent values at 0.5 kc., half-filled circles values at 5.0 kc., and filled circles values at 50 kc.

TABLE II

DIELECTRIC CONSTANTS OF AMINES MEASURED WITH FALLING TEMPERATURE

t, °C.	ε′ 0.5 kc.	ε′ 5 kc.	ε′ 50 kc.
	Octylamine		
12.3	3.90	3.90	3.90
2.0	..	4.05	4.05
0.2	..	..	4.13
− 0.3	..	3.90	3.90
− 0.4	..	3.55	3.53
− 0.4	..	2.70	2.70
− 0.4	3.10	2.65	2.60
− 1.3	3.05	2.58	2.50
− 8.8	3.12	2.55	2.45
−15.7	3.40	2.63	2.47
−18.7	3.48	2.63	2.47
−26.0	3.20	2.56	2.43
−29.7	2.95	2.52	2.42
−38.7	2.80	2.48	2.42
−49.7	2.63	2.44	2.41
−61.7	2.55	2.41	2.40
	Dodecylamine (Cooling)		
35.0	..	3.10	..
32.4	..	3.12	..
29.5	..	3.13	..
26.7	..	3.14	..
26.0	..	3.12	..
26.2	..	3.10	3.09
26.3	3.10	2.97	2.94
26.0	2.92	2.74	2.74
25.8	2.82	2.63	2.63
24.5	2.72	2.48	2.47
21.9	2.74	2.36	2.32
16.7	2.91	2.38	2.28
9.6	3.10	2.50	2.30
3.1	3.14	2.53	2.29
− 1.4	3.04	2.50	2.29
	Tetradecylamine (Cooling)		
39.4	..	2.90	..
36.3	..	2.94	..
36.8	2.78	2.81	2.82
36.9	2.60	2.57	2.54
36.8	2.39	2.41	2.41
36.4	2.32	2.32	2.32
35.4	2.30	2.28	2.28
32.4	2.24	2.24	2.24
28.5	2.23	2.23	2.23

Hexadecylamine (5 kc.)		Octadecylamine (5 kc.)	
55.2	2.71	58.2	2.64
45.3	2.75	53.2	2.67
45.4	2.53	50.6	2.66
45.3	2.40	51.8	2.60
44.2	2.32	51.8	2.55
42.3	2.29	51.7	2.46
34.4	2.25	51.5	2.40
28.4	2.25	49.8	2.33
19.7	2.24	43.7	2.30
		38.3	2.30
		35.5	2.29
		25.4	2.27

function of time as shown in Fig. 5. No values are given for the loss factor since they were negligibly small except for *n*-octylamine and *n*-dodecylamine in the region below the freezing point where direct current conductance was observed. The omitted curve for *n*-hexadecylamine is similar to those in Figures 3 and 4.

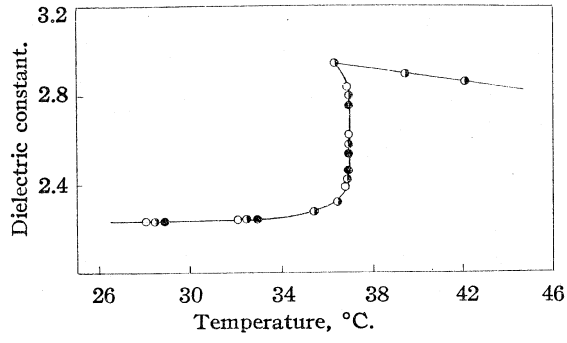


Fig. 3.—Temperature dependence of dielectric constant of *n*-tetradecylamine. Hollow circles represent values at 0.5 kc., half-filled circles values at 5.0 kc., and filled circles values at 50 kc.

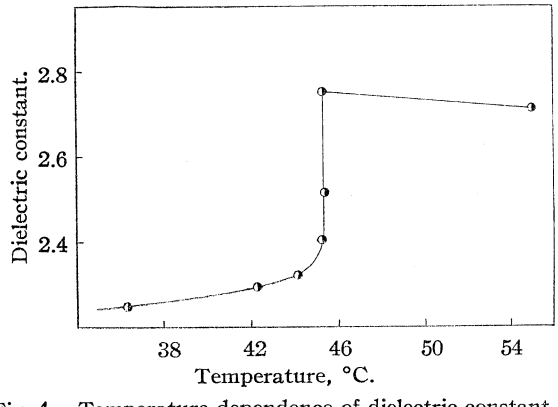


Fig. 4.—Temperature dependence of dielectric constant of *n*-hexadecylamine at 5.0 kc.

Discussion of Results

No transitions in the solid are evident in any of the compounds studied, and all of the materials appear to freeze predominantly into the stable non-rotator form. Thus the large direct current conductivity effect originally sought in this research cannot appear in full force since no α phase producing sheets of rotating $-NH_2$ groups appears. Proton transfer demands molecular rotation and a convenient path such as a sheet of $-NH_2$ or $-OH$ groups.[1a,2] A small conductivity effect appears in the two shorter amines even though few of the molecules are rotating. The effect is thus analogous to the conductivity observed in *n*-tetradecyl, *n*-octadecyl and *n*-docosyl alcohol below the transition point. The conductance is manifested as Maxwell–Wagner polarization as shown in Figs. 1, 2 and 5. The dispersion should not be confused with anomalous dispersion, since, at low frequency, the dielectric constant exceeds the extrapolated liquid value (Fig. 5) and the loss factor, ϵ'', was observed to exceed $(\epsilon_0 - \epsilon_\infty)/2$, where ϵ_0 is the static dielectric constant and ϵ_∞, the so-called optical dielectric constant. It is thus clear that, as in the alcohols, the high dielectric constant is not due to orientation polarization. When $\epsilon'' \geqq \epsilon'$ and when two phases of different conductivity are present, large dielectric constants exceeding those possible by orientation polarization are commonly observed.[1a] In *n*-octylamine and *n*-dodecylamine the high conductivity observed for some distance below the freezing point makes $\epsilon'' \geqq \epsilon'$, and causes the dielectric constant to be abnormally high, suggesting the possible coexistence of two phases with proton transfer occurring in one of them. In Fig. 5 it is shown that the dielectric constant of *n*-dodecylamine at 0° at low frequency drops with time, just as was found for *n*-octadecyl alcohol. This indicates that a slow change of condition perhaps, a trace of vertical phase transforming to tilted, often called a β_1–β_2 transition, is taking place, wherein molecules capable of molecular freedom and proton transfer are reorienting into more stable positions in the lattice. It should be emphasized that the combination of proton transfer and Maxwell–Wagner effect greatly magnifies the effect of what is undoubtedly a rather small amount of molecular freedom in the solid state.

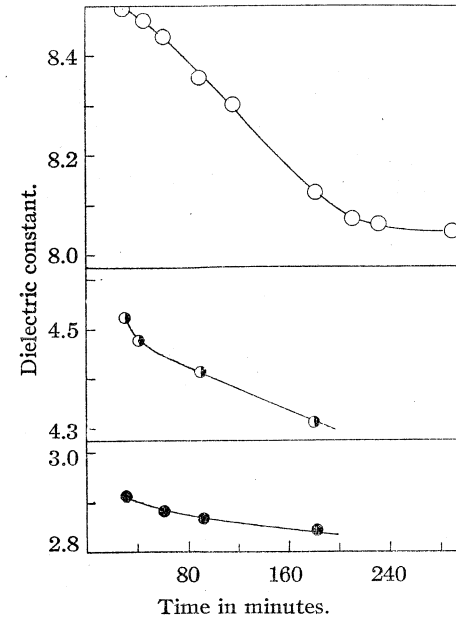


Fig. 5.—Dependence of dielectric constant of *n*-dodecylamine at 0° on time. Sample was cooled rapidly from 100 to 0°. Hollow circles represent values at 0.5 kc., half-filled circles values at 5.0 kc., and filled circles values at 50 kc.

The pronounced maximum in the low frequency dielectric constant which occurs at about 20° below the freezing point in *n*-octylamine and *n*-dodecylamine has no analog in the alcohols. The maximum would seem to suggest a second order transition, but this view must be regarded with

caution. It has been shown that the observed dielectric constant due to Maxwell–Wagner effect depends on the ratios of the conductivities of the two phases.[1a,8] It is much more likely that the ratio of the conductivities of the two phases varies in such a way as to produce a maximum of the type shown in Figs. 1 and 2.

Molecular freedom in the solid state may have several origins. Impurities may cause the formation of small amounts of liquid with corresponding molecular freedom. Premelting[9] has been attributed by Oldham and Ubbelohde to the effect of a network of coöperative flaws which breaks up a crystal into a mosaic producing a sort of unsharp melting and molecular freedom. The flaws may stem from impurities or thermal fluctuations. Premelting is generally considered to be operative only near the melting point. Another cause of molecular freedom in the solid state is the rotation of a molecule from one equilibrium position to another due to coöperative loosening of the lattice. The term "prerotation" has been used to describe this effect below the transition point.[10] This effect will also occur if no transition point is present. Operationally, prerotation differs from premelting in that it covers a much wider temperature range, and its onset is more gradual. Prerotation will be used henceforth in this paper to describe the occasional rotation or reorientation of molecules in a solid at any temperature, probably due to cooperative loosening of the lattice. Finally, molecular freedom may result in a solid from the presence of a stable or unstable rotator phase, or a substance which contains a portion of such a rotator phase. A rotator phase will yield a liquid-like dielectric constant.

In the present case, impurities and premelting may be ruled out as the cause of the molecular freedom in the lattice 20° below the freezing point in the two shorter amines, so the effect must be due to prerotation or the presence of a small amount of a rotator phase which is unstable. Inasmuch as prerotation is an equilibrium phenomenon, it would appear, in view of the drop in dielectric constant with time observed in *n*-dodecylamine, that the major part of the molecular freedom may be due to the presence of a small amount of unstable rotator phase. The longer amines show a definite decrease of dielectric constant with temperature far below the freezing point with no Maxwell–Wagner effect. This is characteristic of prerotation. The decrease of conductivity in the longer amines may be ascribed, in part, to the fact that fewer dipoles are present per cc. and, in part, to a lower cooling rate used in the measurements.

The amines differ from the corresponding alcohols in that they have no rotational transitions in the solid in the range studied. This may be connected with the fact that hydrogen-bonding in the amines is weaker than in alcohols or acids. The differing degree of hydrogen-bonding may be seen by comparison of the boiling points of the eight-carbon acid, alcohol and amine. *n*-Octanoic acid boils at 237°, *n*-octyl alcohol at 195°, and *n*-octylamine at 179°. An unassociated long-chain molecule will generally exhibit rotation about the long axis, as manifested by solid transitions, if it is at least eighteen to twenty-four carbon atoms long. Thus, *n*-docosyl bromide and *n*-docosane show monotropic transitions, while *n*-octadecyl bromide and *n*-hexadecane do not. Since hydrogen-bonding will change the effective chain length, we might expect the compounds with the strongest hydrogen-bonding (*e. g.*, acid dimers) to have transitions at shorter formula weight chain length than weakly bonded substances. In accordance with this, acids show transitions when the chain length is eleven carbons,[11] and alcohols at thirteen carbons,[11] while amines do not show transitions at eighteen or shorter. Thus, the eleven-carbon acid dimer, which has an effective chain length of about twenty-four atoms behaves like a hydrocarbon of that length. It should be pointed out that, in addition to increasing the effective length of a molecule, hydrogen-bonding may stabilize the tilted form, which does not rotate, and thus alter the chain length at which transitions are observed. It is likely that a solid rotator state will be found in amines of twenty-two to twenty-six carbon atoms in length.

The evidence for proton transfer rests mainly on the appearance of direct current conductivity accompanied by strong Maxwell–Wagner polarization below the freezing point in *n*-octylamine and *n*-dodecylamine, and the similarity of this phenomenon to that found below the transition points in the alcohols. The dielectric constant showed time dependence in these materials, which strengthened the correlation with the alcohols. Since molecular rotation is a requirement for proton transfer, some molecular freedom was indicated. It has been pointed out that the failure of any rotational transitions to appear in the amines may be due to the different degree of hydrogen bonding in the amines as compared to the alcohols. Prerotation was observed in the higher members of the series.

Summary

The dielectric constants of *n*-octyl, *n*-dodecyl, *n*-tetradecyl, *n*-hexadecyl, and *n*-octadecyl amines have been investigated in the vicinity of the melting point. No solid phase corresponding to all the molecules rotating about their long axes was detected, so that the large apparent direct current conductivity due to proton transfer associated with the rotator state could not be investigated. In *n*-octylamine and *n*-dodecylamine the dielectric data indicated the presence of a small conductivity in the solid state attributable to proton transfer. The dielectric data for the longer mem-

(8) Frosch, *Ann. Physik*, **42**, 254 (1942).

(9) Oldham and Ubbelohde, *Proc. Roy. Soc.* (*London*), **A176**, 50 (1940).

(10) Smyth, *Trans. Faraday Soc.*, **42A**, 175 (1946).

(11) Meyer and Reid, THIS JOURNAL, **55**, 1574 (1933).

bers indicate some molecular freedom below the freezing point, but no Maxwell–Wagner polarization due to conductivity was encountered in the cases of the three longer molecules. The dielectric properties of the alcohols and amines have been compared, and tentative reasons advanced for the absence of the rotator state in the amines.

PRINCETON, NEW JERSEY RECEIVED MARCH 29, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

A Synthesis of Vinylcyclopropane[1]

BY ROSS VAN VOLKENBURGH, K. W. GREENLEE, J. M. DERFER AND C. E. BOORD

The hydrocarbon vinylcyclopropane is interesting from both the synthetic and theoretical points of view. In 1922, Demjanov and Dojarenko[2] prepared it by exhaustive methylation of the amine obtained from the oxime of methyl cyclopropyl ketone, and they stated that this hydrocarbon could not be prepared by the dehydration of methylcyclopropylcarbinol. It has sometimes been assumed that vinylcyclopropane is "*incapable of existence.*"[3] Recently there has been speculation concerning the possible utility of the hydrocarbon in the manufacture of synthetic rubber.[4] In the present work methylcyclopropylcarbinol was successfully dehydrated to vinylcyclopropane, and some of the hydrocarbon's properties were observed.

The methylcyclopropylcarbinol was prepared by reduction of methyl cyclopropyl ketone; four different methods were tried. Catalytic hydrogenation gave the desired carbinol along with a nearly equal amount of the close-boiling 2-pentanol. Reduction by sodium and ammonium sulfate in liquid ammonia gave ring-opening products exclusively. The Meerwein–Ponndorf method gave the desired carbinol in low yield along with large amounts of condensation products. The only method which gave methylcyclopropylcarbinol exclusively and in high yield was reduction with lithium aluminum hydride.

The dehydration of methylcyclopropylcarbinol was accomplished by refluxing it with a catalytic amount of sulfuric acid, giving 39% yield of vinylcyclopropane with 0.8° boiling range (Fig. 1). The dehydration was extremely slow, apparently because of the influence of the cyclopropane ring adjacent to the carbinol group; this may explain the failure of previous workers to observe it. The structure of the hydrocarbon was proved by an ozonolysis experiment from which both formaldehyde and cyclopropanecarboxaldehyde were identified. The physical properties listed in Table I were determined on a sample of vinylcyclopropane, estimated from a time–temperature freezing curve to be 96 ± 2 mole % pure.

Evidence for conjugation between the double bond and the cyclopropane ring of vinylcyclopropane is seen in the boiling point which is 4.5° higher than that of ethylcyclopropane; by contrast, the double bond produces a 7.8° lowering when the related 2-methylbutane is converted to 3-methyl-1-butene. Similarly, the refractive index of vinylcyclopropane shows an elevation of 0.0264 (at 20°) which approaches the elevation of 0.0332 exhibited by 2-methyl-1,3-butadiene.

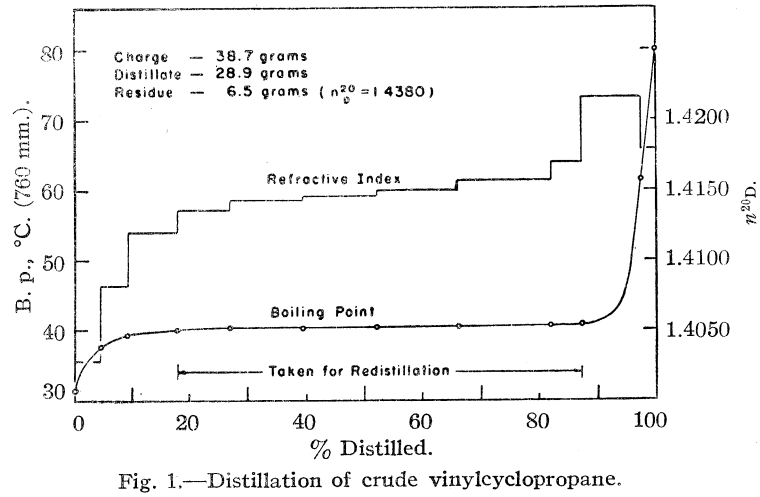


Fig. 1.—Distillation of crude vinylcyclopropane.

TABLE I

VINYLCYCLOPROPANE

	This work	Literature[2]
F. p., °C.	−112.6	....
B. p., °C. (760 mm.)	40.41	40.0 to 40.2 (755 mm.)
d^{20}_4	0.7160	0.723 at 18°
$n^{20}D$	1.4156	1.4172 at 15°

A small portion of the hydrocarbon was hydrogenated over Raney nickel. The product, insufficient for purification by distillation, was identi-

(1) This paper forms part of the dissertation submitted in 1949 by Ross Van Volkenburgh to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. It was presented before the Organic Division at the 116th meeting of the American Chemical Society. The investigation was sponsored by the American Petroleum Institute Research Project 45 in coöperation with The Ohio State University Research Foundation.

(2) Demjanov and Dojarenko, *Ber.*, **55B**, 2718 (1922).

(3) Whitmore, "Organic Chemistry," D. Van Nostrand Company, Inc., New York, N. Y., 1937, p. 632.

(4) Jones, *Chem. Eng. News*, **27**, No. 7, 454 (1949).

fied spectroscopically as ethylcyclopropane containing *n*-pentane as impurity (about 30 mole % on the basis of refractive index). The *n*-pentane was formed by hydrogenolysis of the cyclopropane ring through "1,4-addition" of hydrogen as in the case of a conjugated diene.[5] Other reactions in which the cyclopropane ring appears to possess many of the attributes of a double bond have been observed.[6]

The infrared absorption spectrogram of the vinylcyclopropane on which physical properties were determined is given in Fig. 2. The band at 9.9 μ, believed to be characteristic of the cyclopropane ring,[7] appears to be present, although obscured by strong olefin absorption in this region (type I olefins characteristically show absorption at 9.5 and 10.1 μ).

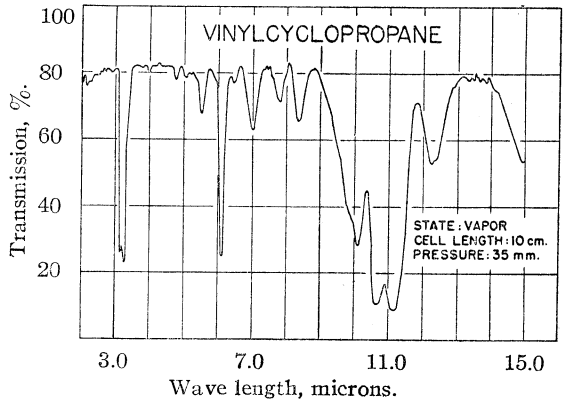


Fig. 2.—Infrared absorption spectrogram of vinylcyclopropane.

Unlike typical conjugated diolefins, vinylcyclopropane does not react with maleic anhydride at temperatures up to 100°. However, preliminary experiments indicate that it does polymerize rapidly in the presence of benzoyl peroxide when exposed to ultraviolet light.

Experimental

Reduction of Methyl Cyclopropyl Ketone

By Catalytic Hydrogenation.—Hydrogenation of methyl cyclopropyl ketone[8] over nickel-on-kieselguhr at 50 to 60° and 600–1100 p. s. i. gave a mixture of 2-pentanol (b. p. 119.85°) and methylcyclopropylcarbinol in the ratio of 2:3; distillation at about 20-plate efficiency indicated the composition but was not nearly adequate for a quantitative separation.

By Sodium and Ammonium Sulfate in Liquid Ammonia.—It has been found previously in this Laboratory that certain ketones are reduced to the corresponding carbinols by sodium in liquid ammonia in the presence of ammonium sulfate. The details of this type of reaction will be published later. When the method was applied to methyl cyclopropyl ketone, distillation of the reaction product gave no evidence for methylcyclopropylcarbinol, the desired product; only 2-pentanone and 2-pentanol were isolated. It is believed that "1,4-addition" of hydrogen first occurs, yielding 2-pentanone in its enolic form; further reduction of this ketone would then yield 2-pentanol.

By Aluminum Isopropoxide.—This reaction was carried out on methyl cyclopropyl ketone by essentially the same procedure given by Wilds[9] for the reduction of crotonaldehyde. Crude methylcyclopropylcarbinol (b. p. 119.2 to 124.1°, $n^{20}D$ 1.4394 to 1.4323) was obtained in 23% yield, along with higher boiling by-products, believed to be carbinols of higher molecular weight.

By Lithium Aluminum Hydride.—The procedure followed was essentially that described by Nystrom and Brown.[10] Distillation of the reaction product gave an 80% yield of methylcyclopropylcarbinol (b. p. 121.8 to 123.7°, $n^{20}D$ 1.4283 to 1.4317). Of this carbinol, about three-fourths had a constant boiling point and refractive index; the physical properties of this material are listed in Table II.

TABLE II

METHYLCYCLOPROPYLCARBINOL

	This work	Henry[11]
B. p., °C. (760 mm.)	123.5	123–124
M. p., °C.	−32.1	.....
d^{20}_4	0.8893	0.88778
$n^{20}D$	1.4316	1.42966

From a sample of this material, the phenyl urethan derivative was prepared by the method of Shriner and Fuson.[12] After two recrystallizations from "Skellysolve C," the melting point of the derivative was 69.6–70.5° (cor.).

Vinylcyclopropane

Preparation.—Methylcyclopropylcarbinol (65.8 g., 0.76 mole), along with 12 drops of concentrated sulfuric acid, was placed in a flask attached to a small fractionating column packed with glass helices. The olefin material distilled as it formed, and the dehydration proceeded steadily but very slowly, yielding only 45 ml. of crude product during two days at reflux temperature (about 120°). Addition of 12 drops of *p*-toluenesulfonic acid gave no noticeable increase in rate, but slow dehydration continued for another day. A considerable amount of carbonaceous material remained in the flask.

After percolation through a 10-cm. column of silica gel, Dry-Ice-cold, the crude product (38.7 g.) was distilled at about 20-plate efficiency to obtain 20.0 g. (a 39% yield from carbinol) of good vinylcyclopropane (b. p. 40.0 to 40.8°, $n^{20}D$ 1.4136 to 1.4170); the curves describing this distillation are given in Fig. 1.

Several differences are to be noted between the dehydration of methylcyclopropylcarbinol and dimethylcyclopropylcarbinol.[6a] The latter, a tertiary alcohol, dehydrated easily over sulfuric acid, giving nearly pure isopropenylcyclopropane in 80% yield. By contrast, methylcyclopropylcarbinol appears to dehydrate very slowly and to give a mixture containing a number of components. The impurity which caused the low initial boiling point in the distillation may have been 1,4-pentadiene, isoprene or fragmentation products. The higher boiling impurity probably was 1,3-pentadiene (*cis* and/or *trans*), causing a gradual rise in refractive index.

(5) Hydrogenolysis of the cyclopropane ring in such pseudoconjugated systems can apparently be avoided by the use of a barium-promoted copper chromite catalyst. See Slabey, Wise and Gibbons, THIS JOURNAL, **71**, 1518 (1949).

(6) (a) Van Volkenburgh, Greenlee, Derfer and Boord, *ibid.*, **71**, 172 (1949). (b) Derfer, Greenlee and Boord, *ibid.*, **71**, 175 (1949). (c) Mariella, Peterson and Ferris, *ibid.*, **70**, 1494 (1948). (d) Rogers, *ibid.*, **69**, 2544 (1947). (e) Allen and Boyer, *Can. J. Research*, **9**, 159 (1933). (f) Carr and Burt, THIS JOURNAL, **40**, 1590 (1918). (g) Kishner, *J. Russ. Phys.-Chem. Soc.*, 1163 (1911).

(7) Derfer, Pickett and Boord, THIS JOURNAL, **71**, 2482 (1949).

(8) U. S. Industrial Chemicals, Inc.

(9) Wilds, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Chapter 5, p. 200. The procedure given was patterned after that of Young, Hartung and Crossley [THIS JOURNAL, **58**, 100 (1936)].

(10) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

(11) Henry, *Bull. soc. chim. Belg.*, **40**, 647–656 (1931).

(12) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 136.

The good fractions from the distillation described above (Fig. 1) were combined with similar material from an identical run, and the composite was redistilled at about 20-plate efficiency to obtain the 16 g. of material on which the physical properties in Table I were determined.

Ozonolysis.—Vinylcyclopropane, 3.6 g. (0.053 mole), was ozonized in the apparatus described by Henne and Perilstein.[13] *n*-Pentane was used as the solvent, and the solution was immersed in a Dry Ice-cooled medium.

The ozonide solution was decomposed by the method of Cook and Whitmore[14] in which the ozonide solution is added dropwise to Raney nickel in *n*-pentane with stirring. The pentane was stripped off through a short Vigreux column, and the residue, after heating one and one-half hours on a steam-bath to assure complete decomposition of the ozonide, was extracted with *n*-pentane. The filtered extract was fractionated to remove the pentane but the residue failed to give a derivative with 2,4-dinitrophenylhydrazine, though it should have contained the bulk of the expected cyclopropanecarboxaldehyde. Presumably the aldehyde was hydrogenated or decarbonylated by contact with the hot Raney nickel.

The pentane stripped from the ozonide decomposition was fractionated at about 20-plate efficiency giving a distillate rich in formaldehyde and a residue from which cyclopropanecarboxaldehyde was isolated as the 2,4-dinitrophenylhydrazone (8% yield). This derivative, after recrystallization, melted at 182–185°, and there was no depression when it was mixed with an authentic sample.[15]

(13) Henne and Perilstein, THIS JOURNAL, **65**, 2183 (1943).

(14) Cook and Whitmore, *ibid.*, **63**, 3540 (1941).

(15) Kindly furnished by Christopher L. Wilson, The Ohio State University.

Formaldehyde was identified by extracting it from the pentane distillates with small amounts of water, and preparing the dimedone derivative. The crude derivative (3.3 g. or 21% yield) was leached with 10 ml. of hot methyl alcohol, filtered and dried to yield 2.8 g. of crystals with a melting point of 187.5–189.5° (cor.). A mixed melting point with an authentic sample (m. p. 188–189°) showed no depression.

Hydrogenation.—A portion (7.3 g., 0.11 mole) of the vinylcyclopropane on which physical properties were determined was hydrogenated over 0.5 g. of Raney nickel in absolute ethanol at 65 p. s. i. g. and 10 to 20°. Absorption of hydrogen ceased after about six hours. The hydrogenate was steam distilled, washed thoroughly with water and dried by percolation through a small column of silica gel to obtain a 64% yield of material with a refractive index of 1.3724. The infrared absorption spectrum of this product corresponded closely to that of an authentic sample of ethylcyclopropane,[7] but showed minor bands indicating the presence of *n*-pentane (about 30% on the basis of refractive index). Similar results had been obtained in the hydrogenation of isopropenylcyclopropane.[6a]

Infrared Absorption Spectra.—The spectra determined in the course of this work were measured on the Beckman IR-2 Spectrophotometer of the Department of Chemistry at The Ohio State University.

Summary

Vinylcyclopropane has been prepared from methyl cyclopropyl ketone. Additional evidence for the double bond character of the cyclopropane ring has been presented.

COLUMBUS, OHIO RECEIVED APRIL 30, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF CARSON–NEWMAN COLLEGE]

Polynitro Paraffins

BY CARL T. BAHNER AND HARVEY T. KITE[1]

Dinitro paraffins in which the nitro groups are in a 1,3-position to each other and the middle carbon atom carries no hydrogen atom have been prepared by Fraser and Kon,[2] Hass and Bourland,[3] and Larrison and Hass[4] by reaction of nitromethane with ketones. Hass[5] has found evidence that the reaction of nitromethane with acetone takes place through the formation of 1-nitro-2-methylpropene which adds nitromethane to form dinitroneopentane. Lambert and Piggott[6] have reported the preparation of dinitro compounds by "heating a primary or secondary nitroparaffin or nitroether or nitrothioether .... with a Δ^{α}-nitroolefin .... in the presence of a basic substance." Prior to the publications by Hass and Lambert and their associates we had undertaken the preparation of polynitro paraffins by the addition of alkali salts of nitro paraffins to nitro olefins. Our experiments throw light on matters not investigated by them.

(1) Present address: Carbide and Carbon Chemicals Corporation, Oak Ridge, Tennessee.

(2) Fraser and Kon, *J. Chem. Soc.*, 604–610 (1934).

(3) Hass and Bourland, U. S. Patent 2,343,256, March 7, 1944.

(4) Larrison and Hass, U. S. Patent 2,383,603, Aug. 28, 1945.

(5) Hass, *Ind. Eng. Chem.*, **35**, 1151 (1943).

(6) Lambert and Piggott, *J. Chem. Soc.*, 1489–1492 (1947); British Patent 584,789, July 24, 1944.

Using nitro olefins of the type $R^1C(NO_2)=CHR^2$, where R^1 and R^2 represent H or an alkyl radical, and nitro paraffins containing two or more carbon atoms we have succeeded in obtaining a type of compound which it is inherently impossible to prepare from ketones by the methods of Fraser and Kon, Hass, Larrison and Bourland. We have found that the alkali metal salts of the nitro paraffins give much better results than the use of nitro paraffins together with a basic catalyst. For example, the gradual addition of 2-nitro-1-butene to an alcoholic solution of an equivalent quantity of potassium salt of *aci*-2-nitropropane gave about 90% of the theoretical yield of crude potassium salt of 3,5-dinitro-3-methylhexane, from which the free dinitro compound was recovered readily by treatment with acetic acid. On the other hand, no 3,5-dinitro-3-methylhexane was isolated from a reaction mixture of equimolecular quantities of 2-nitropropane, diethylamine and 2-nitro-1-butene. The use of a quantity of potassium hydroxide sufficient to convert only one-fourth of the 2-nitropropane into the potassium salt resulted in the formation of a viscous high molecular weight product instead of the dinitro paraffin, while the use of a large excess of so-

dium ethylate over the amount necessary to produce the sodium salt of the 2-nitropropane led to the conversion of a large portion of the nitro olefin into a nitro ether.[7] Metallic sodium added to an equimolecular mixture of 2-nitro-1-butene and 2-nitropropane at 8° did not appear to react immediately, but within a few minutes produced a violent reaction terminating in a mild explosion. For best yields it is desirable that the nitro olefin be added in small quantities with vigorous stirring to a solution of the alkali salt of the nitro paraffin at near or below room temperature and that the reaction mixture be acidified with a weak acid as soon as the addition reaction is complete.

Distillation of the dinitro compounds which we prepared was made more difficult by a tendency toward decomposition at high temperature. However we succeeded in purifying 3,5-dinitroheptane, 3,5-dinitro-3-methylhexane and 1,3-dinitro-2,2-ethyl-3-methylbutane by crystallization from methanol solution at Dry-Ice temperature.

Our chemical process is not limited to the preparation of dinitro paraffins, since the alkali metal salt of the dinitro compound obtained in the first step can be allowed to react in the same manner with one or more additional molecules of nitro olefin to form high molecular weight polynitro compounds.

Experimental

Nitro Paraffins.—The nitro paraffins used in these experiments were supplied by the Commercial Solvents Corporation.

Nitro Olefins.—The nitro olefins used were prepared by heating the acetates of the corresponding nitro alcohols with sodium acetate, by a modification of the method of Schwarz and Nelles.[8] The nitro ester mixed with about 5% by weight of anhydrous sodium acetate in a flask attached to a Vigreux column and condenser was heated in an oil-bath at 110–135° at a pressure of 20–50 mm., thus distilling off the decomposition products as they were formed. This procedure prevented the violent decomposition sometimes encountered when the heating was done at a higher pressure. The distillate was treated with a saturated solution of sodium carbonate to remove the acetic acid, washed with water, dried over calcium chloride, and used at once to avoid polymerization.

3,5-Dinitro-3-methylhexane.—Forty-five grams (0.5 mole) of 2-nitropropane was added to 221 ml. of 2.259 *N* alcoholic potassium hydroxide (0.5 mole) to form the potassium salt. This solution was chilled in an ice-bath and 50.2 g. (0.497 mole) of fresh 2-nitro-1-butene added in small portions with vigorous stirring over a period of thirty minutes, keeping the temperature at 18–20°. At the end of this time the reaction mixture suddenly deposited a large quantity of white crystals of the potassium salt of *aci*-3,5-dinitro-3-methylhexane. After dilution with water to approximately 500 ml. the salt was converted to 3,5-dinitro-3-methylhexane by acidifying with acetic acid, a 90% yield of crude product being obtained. Repeated recrystallization from chilled methanol yielded an analytically pure product in the form of white crystals which could be kept indefinitely in an ice-chest at 4° but melted below 21° to a liquid $n^{25}D$ 1.451. *Anal.* Calcd. for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42. Found: C, 43.93; H, 7.22.[9]

1,3-Dinitro-2-ethyl-3-methylbutane.—An 85% yield of crude 1,3-dinitro-2-ethyl-3-methylbutane was obtained from 1-nitro-1-butene and potassium 2-nitropropane. A sample was crystallized repeatedly from redistilled methanol by chilling with Dry Ice–acetone mixture and the white needle-shaped crystals were washed quickly with chilled methanol. Since the moist crystals melted below 5°, the operation was carried out in a cold storage room. After removal of remaining traces of solvent by warming the melted crystalline material to 50° at 1 mm. it had the following properties: $n^{25}D$ 1.463; d^{25}_4 1.152. MR_D predicted: 45.77. Found: 45.49. *Anal.* Calcd. for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42. Found: C, 43.99; H, 7.34.

3,5-Dinitroheptane.—This compound was prepared from potassium 1-nitropropane and 2-nitro-1-butene in a similar manner, but the yield was not as good as the yields of the two compounds described above, possibly because of its structure. The symmetrical structure resulted in its melting point being above room temperature. The long white needle-shaped crystals, m. p. 33°, have a mild menthol like odor and can be kept for years. *Anal.* Calcd. for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42. Found: C, 44.53; H, 7.26.

Acknowledgments.—The authors wish to express their appreciation to Mrs. Lucia Zachert Stumpe and Mr. William K. Easley for assistance in carrying out laboratory operations and to the Commercial Solvents Corporation for supplying nitro paraffins and 2-nitro-1-butanol.

Summary

New polynitro compounds having the nitro groups in a beta position to one another have been synthesized by the addition of an alkali salt of a nitro paraffin to a nitro olefin and treatment of the resulting salt with a weak acid.

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(7) *Cf.* Bahner, U. S. Patent 2,391,815, Dec. 25, 1945; *J. Tenn. Acad. Sci.*, **23**, 281–282 (1948).

(8) Schwarz and Nelles, U. S. Patent 2,257,980, Oct. 7, 1941.

(9) Analyses were carried by Dr. Carl Tiedcke, 705 George St., Teaneck, N. J.

[CONTRIBUTION FROM PULP MILLS RESEARCH, DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF WASHINGTON]

Lignin. III. Fractional Precipitation of Barium Lignin Sulfonates from Water by Ethanol

BY AARON E. MARKHAM, QUINTIN P. PENISTON AND JOSEPH L. MCCARTHY

Introduction

Several investigations of the empirical composition of lignin sulfonic acids have been carried out by separating the acids or their salts into fractions which were then analyzed. Fractionation was conducted by Erdtman[1] with organic bases, by Racky[2] with hydrofluosilicic acid, by Lautsch and Piazolo[3] with benzacridine and by Schwabe and Hahn[4] with propanol. In all these cases, fractions were precipitated directly from sulfite waste liquor, and considerable departures from uniformity in composition within a particular series of fractions are apparent. Also there seems to be no clear evidence of fractionation on a basis of molecular size of lignin sulfonates. Since these departures might have resulted from the presence of non-lignin substances, it seemed that they might be eliminated by study of lignin sulfonates previously purified by dialysis.[5] Thus the present investigation has been carried out to effect a fractionation of non-dialyzable lignin sulfonates in order to study the uniformity of composition and the range of diffusion coefficients manifested by the several fractions.

Experimental

Preparation of Barium Lignin Sulfonate Solution.—Calcium sulfite waste liquor (from about 85% western hemlock and 15% white fir woods) from a commercial source was subjected to continuous countercurrent dialysis[5] against distilled water to yield an aqueous solution of purified non-dialyzable lignin sulfonates containing about 65% of the methoxyl originally present in the liquor. This calcium lignin sulfonate solution was evaporated under reduced pressure to a concentration of about 130 g. of total solids per liter. Calcium and other metallic ions were removed by cation exchange resin treatment (Ionex No. 2),[6] and the ash-free solution of lignin sulfonic acids was treated with barium carbonate in quantity just sufficient to neutralize the strong acids, as determined by conductometric analysis. A small precipitate of barium sulfate, probably resulting from cleavage and oxidation of small amounts of loosely combined sulfur dioxide, was removed by centrifugation. The aqueous solution of barium lignin sulfonates (121.9 g. of total solids per liter) was fractionally precipitated.

Fractionation Technique.—Fractionation was conducted in triplicate. Into each of three 250-ml. centrifuge flasks was placed 75 ml. of the solution of barium lignin sulfonate. With the flasks in a water-bath at 20.5 ± 0.1°, increments of absolute ethanol (*n*-propyl and isopropyl alcohols were found to be effective as precipitants at lower concentrations than ethanol, but yielded systems of two phases that were not easily separated) were added dropwise to each, with continuous stirring. The addition of each increment required about an hour, and stirring was continued for three hours more. The first increments were of 10 ml. each, this volume being increased to secure the later fractions. After a total of twenty-four hours in the thermostat for each precipitation, the solids were centrifuged from the solution, the solution decanted off, and the solids washed from the flasks with water. The weights of the flasks and contents at each step in the operations were taken. From these data the ethanol content of the solution as each fraction was precipitated was calculated. The final composition of the solution so estimated agreed within 0.1% with the figure obtained by analysis of the final solution by distillation and density determination.

Treatment of Fractions.—The solution of each fraction was evaporated under reduced pressure (about 40°) nearly to dryness, then redissolved in water, and again taken to dryness in a vacuum desiccator over calcium chloride. This repeated evaporation served to remove completely the ethanol, which if present would give rise to erroneously high results in the methoxyl determination. Drying was continued to constant weight in a vacuum oven at 60° and 15 mm. pressure (about four hours). The weights of the corresponding fractions from the triplicate experiments were nearly identical. Corresponding fractions were combined.

Characterization of Fractions.—Methods used for chemical analyses have been previously described.[5] Of the original total solids, methoxyl, sulfur and sulfated ash, 99.9, 97.4, 100.3 and 101.9%, respectively, were accounted for in the several fractions.

Extinction coefficients were calculated from absorption data secured from 3500 to 2400 Å, using a Beckman Quartz Spectrophotometer at minimum slit width. Silica cells with a 10-mm. light path were used. Absorption was measured at 50-Å. intervals for aqueous solutions of the barium lignin sulfonate fractions at two concentrations (1.00 and 5.00 mg. methoxyl per liter) buffered at *p*H 5.0 with 0.001 *M* acetate buffer.

Diffusion coefficients were determined by the solution-to-gel method of Felicetta, Markham, Peniston and McCarthy.[7]

Water Content of Fractions.—The water content of several fractions was estimated by measurement of the volume of water vapor evolved from a sample on heating at low pressure. The apparatus was a modification of that used by Browne and Houlehan,[8] and was so constructed that the evolved vapor could be condensed in an attached capillary tube, and its saturated vapor pressure, melting point and vapor density determined.

Discussion

A purified barium lignin sulfonate preparation has been fractionated by precipitation from aqueous solution by addition of increments of ethanol. Ten fractions were obtained at characteristic ethanol concentrations and the last was recovered from the remaining solution. Sufficient time was allowed at each solvent composition so that equilibrium in precipitation is believed to have been approximated. The several fractions were precipitated from solutions containing lignin sulfonates in rather high concentration in order to

(1) Erdtman, *Svensk. Papperstidn.*, **45**, 374, 392 (1942).
(2) Racky, *Cellulosechem.*, **20**, 22 (1942).
(3) Lautsch and Piazolo, *ibid.*, **22**, 48 (1944).
(4) Schwabe and Hahn, *Holzforschung*, **1**, 42, 79 (1948).
(5) Peniston and McCarthy, THIS JOURNAL, **70**, 1324 (1948).
(6) Manufactured by the Dow Chemical Co., Midland, Mich.
(7) Felicetta, Markham, Peniston and McCarthy, THIS JOURNAL, **71**, 2879 (1949).
(8) Browne and Houlehan, *ibid.*, **35**, 649 (1913).

TABLE I

FRACTIONATION OF BARIUM LIGNIN SULFONATE[a]

Fraction	Cumulative % solids pptd.	Wt. % ethanol in solvent	Methoxyl, %	Sulfur, %	Sulfated ash, %	Carbon,[b] %	Hydrogen,[b] %	Diff. coeff. sq. mm./day
0	0	10.2	...	..	..	...	..	..
1	20.24	18.6	10.78	4.82	18.1	48.38	4.58	6.1
2	29.23	26.0	11.16	4.77	17.4	46.96	4.73	5.7
3	36.78	32.4	10.87	5.06	18.2	...	..	5.8
4	47.40	37.8	10.84	5.28	18.4	45.50	4.77	6.6
5	57.66	42.4	10.78	5.42	19.8	...	..	7.1
6	66.21	46.4	10.53	5.68	20.4	...	..	8.7
7	72.70	49.8	10.65	5.77	20.8	44.12	4.80	9.8
8	77.53	52.8	10.62	5.74	22.1	...	..	10.6
9	83.88	57.9	10.53	5.86	21.8	...	..	12.0
10	90.33	65.5	10.68	6.19	21.5	44.18	4.41	13.4
N	99.90	Not pptd.	10.59	5.67	20.3	44.55	4.58	16.7
Initial material		..	11.03	5.34	19.1	...	..	..

[a] Duplicate analyses for methoxyl, S, ash, C and H departed from the averages not more than 0.06, 0.05, 0.5, 0.10 and 0.06%, respectively, except fract. 6, methoxyl, 0.08%; fract. 2, S, 0.13%; and fract. 8, ash, 0.9%. Diffusion coefficient departed from the averages not more than 0.45 mm.²/day. [b] Microanalyses by Microchemical Specialties Co., Berkeley, Calif.

provide adequate material for careful characterization, although sharpness of fractionation was probably thereby sacrificed.[9]

The analytical characteristics of the several barium lignin sulfonate fractions are found to be quite similar (Table I). These quantities, taken with the weights of the fractions, yield satisfactory material balances. Considering the precipitated fractions in order obtained, there is observed a trend of decrease in content of carbon and methoxyl, and of increase in content of sulfur and sulfated ash. These differences are not large and, while possibly affecting the precipitability of the barium lignin sulfonates, they are not believed to be controlling factors.

Before analysis, the fractions were dried to constant weight in a vacuum oven at 60° and 15 mm. pressure. These mild drying conditions were employed to avoid degradation of the material used for later characterization. To determine how much water might still be contained in the fractions, and if possible to differentiate between water of adsorption and of hydration, measurements of the vapor evolved on heating at reduced pressure were made on fractions 2, 4, 7 and N. The saturated vapor pressures of the condensed vapors from fractions 2 and 7 were determined at 0, 10 and 20° and found to be very close to those of water; the frozen condensate melted around −4 to −5°; and the vapor density, determined from the volume of evolved vapor and the weight of condensate, indicated molecular weights of the vapors from fractions 2 and 7 to be 16 and 17, respectively.

Similar measurements of vapor evolution from sodium tetradecane sulfonate hemihydrate supplied by Dr. E. C. Lingafelter, and from copper sulfate pentahydrate, showed stepwise evolution in four and one steps, respectively, characteristic of hydrates. The evolution of vapor from the barium lignin sulfonate fractions, however, proceeded without discrete steps. Instead, a more or less smooth curve was observed which may indicate evolution of water held by adsorption, or as a rather large number of hydrates, or both. The amount of vapor so liberated at 10 mm. was: at 117°, 3.08, 3.5, 3.67 and 3.8% from fractions 2, 4, 7 and N, respectively; and at 129°, 3.48, 3.9 and 4.1 from fractions 2, 4 and N, respectively. The amount of water evolved is nearly proportional to the number of sulfonate groups present. Thus, from 1.14 to 1.20 moles of water per sulfonate group was driven off at 117°, and from 1.29 to 1.32 moles at 129°. At 150° the amount is about 1.6 moles which appears to be nearly a limiting value. There is evidence of some decomposition at higher temperatures but over 80% of the gas evolved at 175° was re-adsorbed on cooling. From the known tendency of metal sulfonates to form hydrates and from the close proportionality between the water evolved and the amount of sulfonate present, it seems probable that the water is combined in a numb er of hydrates of differing dissociation characteristics.

For those fractions for which carbon and hydrogen analyses were available, the analytical data have been recalculated after subtraction of the indicated 1.6 moles of water per sulfonate group. A basis of nine carbon atoms was chosen because there now exists extensive evidence from degradation experiments[10] indicating that the structural units of gymnosperm lignins consist, in large proportion at least, of phenyl propane skeletons. The data when so calculated show that each fraction contains nearly an identical number of equivalents of barium and sulfur as expected for barium sulfonates, and that the degree of sulfonation of

(9) Scott, *J. Chem. Phys.*, **13**, 178 (1945).

(10) (a) Freudenberg, *Ann. Rev. Biochem.*, **8**, 88 (1939); (b) Hibbert, *ibid.*, **11**, 183 (1942); (c) Erdtman, *Svensk. Papperstidn.*, **44**, 243 (1941); *Pulp Paper Mag. Can.*, **43**, 253 (1942); (d) Percival, *Ann. Repts. Progress Chem. (Chem. Soc. London)*, **39**, 142 (1942); (e) Lewis and Pearl, U. S. Patent 2,433,227 (Dec. 23, 1947).

the several lignins is not quite the same. The first precipitated fraction is sulfonated to the extent of 0.37 mole per C_9 unit and the degree of sulfonation increases, reaching 0.52 in fraction 10. The difference in degree of sulfonation makes desirable a further recalculation of the data to a sulfur-free basis. This has been done by assuming that barium is exactly equivalent to sulfur and, for calculation purposes only, that each sulfonate group replaced a hydrogen atom in the original lignin.

The empirical composition of the several lignin fractions on an anhydrous, and also sulfur-free and ash-free basis is found to be nearly uniform (Table II) in spite of the accumulation of error in the hydrogen and oxygen data.[11] This composition is in general agreement with that reported by Wald, Ritchie and Purves[12] for pine lignin *in situ*, by Brauns[13] for "native" spruce lignin and by Racky[2] for some of his fractions of lignin sulfonic acids from spruce (Table II).

TABLE II

ESTIMATED EMPIRICAL COMPOSITION OF LIGNINS

Lignin	Composition
Fr. 1	C_9 $(OCH_3)_{0.85}$ $H_{7.9}$ $O_{2.4}$
2	C_9 $(OCH_3)_{0.91}$ $H_{8.4}$ $O_{2.7}$
4	C_9 $(OCH_3)_{0.92}$ $H_{8.8}$ $O_{2.7}$
7	C_9 $(OCH_3)_{0.93}$ $H_{9.1}$ $O_{2.5}$
10	C_9 $(OCH_3)_{0.93}$ $H_{7.9}$ $O_{2.2}$
N	C_9 $(OCH_3)_{0.91}$ $H_{8.4}$ $O_{2.6}$
Pine,[12] *in situ*	C_9 $(OCH_3)_{0.91}$ $H_{7.8}$ $O_{2.0}$
Spruce,[13] "native"	C_9 $(OCH_3)_{0.89}$ $H_{8.7}$ $O_{2.6}$
Spruce,[a] from LSA	C_9 $(OCH_3)_{0.93}$ $H_{8.4}$ $O_{2.2}$

[a] Calculated by us to a nine-carbon atom basis from data on lignin sulfonic acids (LSA) given by Racky[2] in his Table 2 using the average composition of his fractions 2, 3, 7 and 9 which were very similar.

The similarity of ultraviolet absorption spectra found for the fractions is in agreement with the uniformity of chemical composition. Extinction coefficients (cm.$^{-1}$ per mg. of methoxyl per liter) obtained in aqueous solutions containing 5.00 mg. of methoxyl per liter were 0.259, 0.243, 0.241, 0.231, 0.227 and 0.241 at 2800 Å., and 0.222, 0.210, 0.205, 0.192, 0.187 and 0.194 at 2650 Å. for fractions 1, 2, 4, 7, 10 and N, respectively.

Diffusion coefficients are found to increase markedly throughout the series of fractions. If molecular weights are calculated on the basis of spherical particles, a range from 100,000 to 4,000 is indicated although the actual molecular weights are probably somewhat lower judging from the few frictional ratios for lignins which have been reported.[14] It thus appears probable that the molecular size of the lignin sulfonates controls the order of precipitation although the latter may be influenced by degree of sulfonation. The characteristics manifested by the lignin sulfonate fractions seem to be in accord with those expected for fractions secured from a polymeric series.

The authors gratefully acknowledge the aid of Mr. Vincent F. Felicetta and of Mrs. H. D. Agar in performance of analyses.

Summary

1. A lignin sulfonate preparation purified by dialysis has been precipitated as a barium salt from aqueous solution by ethanol to yield a number of fractions which have been characterized by chemical analyses, ultraviolet extinction coefficients and diffusion coefficients.

2. When results of the chemical analyses are calculated to an anhydrous, sulfur-free and ash-free basis, the fractions are found to be of nearly uniform composition.

3. Diffusion coefficients of the several fractions are found to increase progressively in order of precipitation and indicate a corresponding decrease in molecular weights over a wide range.

4. The uniformity of chemical composition and of ultraviolet absorption spectrum and the regular trend in diffusion coefficients indicate the polymeric character of lignin sulfonic acids.

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(11) The analytical margins of error in Table I, increased by the assignment of hydrogen and oxygen to methoxyl, sulfonate and hydration groups may amount to as much as 0.75 atom of hydrogen and 0.4 atom of oxygen in the C_9 formulas of Table II.

(12) Wald, Ritchie and Purves, THIS JOURNAL, **69**, 1371 (1947).

(13) Brauns, *ibid.*, **61**, 2120 (1939).

(14) (a) Gralen, *J. Colloid Sci.*, **1**, 453 (1946); (b) Olleman, Pennington and Ritter, *ibid.*, **3**, 185 (1948).

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Coumarins. I. Derivatives of Coumarin-3- and 4-Carboxylic Acids

BY R. O. CLINTON AND S. C. LASKOWSKI

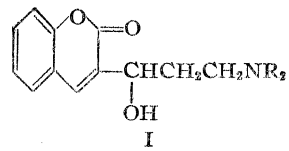
With the exception of a brief publication by Werder,[1] no pharmacological or chemical investigations appear to have been made of the basic esters and amides derivable from coumarins. Werder[1a,c] found that N,N-dialkyl-coumarin-3-carboxamides[2] exhibited remarkable sedative properties, and it is of considerable significance that they also had but slight toxicity. Furthermore, the favorable toxicity indices of coumarin-3-carboxylic acid were also apparent in salts of this acid with certain physiologically active bases such as ephedrine.[1b] These results are striking, since although coumarin itself has a slight narcotic activity, its toxic action is predominant.

In the same publication, Werder[1a] described 2-diethylaminoethyl coumarin-3-carboxylate hydrochloride and N-(2-diethylaminoethyl)-coumarin-3-carboxamide hydrochloride. The therapeutic properties of these compounds were not described; in particular no mention is made of observed local anesthetic activity. Local anesthetic activity in the coumarin-3-carboxylic acid esters and amides is of interest, since the compounds may be regarded as cinnamic acid types (*i. e.*, vinylogs of benzoic acid). In general, the basic esters of cinnamic acid show considerably greater activity than do the corresponding benzoates,[3] although toxicity has been found to increase proportionally.[4]

In the present work we have investigated a series of basic esters and amides derived from coumarin-3-carboxylic and coumarin-4-carboxylic acids. A subsequent communication will cover related compounds in the coumarin-3-acetic and coumarin-4-acetic acid series.

The substituted coumarin-3-carboxylic acids used in the present work were prepared by the conventional Knoevenagel method,[5] from a substituted salicylaldehyde and malonic ester. Modifications necessary in certain cases are detailed in the Experimental section. Only a single example of the coumarin-4-carboxylic acid type was investigated, due to the very low yields obtainable in the synthesis of these types.

An attempt was made to extend the investigation to the preparation of compounds of type I, through use of the Mannich reaction with 3-acetylcoumarin[6] followed by reduction (*e. g.*, by aluminum isopropylate). However, in spite of numerous experiments, under a variety of conditions, we were unable to isolate any reaction product when 3-acetylcoumarin was subjected to the Mannich reaction with diethylamine hydrochloride; in all cases only starting materials were recovered. This lack of reactivity may be due to stabilization of the hydrogen bonded structure II under the conditions of the Mannich reaction, for it is known that 3-acetylcoumarin readily forms an oxime[6] under normal conditions.



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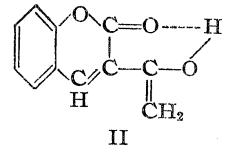


II

Werder[1c] prepared N,N-dimethylcoumarin-3-carboxamide from salicylaldehyde and malonic acid bis-dimethylamide at 145–150°. We were able to extend this method to the preparation of 2-diethylaminoethyl coumarin-3-carboxylate from salicylaldehyde and bis-(2-diethylaminoethyl) malonate, in high yield. It is interesting in this connection that reaction between the two components takes place only slowly at elevated temperature, even though tertiary amino groups are present, whereas the addition of catalytic amounts of piperidine or other secondary amine brought about an exothermic reaction at room temperature.

Among the coumarin-3-carboxylic acid derivatives prepared were a number of *bz*-nitro types. It was hoped that there could thus be prepared a series of *bz*-amino-substituted-coumarin-3-carboxylic acid derivatives, which would be vinylogs of aminobenzoic acid derivatives. The relative inaccessibility of 4-nitrosalicylaldehyde[7] precluded the preparation of 7-aminocoumarin derivatives, although the 6-nitro types are readily available.

In contrast to the easily manipulated reduction of 6-nitrocoumarin to 6-aminocoumarin either by iron–acetic acid[8] or electrolytically,[9] we were unable to prepare basic esters or amides of *bz*-aminocoumarin-3-carboxylic acids by either chemical or catalytic reduction. Part of the difficulty can be

(1) (a) Werder, *Merck Jahresberichte*, 88 (1936); (b) U. S. Patent 2,133,977; (c) U. S. Patent 2,170,127.

(2) Compounds of this type are indexed by *Chemical Abstracts* as 2-oxo-1,2-benzoylpyrone derivatives. For simplicity, we have used the conventional nomenclature.

(3) Gilman, *et al.*, THIS JOURNAL, **47**, 245 (1925); **50**, 437 (1928).

(4) *Cf.* also McElvain, *ibid.*, **49**, 2835 (1927); Bailey and McElvain, *ibid.*, **52**, 2007 (1930).

(5) Knoevenagel, *Ber.*, **31**, 2585 (1898).

(6) Prepared in 95% yield, m. p. 120–121°, by the method of Knoevenagel, *ibid.*, p. 732.

(7) Segesser and Calvin, THIS JOURNAL, **64**, 825 (1942).

(8) Clayton, *J. Chem. Soc.*, **97**, 1350 (1910); Morgan and Micklethwaite, *ibid.*, **85**, 1233 (1904).

(9) Kondo and Ui, *J. Pharm. Soc. Japan*, No. 498, 615 (1923).

ascribed to the ease with which the pyrone ring is opened in the presence of the new amino group or the basic group in the ester or amide linkage[10]; further, from the properties of the highly colored products which we have isolated from chemical reduction experiments it can be assumed that in this case reduction was incomplete. Catalytic reduction, with a variety of catalysts and under varying conditions, gave only the corresponding *bz*-amino dihydrocoumarins.[11] Judging from hydrogenation experiments there was no perceptible difference in the rate of reduction between the nitro group and the double bond.

Therapeutic assay of the coumarin-3-carboxylic acid derivatives for local anesthetic activity has been carried out by Drs. T. J. Becker and F. P. Luduena of these laboratories. A complete report will be published by these authors at a later date.

Experimental[12]

Salicylaldehydes.—The nitration of salicylaldehyde with fuming nitric acid (d. 1.49–1.50) in glacial acetic acid, and separation of the mixture of 3-nitro- and 5-nitrosalicylaldehydes, was carried out essentially by the method of Miller.[13] Bromination of the 3-nitro isomer according to the method of Auwers and Bürger,[14] or the nitration of 5-bromosalicylaldehyde,[14,15] gave high yields of 3-nitro-5-bromosalicylaldehyde. 2-Hydroxy-3-methoxy-5-nitrobenzaldehyde was prepared by the method of Dey and Kutti.[16] The bromination of 5-nitrosalicylaldehyde with bromine in glacial acetic acid solution at 30–40° gave a 70% yield of **3-bromo-5-nitrosalicylaldehyde,** long slender white needles from dilute acetic acid or from alcohol, m. p. 149–150°.

Anal. Calcd. for $C_7H_4BrNO_4$: C, 34.17; H, 1.64; N, 5.69. Found: C, 34.17; H, 1.87; N, 5.85.

The oxime formed pale yellow needles from dilute alcohol, m. p. 222.1–223.0°.

Anal. Calcd. for $C_7H_5BrN_2O_4$: N, 10.73. Found: N, 10.60.

The position of the bromine was proven by oxidation of the aldehyde to the known 3-bromo-5-nitrosalicylic acid with potassium permanganate in acetone. The product crystallized from 4% hydrochloric acid in long slender white needles, m. p. 225–226° (lit.,[17] m. p. 223–224° uncor.).

Ethyl Coumarin-3-carboxylates.—In general, the usual Knoevenagel procedure[5] was used to prepare the intermediate coumarin-3-carboxylates. However, in certain cases the salicylaldehydes (*e. g.*, 2-hydroxy-3-methoxy-5-nitrobenzaldehyde, 3-bromo-5-nitrosalicylaldehyde, etc.) were relatively slow in condensing by this method, and it was found necessary to force the reaction by heating and through use of increased amounts of the piperidine catalyst. A typical example follows:

A mixture of 25.0 g. (0.126 mole) of 2-hydroxy-3-methoxy-5-nitrobenzaldehyde, 25.0 g. (0.156 mole) of ethyl malonate, 30 ml. of absolute alcohol and 2 ml. of piperidine was refluxed for six hours. The orange colored reaction mixture was diluted with 400 ml. of alcohol, filtered, and the crystalline material was washed well with alcohol. Recrystallization from ethyl acetate gave 31.5 g. (85%) of ethyl 8-methoxy-6-nitrocoumarin-3-carboxylate as pale yellow needles.

The difficulty of preparing 2-hydroxy-3-methoxy-6-nitrobenzaldehyde[16] precluded the possibility of preparing 8-methoxy-5-nitrocoumarin-3-carboxylic acid in this manner. Dey and Kutti[16] have reported that the nitration of 8-methoxycoumarin-3-carboxylic acid takes place exclusively in the 5-position; in our hands, however, the method did not prove adaptable to large-scale preparations. We have found that nitration of the ethyl ester gives fair results, although the yields are low:

To 100 ml. of concentrated nitric acid (d. 1.42) at 25° was slowly added 24.8 g. (0.10 mole) of ethyl 8-methoxycoumarin-3-carboxylate[18] with stirring. The resulting solution was slowly heated to 40–45° and maintained at this temperature (the reaction becomes uncontrollable above 55°) by alternate cooling and heating for one hour. The solution was poured into one liter of ice-water with stirring, and the resulting precipitate was filtered and washed thoroughly with water. After two recrystallizations of the air-dried material from ethyl acetate with decolorization there was obtained a 22% yield of ethyl 8-methoxy-5-nitrocoumarin-3-carboxylate as pale yellow needles, m. p. 184–186°.

Anal. Calcd. for $C_{13}H_{11}NO_7$: N, 4.78. Found: N, 4.75.

Saponification of the ethyl ester gave a 92% yield of 8-methoxy-5-nitrocoumarin-3-carboxylic acid, m. p. 215–217° (lit.,[16] m. p. 203° uncor.).

Anal. Calcd. for $C_{11}H_7NO_7$: C, 49.81; H, 2.64. Found: C, 50.04; H, 2.73.

Coumarin-3-carboxylic Acids.—The ethyl esters were saponified by refluxing with an excess of dilute sodium hydroxide solution for several hours, followed by acidification with hydrochloric acid. It was generally preferable to pour the solution of the sodium salt into an excess of strong hot hydrochloric acid, since by the reverse process there was sometimes obtained a substantial amount of the coumaric acid.

Coumarin-3-carbonyl Chlorides.—The acid chlorides were prepared by the action of thionyl chloride on the acid, without solvent[19]:

A mixture of 20 g. (0.075 mole) of 8-methoxy-6-nitrocoumarin-3-carboxylic acid and 119 g. (1.0 mole) of pure thionyl chloride[20] was refluxed under anhydrous conditions for two hours. Solution was complete after twenty minutes. The excess thionyl chloride was distilled under reduced pressure, and the crystalline residue was taken down twice with 250-ml. portions of dry benzene. Recrystallization of the residual solid from dry benzene gave 21.2 g. (97%) of 8-methoxy-6-nitrocoumarin-3-carbonyl chloride.

Coumarin-3-carboxylates, -thiolcarboxylates and -carboxamides.—The coumarin-3-carboxylates were prepared by several methods. Reaction between the basic alcohol and a coumarin-3-carbonyl chloride in dry benzene gave high yields, as did the reaction between a coumarin-3-carboxylic acid and an ω-dialkylaminoalkyl halide in iso-

(10) Both Clayton and Morgan, ref. 8, have pointed out the intense yellow and orange colors of the pure *bz*-aminocoumarins. On structural grounds it is apparent from these observations and from the observed high melting points that the *bz*-aminocoumarins must exist at least partially in the open (cinnamic acid salt) forms.

(11) *Cf.* Smith and Byers, THIS JOURNAL, **63**, 612 (1941).

(12) All melting and boiling points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

(13) Miller, *Ber.*, **20**, 1927 (1887).

(14) Auwers and Bürger, *ibid.*, **37**, 3934 (1904).

(15) Auwers and Walker, *ibid.*, **31**, 3037 (1898); Raiford and Tanzer, *J. Org. Chem.*, **6**, 730 (1941). The latter authors do not give preparation details nor yields. In the present work the compound was prepared by the addition, during four hours, of two moles of bromine to two moles of salicylaldehyde (each dissolved in four volumes of chloroform) with stirring, at 30°. The mixture was then refluxed for two hours, allowed to stand overnight, and the chloroform removed *in vacuo*. Crystallization of the residue from Skellysolve C gave an 84% yield of white product, m. p. 105–106°.

(16) Dey and Kutti, *Proc. Nat. Inst. Sci., India*, **6**, 641 (1940); *cf.* Davies, *J. Chem. Soc.*, **123**, 1575 (1923).

(17) Lallmann and Grothmann, *Ber.*, **17**, 2724 (1884); Chattaway and Goepp, *J. Chem. Soc.*, 699 (1933).

(18) Perkin and Robinson, *J. Chem. Soc.*, **105**, 2382 (1914).

(19) *Cf.* Boehm and Schumann, *Arch. Pharm.*, **271**, 490 (1933).

(20) The high ratio of thionyl chloride to acid was used to increase the rate of reaction through increased solubility.

propyl alcohol.[21] A third method consisted of the trans-esterification of the ethyl coumarin-3-carboxylate with a basic alcohol, in certain cases using toluene as a diluent. The yields by this latter method were quite good, but purification of the product from traces of starting materials often proved difficult. A further method was the direct synthesis from suitable malonic esters, although this method gave low over-all yields because of the difficulty of preparing the required basic esters of malonic acid:

A mixture of 160 g. (1.0 mole) of redistilled diethyl malonate, 250 g. (2.14 moles) of redistilled 2-diethylaminoethanol and 400 ml. of dry toluene was distilled slowly during eight hours through a 14" vacuum-jacketed Vigreux column surmounted by a total reflux, variable take-off distillation head. A total of 435 ml. of distillate was collected, and the final internal temperature was 152°. Fractionation of the pale yellow-colored still residue gave 95.2 g. of a colorless liquid, b. p. 91–102° at 0.2–0.5 mm. (with slight decomposition).[22]

A mixture of 12.2 g. of salicylaldehyde and 30.2 g. of the above crude bis-(2-diethylaminoethyl) malonate gave no evidence of reaction, either when heated at 100° or when treated with, *e. g.*, pyridine. However, the addition of 10 drops of piperidine brought about an immediate coloration and an exothermic reaction. After heating on the steam-bath at 100° for three hours, the product was recrystallized from alcohol and converted to the hydrochloride with alcoholic hydrogen chloride. The yield of 2-diethylaminoethyl coumarin-3-carboxylate hydrochloride, m. p. 211–212°,[1a] was excellent.

The thiolcarboxylates were prepared by the direct reaction between a coumarin-3-carboxyl chloride and an ω-dialkylaminoalkanethiol in dry benzene.[23] The yields were essentially quantitative, and the products were easily purified.

The preparation of the coumarin-3-carboxamides was most conveniently carried out by direct interaction between a coumarin-3-carbonyl chloride and the dialkylaminoalkylamine in cold dry benzene. In certain cases (*e. g.*, with 4-diethylamino-1-methylbutylamine) a purer product was obtained by amination in a mixture of chloroform, water and sodium bicarbonate.[24] Amination by reaction between the ethyl ester and an amine gave unworkable mixtures (ring opening was very extensive under these conditions).

The properties and yields of the coumarin-3-carboxylates, -thiolcarboxylates, -carboxamides, and intermediates in their preparation, are given in Table I.

7-Hydroxycoumarin-4-carboxylic Acid.—The method of v. Pechman and Graeger[25] was modified through substitution of commercial sodio-oxalacetic ester for the oxalacetic ester–sodium ethylate mixture used by these workers. The yield (on one-mole runs) was 46%. Saponification of the ethyl ester according to v. Pechman and Graeger[25,26] gave 98% yields of purified acid, m. p. 245–246° (reported,[25] m. p. 247–248° uncor.).

2-Diethylaminoethyl 7-Hydroxycoumarin-4-carboxylate Hydrochloride.—A mixture of 5 g. of 7-hydroxycoumarin-4-carboxylic acid, 3 g. of 2-diethylaminoethyl chloride and 50 ml. of isopropyl alcohol was refluxed for one hour. A yellow crystalline precipitate appeared after twenty minutes. The reaction mixture was cooled, filtered, and the product was washed with cold isopropyl alcohol. Two recrystallizations from a large volume of ethanol gave 7.0 g. of long slender yellow needles, m. p. 192.7–193.9°.

Anal. Calcd. for $C_{16}H_{20}ClNO_5$: C, 56.22; H, 5.90; Cl, 10.38. Found: C, 56.31; H, 5.65; Cl, 10.30.

The following compounds were prepared by a similar method:

2-(1-Piperidyl)-ethyl 7-hydroxycoumarin-4-carboxylate hydrochloride, yellow leaflets from hot water, m. p. 213.4–215.0°.

Anal. Calcd. for $C_{17}H_{20}ClNO_5$: C, 57.72; H, 5.70; N, 3.96; Cl, 10.02. Found: C, 57.81; H, 5.49; N, 3.92; Cl, 9.90.

3-(4-Morpholinyl)-propyl 7-hydroxycoumarin-4-carboxylate hydrochloride, pale yellow prisms from dilute hydrochloric acid, m. p. 233.0–233.8°.

Anal. Calcd. for $C_{17}H_{20}ClNO_6$: C, 55.21; H, 5.45; N, 3.79; Cl, 9.59. Found: C, 55.44; H, 5.46; N, 3.67; Cl, 9.53.

The reaction failed with 2-dimethylaminoethyl chloride. The trans-esterification of ethyl 7-hydroxycoumarin-4-carboxylate by means of a basic alcohol in toluene gave good results, although purification proved difficult. Attempts to aminate the ethyl ester by means of an ω-dialkylaminoalkylamine failed.

The Reduction of Nitrocoumarin-3-carboxylic Acid Derivatives.—Both chemical and catalytic reductions were tried as means of securing *bz*-aminocoumarin-3-carboxylic acid derivatives; both methods failed.

Catalytic Reductions.—Hydrogenation of the nitrocoumarin derivatives was carried out in a modified[27] Parr–Burgess apparatus. No difference was observed in products obtained when the catalyst was varied between platinum, palladium or Raney nickel. Plots of hydrogen uptake *versus* time showed no definite change in slope ascribable to a difference in the rates of reduction between a nitro group and a double bond. A typical reduction follows:

A solution of 3.0 g. of ethyl 6-nitrocoumarin-3-carboxylate in 100 ml. of ethyl acetate was mixed with 5 g. of neutral Raney nickel **catalyst** and shaken with hydrogen at 2.5–3 atmospheres. Only a slow hydrogen uptake was evident at room temperature (ninety-six hours for completion) but reduction was initially rapid at 50°. During the latter stages of the reduction an orange precipitate appeared in the mixture (*vide infra*), and the reduction rate slowed while this precipitate gradually redissolved. At completion of the reduction (twelve to forty-eight hours at 50°) the solution was clear and colorless. After filtration of catalyst, the filtrate was diluted with a large volume of Skellysolve A. The resulting precipitate was filtered and recrystallized from a warm ethyl acetate–Skellysolve A mixture. **Ethyl 6-amino-3,4-dihydrocoumarin-3-carboxylate** crystallized in clusters of white cottony needles, m. p. 90–91° (dec.). The yield was 90%.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.23; H, 5.53; N, 5.96. Found: C, 61.33; H, 5.45; N, 6.02.

The hydrochloride precipitated as white needles when an ethyl acetate solution of the base was treated with ethereal hydrogen chloride, m. p. 211–212° (dec.).

Anal. Calcd. for $C_{12}H_{14}ClNO_4$: C, 53.04; H, 5.16; N, 5.16. Found: C, 53.08; H, 4.96; N, 5.10.

The use of platinum or palladium catalysts increased the rate of reduction but did not affect the phenomena observed. In a manner similar to the above, there were prepared:

Ethyl 5-amino-8-methoxy-3,4-dihydrocoumarin-3-carboxylate, *via* an intermediate insoluble red-brown precipitate (*vide infra*); cottony white needles from ethyl acetate–Skellysolve A, m. p. 126–128°, yield 92%.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66; N, 5.28. Found: C, 58.52; H, 5.64; N, 5.22.

The hydrochloride crystallized from absolute alcohol–ethyl acetate in white needles, m. p. 185–186°.

Anal. Calcd. for $C_{13}H_{16}ClNO_5$: N, 4.64. Found: N, 4.56.

(21) Hörenstein and Pählicke, *Ber.*, **71**, 1644 (1938). In the special case of nitrosubstituted coumarin-3-carboxylic acids the yields were lowered.

(22) Gilman and Johnson, THIS JOURNAL, **50**, 3346 (1928), prepared the compound from malonyl chloride and 2-diethylaminoethanol. They record a b. p. of 163° at 4.5 mm.

(23) Clinton, Salvador and Laskowski, *ibid.*, **71**, 3366 (1949).

(24) Clinton, Salvador, Laskowski and Suter, *ibid.*, **70**, 950 (1948).

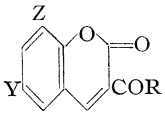
(25) v. Pechman and Graeger, *Ber.*, **34**, 378 (1901).

(26) *Cf.* Dey, *J. Chem. Soc.*, **107**, 1606 (1915).

(27) Buck and Jenkins, THIS JOURNAL, **51**, 2163 (1929).

TABLE I

COUMARIN-3-CARBOXYLIC ACID DERIVATIVES



Y	Z	R	M. p., °C.	Yield, %	Analyses, % Calcd.	Found	Calcd.	Found
H	H	$-OCH_2CH_3$[a]	95–96	77	C, 66.06	66.03	H, 4.59	4.69
H	H	$-OH$[b]	191–192	96	C, 63.16	63.26	H, 3.16	3.38
H	H	$-Cl$[c]	147–148	78				
H	H	$-OCH_2CH_2N(C_2H_5)_2\cdot HCl$[d]	211–212	75				
H	H	$-OCH(CH_3)(CH_2)_3N(C_2H_5)_2\cdot HCl$	125–126	76	Cl, 9.66	9.52	N, 3.81	3.79
H	H	$-SCH_2CH_2N(C_2H_5)_2\cdot HCl$	189–191	77	S, 9.37	9.11	N, 4.10	4.13
H	H	$-OCH_2CH_2SCH_2CH_2CH_2NC_5H_{10}$[e]$\cdot HCl$	118–119	69	S, 7.78	7.79	N, 3.40	3.36
H	H	$-N(C_2H_5)_2$[d]	77–78	80	N, 5.71	5.77		
H	H	$-NHCH(CH_3)(CH_2)_3N(C_2H_5)_2\cdot HCl$[f]	141–144	70	Cl, 9.69	9.89	N, 7.64	7.63
NO_2	OCH_3	$-OCH_2CH_3$[g]	210–210.5	85	C, 53.25	53.20	H, 3.75	3.52
NO_2	OCH_3	$-OH$[h]	219–220	99	C, 49.81	49.76	H, 2.64	2.83
NO_2	OCH_3	$-Cl$	179–180	85	Cl, 12.52	12.60		
NO_2	OCH_3	$-OCH_2CH_2N(C_2H_5)_2\cdot HCl$	191–192	90	Cl, 8.86	8.80	N, 6.99	6.83
NO_2	OCH_3	$-N(C_2H_5)_2$	192–193	93	N, 8.75	8.68		
H	OCH_3	$-OCH_2CH_3$[i]	95–96	81				
H	OCH_3	$-OH$[i]	212–213	99	C, 60.00	60.00	H, 3.64	3.73
H	OCH_3	$-Cl$	171–172	99	Cl, 14.88	14.91		
H	OCH_3	$-OCH_2CH_2N(C_2H_5)_2\cdot HCl$	195–196	75	Cl, 9.99	9.99	N, 3.94	3.74
H	OCH_3	$-N(C_2H_5)_2$	107–108	51	N, 5.09	4.90		
H	NO_2	$-OCH_2CH_3$[j]	160–161	40	C, 54.75	54.63	H, 3.42	3.22
H	NO_2	$-OH$[k]	191–192	90	C, 51.06	51.12	H, 2.12	2.27
NO_2	H	$-OCH_2CH_3$[l]	200–201	66				
NO_2	H	$-OH$[l]	235–236	97	N, 5.96	5.99		
NO_2	H	$-Cl$[l]	172–173	90				
NO_2	H	$-OCH_2CH_2N(C_2H_5)_2\cdot HCl$	197–198	90	N, 7.56	7.65		
NO_2	H	$-N(C_2H_5)_2$[m]	184–185	72	C, 57.93	58.04	H, 4.83	4.86
NO_2	Br	$-OCH_2CH_3$	184–185	10	N, 4.09	4.10		
NO_2	Br	$-OH$	221–222	40	Br, 25.47	25.42	N, 4.46	4.69
Br	H	$-OCH_2CH_3$[n]	168–169	88	C, 48.48	48.24	H, 3.03	3.00
Br	H	$-OH$[o]	199	99	Br, 29.74	29.55		
Br	H	$-Cl$	160–161	94	Cl, 12.35	12.30		
Br	H	$-OCH_2CH_2N(C_2H_5)_2\cdot HCl$	193–194	89	Cl, 8.78	8.94	N, 3.46	3.53
Br	H	$-N(C_2H_5)_2$	160–161	71	Br, 24.69	24.27	N, 4.32	4.36
Br	H	$-NHCH(CH_3)(CH_2)_3N(C_2H_5)_2\cdot HCl$	170–172	75	Cl, 7.97	7.96	N, 6.29	6.08
Br	H	$-OCH_2CH_2SCH_2CH_2N(C_2H_5)_2\cdot HCl$	166–167	75	S, 6.89	6.65	N, 3.01	3.01
Br	H	$-SCH_2CH_2CH_2CH_2N(C_2H_5)_2\cdot HCl$	209–210	80	Cl, 7.92	8.02		
Br	H	$-SCH_2CH_2N(C_2H_5)_2\cdot HCl$	210–212	37	S, 7.61	7.34	N, 3.33	2.39
Br	H	$-SCH(CH_3)(CH_2)_3N(C_2H_5)_2\cdot HCl$	111–113	65	S, 6.92	6.61	N, 3.03	2.90

[a] Baker and Lapworth, *J. Chem. Soc.*, **127**, 566 (1925). [b] Knoevenagel, *Ber.*, **31**, 2618 (1898). [c] Boehm and Schumann, *Arch. Pharm.*, **271**, 490 (1933), report m. p. 147–148°; the m. p. of 136–137° reported by Lampe and Trenknerowna, *Roczniki Chem.*, **14**, 1231 (1934), is apparently in error. [d] Werder, *Merck Jahresb.*, 88 (1936). [e] $-NC_5H_{10}$ is 1-piperidyl. [f] This compound was also prepared as a salt of coumarin-3-carboxylic acid: needles from methanol–ether, m. p. 156–157°. Calcd. for $C_{19}H_{26}N_2O_3\cdot C_{10}H_6O_4$: N, 5.38. Found: N, 5.31. [g] Calcd. for $C_{13}H_{11}NO_7$: N, 4.78. Found: N, 4.76. [h] Calcd. for $C_{11}H_7NO_7$: N, 5.28. Found: N, 5.39. [i] Perkin and Robinson, *J. Chem. Soc.*, **105**, 2382 (1914). [j] Calcd. for $C_{12}H_9NO_6$: N, 5.32. Found: N, 5.38. [k] Calcd. for $C_{10}H_5NO_6$: N, 5.96. Found: N, 5.96. [l] Lampe and Macierewicz, *Roczniki Chem.*, **18**, 668 (1938). [m] Calcd. for $C_{14}H_{14}N_2O_5$: N, 9.66. Found: N, 9.66. [n] Calcd. for $C_{12}H_9BrO_4$: Br, 26.94. Found: Br, 26.70. [o] Pandya and Pandya, *Proc. Indian Acad. Sci.*, **18A**, 164 (1943).

Ethyl 6-amino-8-methoxy-3,4-dihydrocoumarin-3-carboxylate, *via* an intermediate insoluble red-orange precipitate (*vide infra*); rosets of white needles from ethyl acetate–Skellysolve B, m. p. 81–82°, yield 93%.

Anal. Calcd. for $C_{13}H_{15}NO_5$: N, 5.28. Found: N, 5.32.

The hydrochloride formed white needles from absolute alcohol–ether, m. p. 185–190° (dec.).

Anal. Calcd. for $C_{13}H_{16}ClNO_5$: N, 4.64; Cl, 11.77. Found: N, 4.66; Cl, 11.65.

In solution the 3,4-dihydrocoumarin-3-carboxylates were very unstable to heat and to air. This phenomenon has been observed in a similar case by Smith and Byers.[11]

Chemical Reductions.—Application of the iron–acetic acid method of Clayton[8] to ethyl 8-methoxy-6-nitrocoumarin-3-carboxylate gave no reduction. Use of the general reduction procedure of West[28] afforded a high yield of a product which crystallized in red-orange needles from dilute alcohol, m. p. 149–150°. This material, of unknown constitution, proved to be identical (mixed

(28) West, *J. Chem. Soc.*, **127**, 494 (1925).

m. p.) with the intermediate colored insoluble reduction product observed during the catalytic reduction of ethyl 8-methoxy-6-nitrocoumarin-3-carboxylate (*vide supra*).

Anal. Found: C, 57.75; H, 4.98; N, 5.95.

A similar reduction of 2-diethylaminoethyl 8-methoxy-6-nitrocoumarin-3-carboxylate hydrochloride gave, as the only isolatable reduction product, a solid crystallizing from absolute alcohol–Skellysolve A in white needles, m. p. 134–135°.

Anal. Found: C, 46.06; H, 9.09.

The reduction of ethyl 6-nitrocoumarin-3-carboxylate by West's method gave a brown solid, crystallizing from dilute alcohol in bright yellow needles, m. p. 161–163°. This solid was identical (mixed m. p.) with the intermediate insoluble precipitate observed during catalytic reduction of the same compound (*vide supra*).

Anal. Found: C, 58.47; H, 4.73.

Similarly, the chemical reduction of N,N-diethyl-6-nitrocoumarin-3-carboxamide gave a bright yellow unstable solid, m. p. 110–115° (from benzene–Skellysolve A).

Anal. Found: C, 68.97; H, 5.83; N, 10.41.

Summary

There has been described the preparation of a series of substituted coumarin-3- and coumarin-4-carboxylic acid derivatives. Attempts to prepare *bz*-amino members of this series resulted either in 3,4-dihydrocoumarins or in highly colored compounds of unknown constitution.

Rensselaer, New York Received June 6, 1949

[Contribution from the Eastern Regional Research Laboratory[1]]

A Crystalline Compound of β-Lactoglobulin with Dodecyl Sulfate[2]

By T. L. McMeekin, B. D. Polis, E. S. DellaMonica and J. H. Custer

Previous studies[3,4,5,6] have shown that proteins are precipitated from solution by synthetic detergents. Anionic detergents such as dodecyl sulfate precipitate proteins from acid solutions, whereas cationic detergents precipitate proteins from alkaline solutions. In the *p*H region close to the isoelectric point, neither cationic nor anionic detergents form precipitates with proteins.[6] Precipitated protein detergent complexes are soluble in an excess of detergent, accompanied by the denaturation of the protein and the liberation of free sulfhydryl groups.[3] The interaction of proteins with synthetic detergents has been extensively reviewed by Putnam.[7]

The work reported here deals with the preparation and properties of a crystalline complex of β-lactoglobulin combined with small quantities of dodecyl sulfate.

Experimental

Preparation of β-Lactoglobulin.—Crystalline β-lactoglobulin was prepared from unpasteurized milk by the method of Palmer.[8] The β-lactoglobulin contained 15.6% nitrogen and was electrophoretically homogeneous at *p*H 8.4 but inhomogeneous at *p*H 4.7, as was demonstrated by Li.[9]

Purified sodium dodecyl sulfate was used. A 0.01 molar aqueous solution, made to *p*H 4.2 with acetic acid, was used in precipitating β-lactoglobulin.

Preparation of Crystalline β-Lactoglobulin-dodecyl Sulfate.—β-Lactoglobulin–dodecyl sulfate was prepared by several procedures, in which the proportion of dodecyl sulfate to protein ranged from 4.2 to 14.0 cc. of 0.01 molar dodecyl sulfate per gram of protein. In every case, the crystalline protein prepared by dialysis at *p*H 5.1–5.2 after the removal of dodecyl sulfate with barium chloride, as described by Putnam and Neurath,[6] differed from β-lactoglobulin in solubility and mobility. Figure 1 gives a comparison of normal and dodecyl sulfate β-lactoglobulin electrophoretic patterns and mobilities in acetate buffer at *p*H 4.8 and veronal buffer at *p*H 8.4.

By adding 4.4 cc. of 0.01 *M* dodecyl sulfate to 50 cc. of a 2.1% solution of protein at *p*H 4.8, it was possible to crystallize the modified β-lactoglobulin directly, without the preliminary formation of a precipitate or the use of barium chloride to remove dodecyl sulfate. On standing for several hours, characteristic crystals appeared which had the electrophoretic mobility of modified β-lactoglobulin, demonstrating that only a small amount of dodecyl sulfate is necessary to modify the properties of β-lactoglobulin and that barium ions or barium sulfate do not produce the modification. The preparation which has been analyzed most completely was made as follows: approximately 10 g. of crystalline β-lactoglobulin suspended in 250 cc. of water was dissolved in dilute acetic acid and made to *p*H 4.2. Then 70 cc. of 0.1 *N* dodecyl sulfate at *p*H 4.2 was added with stirring. The small amount of precipitate formed was ignored. The solution then was made to *p*H 6.0 by adding dilute ammonia. The excess dodecyl sulfate was precipitated by adding 5 cc. of a 5% solution of barium chloride. After thirty minutes, the precipitated barium dodecyl sulfate was removed by centrifugation, and the supernatant was adjusted to *p*H 5.1. On dialysis, a yield of about 8 g. of crystalline protein was obtained. This material had a mobility u(sq. cm. volt^{-1} sec.$^{-1}$ $\times 10^5$) of 1 $u \times 10^5$ at *p*H 4.7 in acetate buffer and a mobility of $-5.9\ u \times 10^5$ at *p*H 8.4 in veronal buffer of 0.1 ionic strength. After several recrystallizations of the protein by dialysis from salt solutions, the properties were unchanged.

Table I shows the total nitrogen, α-amino nitrogen and total sulfur contents.

Properties of β-Lactoglobulin Dodecyl Sulfate

The analytical data in Table I indicate that two molecules of dodecyl sulfate are bound to one molecule of β-lactoglobulin. The method of preparation involving dialysis and treatment with barium to remove the insoluble barium salt of do-

(1) One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture, Philadelphia. Article not copyrighted.

(2) A preliminary report of this work was presented at the meeting of the American Society of Biological Chemists, Atlantic City, March, 1948; *Federation Proc.*, **7**, 172 (1948).

(3) Anson, *J. Gen. Physiol.*, **23**, 239 (1939).

(4) McMeekin, *Federation Proc.*, **1**, 125 (1942).

(5) Putnam and Neurath, *J. Biol. Chem.*, **150**, 263 (1943).

(6) Putnam and Neurath, This Journal, **66**, 692 (1944).

(7) Putnam, "Advances in Protein Chemistry," Vol. IV, Academic Press, Inc., New York, N. Y., 1948, p. 79.

(8) Palmer, *J. Biol. Chem.*, **104**, 359 (1934).

(9) Li, This Journal, **68**, 2746 (1946).

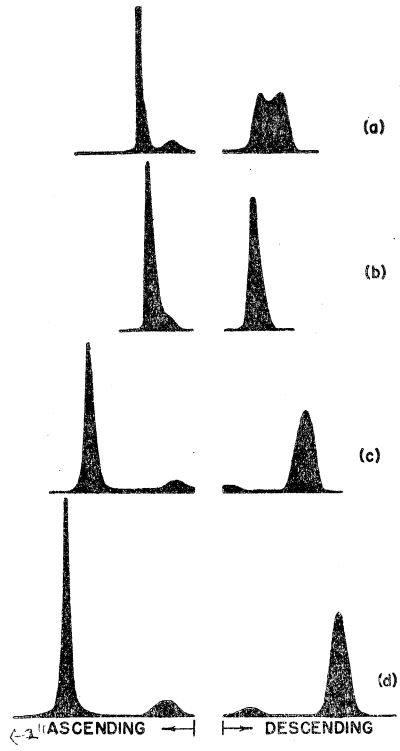


Fig. 1.—Comparison of electrophoretic patterns of normal β-lactoglobulin with those of its dodecyl sulfate derivative. In acetate buffer at *p*H 4.8, ionic strength 0.1: (a) β-lactoglobulin after 10,800 sec. at 4.37 volts/cm., (b) β-lactoglobulin dodecyl sulfate derivative after 10,800 sec. at 4.0 volts/cm. In veronal buffer at *p*H 8.4: (c) β-lactoglobulin after 10,800 sec. at 4.7 volts/cm., (d) β-lactoglobulin dodecyl sulfate derivative after 10,800 sec. at 4.6 volts/cm. Mobilities (a) 1.3, 2.5 *u*, (b) 1.0 *u*, (c) −5.1 *u*, (d) −5.9 *u*.

decyl sulfate indicates that the dodecyl sulfate is firmly held by the protein. It would be of great interest to locate the position of attachment of the dodecyl sulfate to the protein. It was thought that some information on the place of attachment between β-lactoglobulin and dodecyl sulfate might be obtained from a comparison of the properties of the normal and the modified protein.

TABLE I

COMPOSITION OF β-LACTOGLOBULIN AND ITS DODECYL DERIVATIVE

	Weight percentages		
	Total N	α-Amino N	Total S
β-Lactoglobulin	15.67	1.26	1.58
β-Lactoglobulin dodecyl sulfate	15.39	1.24	1.76
Calculated for:			
1 *M* β-lactoglobulin (mol. wt. 35000)			
2 *M* dodecyl sulfate (mol. wt. 265)			
	15.43	1.24	1.74

Titration Curve.—The combination of β-lactoglobulin–dodecyl sulfate with acid and alkali was compared with that of untreated β-lactoglobulin in potassium chloride solutions of 0.1 ionic strength, according to the method described by Cannan, *et al.*[10] Figure 2 shows the results. The combining capacity is consistent with the electrophoretic mobilities, in that at *p*H 4.7 the β-lactoglobulin–dodecyl sulfate with the smaller mobility combines with less acid than does β-lactoglobulin, whereas at *p*H 8.4 the alkali-combining capacity of the β-lactoglobulin–dodecyl sulfate is about two equivalents greater than that of β-lactoglobulin and the mobility is also greater. The two titration curves for solutions more acid than *p*H 4 are essentially the same; apparently the change in dissociation takes place between *p*H 4 and 6, which could not be that of the sulfate group, since it is a very strong acid and does not give a measurable *pK*.

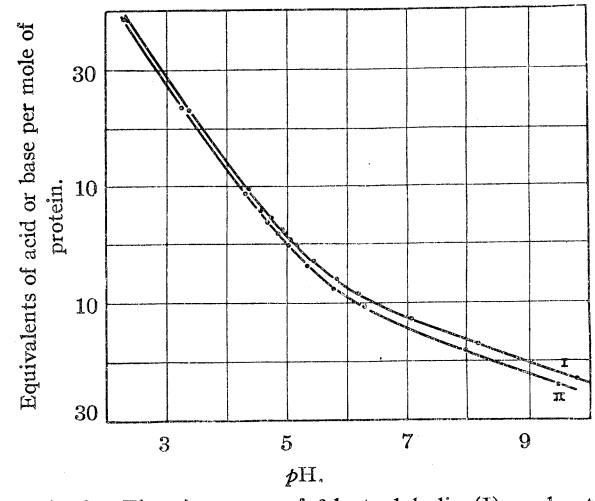


Fig. 2.—Titration curve of β-lactoglobulin (I), mol. wt. 35,000, and of β-lactoglobulin–dodecyl sulfate (II), mol. wt., 35,530.

Solubility.—There is a striking difference in the solubility of β-lactoglobulin and its dodecyl sulfate derivative. With the technique used by Gronwall,[11] the solubility of β-lactoglobulin at 25° was found to be 0.16 mg. of nitrogen per cubic centimeter in water and 1.7 mg. per cubic centimeter in 0.02 *M* sodium chloride. The solubility of dodecyl sulfate derivative was 0.08 mg. of nitrogen per cubic centimeter in water and 0.5 mg. of nitrogen per cubic centimeter in 0.02 *M* sodium chloride. Figure 3 shows the influence of *p*H on the solubility in water in 0.02 *M* sodium chloride.

Temperature of Coagulation.—Luck and his associates[12] have determined the effect of a variety of substances on temperature of coagulation or cloud point of serum albumin. These investigators have reported that small amounts of sodium dodecyl sulfate are particularly effective in preventing urea denaturation of serum albumin.

(10) Cannan, Palmer and Kibrick, *J. Biol. Chem.*, **142**, 803 (1942).
(11) Gronwall, *Compt. rend. trav. lab. Carslberg*, **24**, No. 8-11, 185 (1942).
(12) Ballou, Boyer, Luck and Lum, *J. Biol. Chem.*, **153**, 589 (1944).

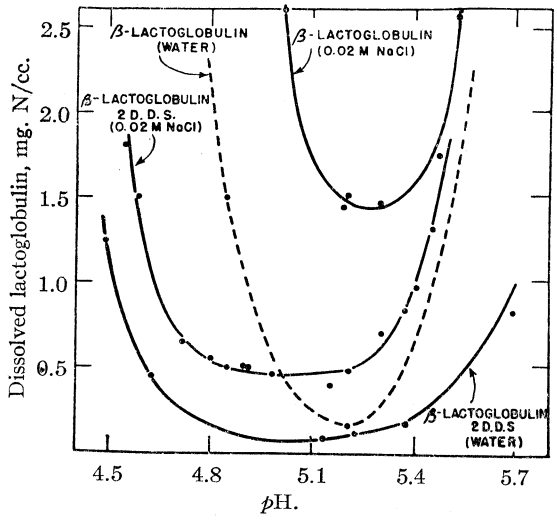


Fig. 3.—Comparison of the solubility of β-lactoglobulin with that of its dodecyl sulfate (D. D. S.) derivative.

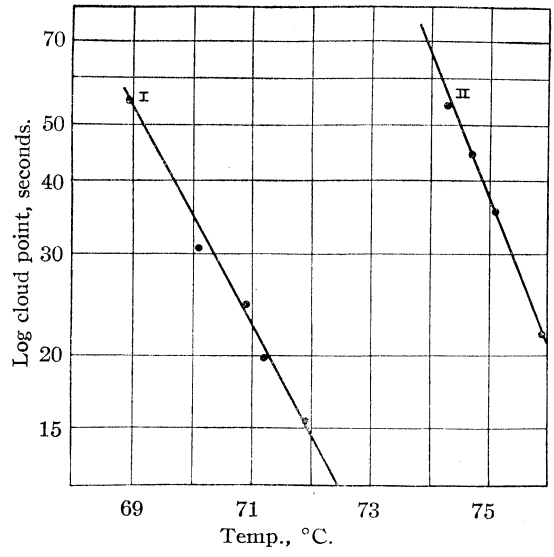


Fig. 4.—Comparison of log cloud point of β-lactoglobulin (I) with that of β-lactoglobulin–dodecyl sulfate (II) (1% solutions in 0.05 *M* sodium chloride, *p*H 5.2).

Cloud points of a 1% solution of β-lactoglobulin and its dodecyl sulfate derivative were determined in 0.05 *M* sodium chloride at *p*H 5.2. These are illustrated in Fig. 4. The presence of combined dodecyl sulfate increases the cloud point of β-lactoglobulin approximately 5°.

Optical Activity.—When dissolved in 0.1 *M* acetate buffer at *p*H 4.8, the β-lactoglobulin-dodecyl sulfate derivative had a specific rotation of $[\alpha]^{25}D$ −23.6°, as compared with a specific rotation of −30.5 for the untreated β-lactoglobulin.

Discussion

Exploratory studies with substances other than dodecyl sulfate, such as the dioctyl ester of sulfosuccinic acid and orange II, indicate that the combination of β-lactoglobulin with small amounts of large anions is rather general. Davis and Dubos[13] have found th t β-lactoglobulin combines with fatty acids, but to a smaller extent than does serum albumin.

Efforts to remove the two equivalents of dodecyl sulfate from β-lactoglobulin have not been successful. Long dialysis at *p*H 8.4 or treatment with barium hydroxide at *p*H 9.0 did not remove the dodecyl sulfate. Modification of the mobility of β-lactoglobulin by the presence of two molecules of unremovable dodecyl sulfate appears to be analogous to the difference in mobility between serum albumin and regenerated detergent-treated serum albumin,[6] indicating that barium chloride does not remove all the detergent from serum albumin.

The electrophoretic results of Li[9] indicate that β-lactoglobulin is heterogeneous. A partial separation of the electrophoretic components has been attained by fractionation,[14] giving crystalline fractions differing in solubility in water and salt solutions. It was hoped that dodecyl sulfate would be a useful substance for separating the components of β-lactoglobulin. However, all the fractions obtained by means of dodecyl sulfate had the same electrophoretic composition and behavior, indicating that the component proteins of β-lactoglobulin were all modified in a similar manner by the addition of dodecyl sulfate.

It is possible that the electrophoretic heterogeneity of β-lactoglobulin is due to the presence of non-amino acid groups combined with a portion of the β-lactoglobulin molecules in a manner similar to the combination of dodecyl sulfate. Electrophoretic determinations made on mixtures of equal parts of β-lactoglobulin and its dodecyl sulfate derivative are consistent with this hypothesis. In veronal buffer at *p*H 8.4, the normal β-lactoglobulin and the dodecyl sulfate derivative have markedly different mobilities, −5.1 and −5.9 *u*, respectively. The mixture moved as a single component with a mobility of −5.7 *u*. At *p*H 4.8 in acetate buffer, the electrophoretic pattern of the normal β-lactoglobulin indicated two components, with 60% of the protein in the faster component. The dodecyl sulfate derivative gave an electrophoretic pattern which was almost homogeneous, being composed largely of a component moving with a mobility of the slowest of the two β-lactoglobulin components. Mixtures of the normal protein and dodecyl derivative had a composite electrophoretic pattern. It will be necessary, however, to await the separation and analysis of the electrophoretic components of β-lactoglobulin before this hypothesis gains further credence.

Acknowledgment.—We are indebted to Dr. S. Lenher of E. I. du Pont de Nemours Company for the purified and analyzed sodium dodecyl

(13) Davis and Dubos, *J. Expt. Medicine*, **86**, 215 (1947).

(14) McMeekin, Polis, DellaMonica and Custer, This Journal, **70**, 881 (1948).

sulfate; and also to Dr. S. R. Hoover for the α-amino nitrogen determinations and Dr. C. L. Ogg for the sulfur determinations.

Summary

Preparation of a crystalline derivative of β-lactoglobulin containing two equivalents of firmly bound dodecyl sulfate is described. The solubility, mobility, titration curve and denaturation temperatures of the derivative are compared with the corresponding properties of β-lactoglobulin.

PHILADELPHIA 18, PA. RECEIVED MAY 9, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of Naphthoquinones for Studies of the Inhibition of Enzyme Systems[1]

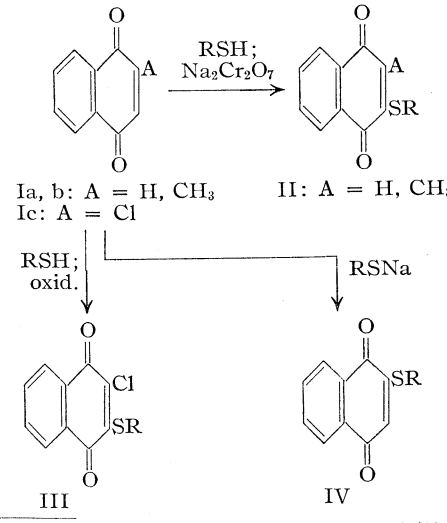
BY LOUIS F. FIESER AND RUSSELL H. BROWN[2]

Bueding, Peters and Waite[3] have reported the interesting finding that 2-methyl-1,4-naphthoquinone has the power to inhibit the anaerobic glycolysis of *Schistosoma mansoni* in *in vitro* tests at low concentrations, and that in experimental schistosomiasis in mice the quinone potentiates the action of subcurative doses of fuadin; the effect apparently vanishes when the dose is increased to the limit of tolerance. In coöperation with the program of pharmacological testing conducted by Dr. E. Bueding and Dr. L. Peters, we synthesized a number of additional naphthoquinones in the search for compounds of value in the chemotherapy of schistosomiasis. The assay data to be reported elsewhere show that, although several of the hydroxyl-free 2,3- and 2,6-disubstituted naphthoquinones described in this paper are considerably more potent than 2-methyl-1,4-naphthoquinone in the inhibition of the glycolytic enzyme concerned; the effect invariably is subject to strong antagonism by plasma proteins and the *in vivo* efficacy is in no instance appreciably greater than that of the simpler quinone.[4] A few of the compounds were tested against *Trichinella spiralis* in rats with completely negative results.[5]

Nachmansohn and Berman[6] observed that 2-methyl-1,4-naphthoquinone effects half-inhibition of choline esterase at dilutions in the order of 5×10^{-4} *M*, and Dr. Nachmansohn has found several of the new quinones here described to be distinctly more potent than methylnaphthoquinone against this enzyme system. The compounds are being studied for antitubercular activity at the Merck Institute for Therapeutic Research, following an observation by Dr. R. Dubos that some of the antimalarial 2-hydroxy-3-alkyl-1,4-naphthoquinones[7] show considerable *in vitro* potency, although the effect is greatly diminished in the presence of plasma proteins. 2-Methyl-6-valeryl-1,4-naphthoquinone appeared particularly promising in the *in vitro* assays but proved to be too toxic for *in vivo* evaluation in infected mice.

Specific naphthoquinones are recognized to influence the synthesis of prothrombin and the respiratory enzymes of malaria parasites, as well as enzymes associated with glycolysis, esterification, and the functioning of the *tubercle bacillus*. The present assay data indicate considerable specificity of action: a naphthoquinone showing high potency against one of the systems is not necessarily active against the others.

One route to compounds possessing enzyme-inhibiting activity was addition of an alkyl or aryl mercaptan to 1,4-naphthoquinone or its 2-methyl (Ia, b) derivative in methanol and oxidation of the resulting substituted hydroquinone by pouring the reaction mixture onto dichromate solution. Quinones of Type II are thus obtained more conveniently and in higher yield than by earlier procedures[8,9]; a similar method has recently been reported for the preparation of 2-thiomethyl-1,4-naphthoquinone, which was found to have high antifungicidal activity.[10] The



(1) This work was supported in part by grants from the Rockefeller Foundation and Research Corporation.

(2) Abbott Laboratories Postwar Fellow, 1945–1948.

(3) Bueding, Peters and Waite, *Proc. Soc. Exp. Biol. Med.*, **64**, 111 (1947).

(4) We are indebted to Dr. S. Rajagopalan for the preparation of large samples of fourteen of the quinones for *in vivo* tests.

(5) Oliver-Gonzalez and Bueding, *Proc. Soc. Exp. Biol. Med.*, **69**, 659 (1948).

(6) Nachmansohn and Berman, *J. Biol. Chem.*, **165**, 551 (1946).

(7) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3151 (1948).

(8) Dimroth, Kraft and Aichinger, *Ann.*, **545**, 124 (1940).

(9) Fieser and Turner, THIS JOURNAL, **69**, 2335 (1947).

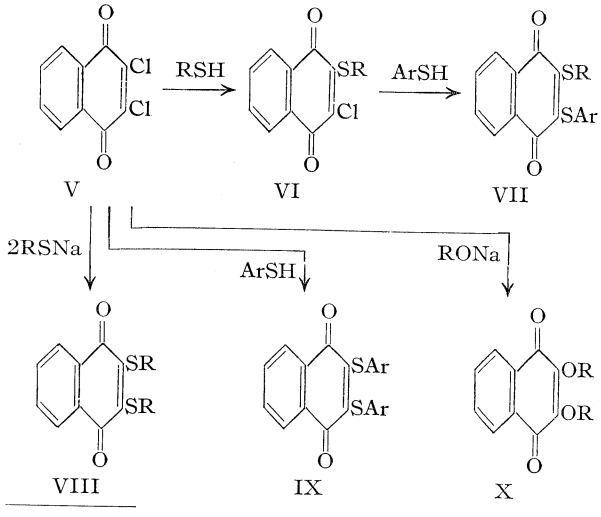
(10) Little, Sproston and Foote, *ibid.*, **71**, 1124 (1949).

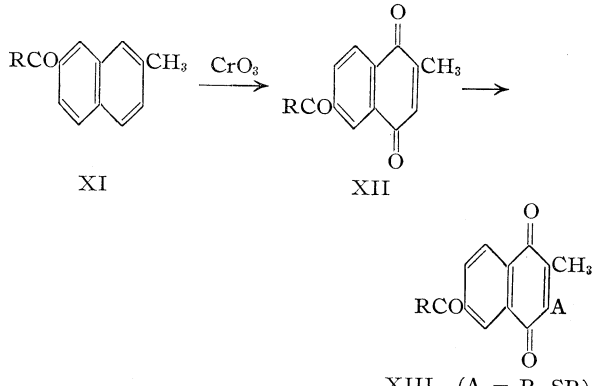
method served well for the preparation of 2-thioalkyl derivatives containing 1–12 carbon atoms in the alkyl group, 2-thioaryl derivatives, 2-methyl-3-thioalkyl and 2-methyl-3-thioaryl derivatives. 2-Chloro-1,4-naphthoquinone (Ic) is known to react with alkali[11] and with aniline[12] not by halogen displacement but by hydroxylation or arylamination at the 3-position, probably through an addition–oxidation mechanism. The reaction with mercaptans follows a similar course and leads to 2-chloro-3-thioalkyl-1,4-naphthoquinones (III). We have found, however, that treatment of the chloroquinone with a sodium mercaptide results in smooth displacement of chlorine to give the 2-thioalkyl derivative (IV). By the same method the chlorine atom of 2-chloro-3-anilino-1,4-naphthoquinone can be replaced by the thioalkyl group; 2-anilino-3-thiomethyl-1,4-naphthoquinone has been prepared previously by a lengthier method.[13] A related observation is that 2-chloro-1,4-naphthoquinone can be converted in good yield into 2-methoxy-1,4-naphthoquinone by reaction with sodium methoxide under anhydrous conditions; the reaction is in contrast to that occurring in aqueous alkali.

Further thio-derivatives were obtained from 2,3-dichloro-1,4-naphthoquinone.[14] When this substance (V) is refluxed in alcoholic solution with an aliphatic mercaptan only one of the chlorine atoms is replaced and the product (VI) is not affected by an excess of reagent. Aryl mercaptans react readily with replacement of both chlorine atoms (IX), and we were unable to isolate a monosubstitution product in experiments utilizing excess dichloronaphthoquinone.[15] Furthermore the chlorine atom of the 2-chloro-3-thioalkyl-1,4-naphthoquinones, although inert to alkyl mercaptans, is easily displaced by reaction with an aryl mercaptan to give VII. As in the examples cited above, the greater reactivity of the sodium salts of the alkyl mercaptans is manifested in the ability of these salts to replace both chlorine atoms of V and afford the 2,3-dithioalkyl derivatives (VIII). 2,3-Dimethoxy-1,4-naphthoquinone (X) was similarly obtained by treatment of dichloronaphthoquinone with sodium methoxide in methanol. The 2,3-diphenoxy derivative has previously been prepared by reaction with potassium phenolate in phenol solution,[16] and the condensation of dichloronaphthoquinone with β-naphthol in pyridine has been shown to proceed with closure of a furan ring.[17] We obtained the isomeric *brazanquinone* by reaction with α-naphthol. An attempt to prepare the thiophene analog led only to 2,3-dithio-β-naphthyl-1,4-naphthoquinone.

Other workers in this Laboratory have attempted without success to introduce the benzyl group into 2-methyl- or 2-hydroxy-1,4-naphthoquinone by peroxide alkylation,[18] but in the present work conditions were found for the satisfactory peroxide benzylation of these compounds and of the 2-chloro derivative by diphenacetyl peroxide. Whereas 2-methyl-3-benzyl-1,4-naphthoquinone was difficultly accessible by previous methods,[19] a 7-g. sample for *in vivo* assay was readily prepared by the present procedure.

A series of 6-acyl-2-methyl-1,4-naphthoquinones (XII) were prepared by oxidation of the 6-acyl-2-methylnaphthalenes (XI) available by Friedel–Crafts acylation of β-methylnaphthalene in nitrobenzene solution according to Haworth.[20] 3-Alkyl and 3-thioalkyl derivatives (XIII) of the 6-acyl quinones were obtained by the methods described above.





(11) Zincke, *Ber.*, **27**, 2758 (1894).

(12) Cleve, *ibid.*, **21**, 93 (1888); Zincke and Kegel, *ibid.*, **21**, 1036 (1888).

(13) Fries and Kerkow, *Ann.*, **427**, 281 (1922).

(14) We are indebted to the Naugatuck Chemical Co. for generous supplies of this chemical and of α-naphthoquinone.

(15) Compare Fries and Ochwat, *Ber.*, **56**, 1291 (1923).

(16) Ullmann and Ettisch, *ibid.*, **54**, 259 (1921).

(17) Eistert, *Chem. Ber.*, **1**, 80 (1947).

(18) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3197 (1948).

(19) Fieser, Campbell, Fry and Gates, *ibid.*, **61**, 3216 (1939); Fieser and Chang, *ibid.*, **64**, 2043 (1942).

(20) Haworth, Letsky and Mavin, *J. Chem. Soc.*, 1784 (1932); Haworth and Bolam, *ibid.*, 2248 (1932); Kon and Weller, *ibid.*, 792 (1939).

TABLE I

2-THIOALKYL(ARYL)-1,4-NAPHTHOQUINONES

No.	2-Substituent	M. p., °C.	Solv.	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	$-SCH_3$[a]	185–186	EtOH–C_6H_6	Needles	$C_{11}H_8O_2S$	64.70	64.67	3.95	4.06
2	$-SC_2H_5$[b]	142–143	MeOH	Needles	$C_{12}H_{10}O_2S$				
3	$-SC_3H_7$-*n*	121–122	MeOH	Leaves	$C_{13}H_{12}O_2S$	67.20	67.04	5.21	5.40
4	$-SC_3H_7$-*i*	103–104	MeOH	Plates	$C_{13}H_{12}O_2S$	67.20	67.31	5.21	5.22
5	$-SC_4H_9$-*n*	102–103	MeOH	Needles	$C_{14}H_{14}O_2S$	68.28	68.39	5.73	5.82
6	$-SCH_2CH(CH_3)_2$	135–136	MeOH	Needles	$C_{14}H_{14}O_2S$	68.28	68.25	5.73	5.55
7	$-SC(CH_3)_3$	150–151	Lig.	Prisms	$C_{14}H_{14}O_2S$	68.28	68.40	5.73	5.72
8	$-SC_5H_{11}$-*n*	112–113	EtOH	Needles	$C_{15}H_{16}O_2S$	69.20	69.30	6.20	6.20
9	$-S(CH_2)_2CH(CH_3)_2$	117–118	MeOH	Leaves	$C_{15}H_{16}O_2S$	69.20	69.34	6.20	6.26
10	$-SC_8H_{17}$-*n*	110–111	MeOH	Leaves	$C_{18}H_{22}O_2S$	71.49	71.63	7.34	7.42
11	$-SC_{12}H_{25}$-*n*	115–116	EtOH–C_6H_6	Leaves	$C_{22}H_{30}O_2S$	73.70	73.51	8.43	8.31
12	$-SC_6H_5$[c]	159–161	Lig.	Prisms					
13	$-SCH_2C_6H_5$	136–137	MeOH	Needles	$C_{17}H_{12}O_2S$	72.83	72.63	4.32	4.47
14	$-SC_6H_4CH_3$-*o*	119–120	MeOH	Plates	$C_{17}H_{12}O_2S$	72.83	73.07	4.32	4.53
15	$-SC_6H_4CH_3$-*m*	142–143	Lig.	Plates	$C_{17}H_{12}O_2S$	72.83	72.81	4.32	4.60
16	$-SC_6H_4CH_3$-*p*	121–122	MeOH	Needles	$C_{17}H_{12}O_2S$	72.83	73.03	4.32	4.41
17	$-S$-β-Naphthyl	180–181	EtOH	Needles	$C_{20}H_{12}O_2S$	75.91	75.74	3.82	3.69

[a] Little, Sproston and Foote, ref. 10. [b] Ricsei, *Ber.*, **60**, 1836 (1927). [c] Dimroth, Kraft and Aichinger, ref. 8.

TABLE II

2-METHYL-3-THIOALKYL(ARYL)-1,4-NAPHTHOQUINONES

No.	3-Substituent	M. p., °C.	Solvent	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
18	$-SCH_3$	91–93	MeOH	Needles	$C_{12}H_{10}O_2S$	66.01	66.03	4.62	4.90
19	$-SC_2H_5$	77–78	MeOH	Needles	$C_{13}H_{12}O_2S$	67.02	67.10	5.21	5.28
20	$-SC_3H_7$-*n*	41–43	MeOH	Prisms	$C_{14}H_{14}O_2S$	68.28	68.43	5.73	5.93
21	$-SC_3H_7$-*i*	66–68	MeOH	Leaves	$C_{14}H_{14}O_2S$	68.28	68.42	5.73	5.70
22	$-SC_4H_9$-*n*	44–46	MeOH	Plates	$C_{15}H_{16}O_2S$	69.20	69.19	6.20	6.25
23	$-SC(CH_3)_3$	125–126	MeOH	Blades	$C_{15}H_{16}O_2S$	69.20	69.42	6.20	6.09
24	$-SC_8H_{17}$-*n*	67–69	MeOH	Leaves	$C_{19}H_{24}O_2S$	72.12	72.12	7.64	7.59
25	$-SC_{12}H_{25}$-*n*	79–80	EtOH	Blades	$C_{23}H_{32}O_2S$	74.15	74.19	8.66	8.63
26	$-SCH_2C_6H_5$[a]	70–71	MeOH	Prisms	$C_{18}H_{14}O_2S$	73.45	73.70	4.79	4.72
27	$-SC_6H_5$	109–110	MeOH	Orange blades	$C_{17}H_{12}O_2S$	72.83	72.78	4.32	4.29
28	$-SC_6H_4CH_3$-*o*	121–122	EtOH	Orange-red plates	$C_{18}H_{14}O_2S$	73.45	73.59	4.79	4.74
29	$-SC_6H_4CH_3$-*m*	103–104	EtOH	Red prisms	$C_{18}H_{14}O_2S$	73.45	73.43	4.79	4.91
30	$-SC_6H_4Cl$-*p*	116–117	EtOH	Red-orange plates	$C_{17}H_{11}O_2SCl$	64.86	65.07	3.52	3.62

[a] Fieser and Turner, ref. 9.

Experimental[21]

2-Thioalkyl-(aryl)-1,4-naphthoquinones (Table I). Example: R = CH_3.[10]—A suspension of 15.8 g. (0.1 mole) of α-naphthoquinone in 140 cc. of methanol was treated at 0° with a cold solution of 5.06 g. (0.125 mole) of methyl mercaptan in 20 cc. of methanol and the mixture allowed to stand at room temperature for two hours, when considerable solid reaction product had separated. The mixture was then poured into a vigorously stirred mixture of 20 g. of sodium dichromate dihydrate, 10 cc. of concentrated sulfuric acid, ice and water. The crude product collected by filtration weighed 17.7 g., m. p. 105–145°. Crystallization from 200 cc. of 95% ethanol and 100 cc. of benzene gave 10.22 g. (51%) of 2-thiomethyl-1,4-naphthoquinone, m. p. 180–184°; the fully purified quinone melted at 185–186° (No. 1).

Other Examples.—A similar preparation conducted with 7.91 g. (0.05 mole) of α-naphthoquinone and 3.10 g. (0.05 mole) of ethyl mercaptan yielded 8.72 g. of crude material, m. p. 97–115°; crystallization from 100 cc. of methanol and 75 cc. of 95% ethanol gave 4.45 g. (41%) of 2-thioethyl-1,4-naphthoquinone (no. 2), m. p. 139–142°. The yield was substantially the same when the amount of ethyl mercaptan was increased to 4.65 g. (0.075 mole): 4.87 g. (45%), m. p. 138–142°. 2-Thioisoamyl-1,4-naphthoquinone was prepared from a mixture of 3.16 g. (0.02 mole) of α-naphthoquinone and 2.08 g. (0.02 mole) of isoamyl mercaptan in 50 cc. of methanol. After standing for eighteen hours at room temperature long colorless needles of the substituted hydroquinone had separated. Oxidation as above and crystallization from 40 cc. of methanol gave 2.15 g. (41%) of large yellow leaves of nearly pure quinone (no. 9).

2-Thioisoamyl-1,4-naphthoquinone was also obtained by adding a solution of 1.04 g. of isoamyl mercaptan and 0.4 g. of sodium hydroxide in 10 cc. of methanol and 1 cc. of water to a solution of 1.93 g. of 2-chloro-1,4-naphthoquinone in 25 cc. of acetone at room temperature. After one hour the solution was diluted and the precipitated material crystallized from methanol (charcoal). A second crystallization from 40 cc. of methanol gave 0.9 g. (35%) of pure no. 9, identical with that of the above synthesis.

2-Thioalkyl-(aryl)-3-methyl-1,4-naphthoquinone (Table II). Example: R = $CH_2C_6H_5$.—A mixture of 3.44 g. (0.02 mole) of 2-methyl-1,4-naphthoquinone and 2.48 g. (0.02 mole) of benzyl mercaptan in 40 cc. of methanol was allowed to stand at room temperature for twenty-four hours and poured with stirring into a mixture of 5 g. of sodium dichromate dihydrate, 5 cc. of 96% sulfuric acid, 50 cc. of water and 150 g. of ice. The crude

(21) All melting points are corrected.

TABLE III

2-HALO-(METHYL)-3-THIOALKYL(ALKOXYL)-1,4-NAPHTHOQUINONES

No.	Substituents 2-	Substituents 3-	M. p., °C.	Solv.	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
31	Cl	$-SC_2H_5$	115–116	EtOH	Leaves	$C_{12}H_9O_2SCl$	57.03	56.88	3.59	3.72
32	Cl	$-SC_3H_7$-*n*	50–51	MeOH	Small plates	$C_{13}H_{11}O_2SCl$	58.54	58.64	4.15	4.01
33	Cl	$-SC_4H_9$-*n*	67–68	MeOH	Leaves	$C_{14}H_{13}O_2SCl$	59.88	59.79	4.67	4.78
34	Cl	$-SC_5H_{11}$-*n*	51–52	MeOH	Long leaves	$C_{15}H_{15}O_2SCl$	61.11	61.16	5.13	5.24
35	Cl	$-SC_8H_{17}$-*n*	73–74	MeOH	Small plates	$C_{18}H_{21}O_2SCl$	64.16	64.19	6.28	6.22
36	Cl	$-SC_{12}H_{25}$-*n*	83–84	EtOH	Small plates	$C_{22}H_{29}O_2SCl$	67.23	67.36	7.44	7.47
37	Br	$-SC_4H_9$-*n*	85–86	MeOH	Small plates	$C_{14}H_{13}O_2SCl$	51.70	51.96	4.02	4.00
38	Br	$-OCH_3$	163–164	MeOH	Long needles	$C_{11}H_7O_3Br$	49.46	49.38	2.64	2.53
39	Br	$-OC_2H_5$	116–117	MeOH	Needles	$C_{12}H_9O_3Br$	51.26	51.44	3.23	3.11
40[a]	Cl	$-OC_2H_5$	97–98	MeOH	Feathery needles	$C_{12}H_9O_3Cl$	60.90	61.03	3.83	4.02
41	Br	$-OC_4H_9$-*n*	48–49	EtOH	Fine blades	$C_{14}H_{13}O_3Cl$	54.39	54.32	4.24	4.06
42[b]	CH_3	$-OCH_3$	93–94	MeOH	Long needles					
43	CH_3	$-OC_2H_5$	73–74	MeOH	Needles	$C_{13}H_{12}O_3$	72.22	72.23	5.60	5.78
44	CH_3	$-OCH_2CH{=}CH_2$	62–63	Lig.	Fine blades	$C_{14}H_{12}O_3$	73.67	73.46	5.30	5.63
45	CH_3	$-OC_3H_7$-*n*			Liquid	$C_{14}H_{14}O_3$	73.03	72.74	6.13	6.39
46	CH_3	$-OC_4H_9$-*n*			Liquid	$C_{15}H_{16}O_3$	73.75	73.59	6.60	6.63
47	CH_3	$-CH_2C_6H_5$	53–54	MeOH	Large blades	$C_{18}H_{14}O_3$	77.67	77.43	5.07	5.04

[a] Fieser, THIS JOURNAL, **48**, 2922 (1926). [b] Madinaveitia, *Ann. Soc. Expan. Quim. Fis.*, **31**, 750 (1933).

product (5.33 g.) on crystallization from 40 cc. of methanol yielded 4.11 g. (70%) of 2-methyl-3-thiobenzyl-1,4-naphthoquinone (no. 26), m. p. 68–70°. One more crystallization gave 3.74 g. of product m. p. 71–72°. The compound was obtained previously (Table II, Note *a*) in only 28% yield.

The same procedure was applied to the preparation of the other compounds listed, usually with substantially the same results: 70% yield of once crystallized product. The reaction of 2-methyl-1,4-naphthoquinone (17.2 g.) with *t*-butyl mercaptan (9 g.) in methanol (200 cc.) proceeded less smoothly. After standing for eight days the mixture was refluxed for twenty-four hours and on cooling deposited 3 g. of 2-methyl-3-thio-*t*-butyl-1,4-naphthoquinone.

Derivatives. (a) **Ethyl-(2-methyl-1,4-naphthoquinonyl-3)-sulfoxide.**—2-Methyl-3-thioethyl-1,4-naphthoquinone (2 g.) was covered with 5 cc. of fuming nitric acid and the mixture kept at room temperature for ten minutes and poured into 25 cc. of cold water. Crystallization of the precipitated material from 20 cc. of methanol yielded 1.55 g. (72%) of well-formed red-orange needles, m. p. 140–142°. A recrystallized sample melted at 143–144°.

Anal. Calcd. for $C_{13}H_{12}O_3S$: S, 62.87; H, 4.87. Found: C, 62.99; H, 5.12.

(b) ***n*-Dodecyl-(2-methyl-1,4-naphthoquinonyl-3)-sulfoxide** was obtained by the same method in 70% yield. The compound formed small tan balls from ethanol, m. p. 105–106°.

Anal. Calcd. for $C_{23}H_{32}O_3S$: C, 71.10; H, 8.30. Found: C, 71.46; H, 7.99.

2-Methyl-3-thioethyl-1,4-naphthohydroquinone dibenzoate was prepared in 78% yield (m. p. 138–140°) by the action of benzoyl chloride on the hydroquinone in pyridine. The pure material formed tiny white needles from ethanol–acetone, m. p. 143–145°.

Anal. Calcd. for $C_{27}H_{22}O_4S$: C, 73.26; H, 5.01. Found: C, 73.01; H, 5.28.

2-Halo-3-thioalkyl-1,4-naphthoquinones (Table III). (a) **From 2,3-Dichloro-1,4-naphthoquinone.**—Treatment of the dichloroquinone in alcoholic suspension with as much as two moles of an aliphatic mercaptan results in replacement of only one of the chlorine atoms. Thus 2-chloro-3-thio-*n*-octyl-1,4-naphthoquinone (No. 35) was prepared by heating a mixture of 6.81 g. (0.03 mole) of 2,3-dichloro-1,4-naphthoquinone and 8.76 g. (0.06 mole) of *n*-octyl mercaptan in 100 cc. of 95% ethanol under reflux for two hours. The resulting clear solution when cooled deposited a solid product that when recrystallized from 100 cc. of 95% ethanol afforded 6.30 g. (62%) of the substituted quinone, m. p. 61–65°. Further crystallizations from ligroin and from methanol gave material melting at 73–74°.

(b) **From 2-Chloro-1,4-naphthoquinone.**—2-Chloro-3-thio-*n*-dodecyl-1,4-naphthoquinone was prepared from a suspension of 1.93 g. (0.01 mole) of the monochloroquinone in 50 cc. of methanol, treated with a solution of 2.02 g. (0.01 mole) of *n*-dodecyl mercaptan in 25 cc. of 95% ethanol. After six hours at room temperature a solid reaction product that had separated was collected and recrystallized from 20 cc. of ethanol and afforded 1.0 g. (51%) of the 2-chloro-3-thio-*n*-dodecyl compound (no. 36), m. p. 83–84°.

(c) **By Halogenation.**—A mixture of 0.7 g. of 2-*n*-thiobutyl-1,4-naphthoquinone, 1 g. of fused sodium acetate, and 5 cc. of acetic acid was treated with 15 cc. of a solution of 1 cc. of bromine in 100 cc. of acetic acid. After standing for three hours at room temperature, the mixture was poured into 50 cc. of cold water and the precipitated solid collected, washed and dried: 0.83 g. (90%), m. p. 72–76°. Crystallization from 20 cc. of methanol gave 0.52 g. of 2-bromo-3-thio-*n*-butyl-1,4-naphthoquinone (No. 37), m. p. 82–84°.

2-Halo-3-alkoxy-1,4-naphthoquinones (Table III). (a) **By Halogenation.**—For the preparation of 2-bromo-3-methoxy-1,4-naphthoquinone (no. 38), a mixture of 0.51 g. of 2-methoxy-1,4-naphthoquinone and 1 g. of fused sodium acetate was treated with 15 cc. of a solution of 3.12 g. of bromine in 100 cc. of acetic acid at room temperature. There resulted a clear solution from which a yellow solid separated. Precipitation with 50 cc. of water after eight hours gave 0.68 g. (94%) of crude product, m. p. about 150°. This was crystallized to constant m. p. (163–164°) from methanol. The bromoethoxy and bromobutoxy derivatives (nos. 39–41) were prepared by the same method in comparable high yield. 2-Chloro-3-ethoxy-1,4-naphthoquinone (no. 40, known) was prepared by chlorination of 2.02 g. of 2-ethoxy-1,4-naphthoquinone in 25 cc. of acetic acid in the presence of 3.6 g. of fused sodium acetate with 15 cc. of an acetic acid solution containing 0.48 g. of chlorine for sixteen hours at room temperature. The precipitated product (1.96 g., 83%) melted at 80–85° and afforded pure material, m. p. 97–98°, on one crystallization.

(b) **From 2,3-Dichloro-1,4-naphthoquinone.**—A mixture of 2.27 g. of the dichloroquinone and 0.9 g. of sodium acetate in 60 cc. of absolute ethanol was refluxed for two hours, water was added, and the solid product was crystallized from methanol (charcoal). The resulting 2-chloro-

TABLE IV

2,3-DITHIOALKYL(ARYL)-1,4-NAPHTHOQUINONES AND RELATED COMPOUNDS

No.	Substituents 2-	3-	M. p., °C.	Solvent	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
48	$-SCH_3$	$-SCH_3$	115–116	MeOH	Fine orange-red needles	$C_{12}H_{10}O_2S_2$	57.58	57.22	4.03	4.15
49	$-SC_2H_5$	$-SC_2H_5$	83–84	MeOH	Purple blades	$C_{14}H_{14}O_2S_2$	60.42	60.23	5.07	4.84
50	$-SC_{12}H_{25}$-*n*	$-SC_{12}H_{25}$-*n*	71–73	EtOH	Purple micro-needles	$C_{34}H_{54}O_2S_2$	73.06	73.07	9.74	9.76
51	$-SC_6H_5$	$-SC_6H_5$	151–152	EtOH	Orange needles	$C_{22}H_{14}O_2S_2$	70.55	70.77	3.77	3.82
52	$-SC_6H_4CH_3$-*p*	$-SC_6H_4CH_3$-*p*	173–174	EtOH	Crimson needles	$C_{24}H_{18}O_2S_2$	71.63	71.53	4.51	4.71
53	-S-β-Naphthyl	-S-β-Naphthyl	196–197	EtOH–C_6H_6	Orange needles	$C_{30}H_{18}O_2S_2$	75.93	76.02	3.82	3.98
54	$-SC_2H_5$	$-SC_6H_4CH_3$-*p*	118–119	EtOH	Orange needles	$C_{19}H_{16}O_2S_2$	67.03	66.92	4.74	4.90
55	$-SC_4H_9$-*n*	$-SC_6H_4CH_3$-*p*	105–106	EtOH	Orange needles	$C_{21}H_{20}O_2S_2$	68.45	68.60	5.47	5.75
56	$-SCH_2C_6H_5$	$-SC_6H_4CH_3$-*p*	103–104	EtOH	Red needles	$C_{24}H_{18}O_2S_2$	71.63	71.76	4.51	4.69
57	$-C_4H_9$-*n*	$-SC_6H_5$	112–113	Lig.	Micro cryst.	$C_{20}H_{18}O_2S$	74.50	74.73	5.63	5.72
58	$-NHC_6H_5$	$-SC_5H_{11}$-*n*	114–116	EtOH	Purple needles	$C_{21}H_{21}O_2SN$	71.79	72.05	6.02	5.95
59	$-NHC_6H_5$	$-SC_6H_5$	197–199	EtOH	Purple leaves	$C_{22}H_{15}O_2SN$	73.93	74.07	4.23	4.18
60	-Cl	$-C_2H_5$	111–112	MeOH	Blades	$C_{12}H_9O_2Cl$	65.31	65.54	4.11	4.29
61	-Cl	$-C_{11}H_{23}$-*n*	82–83	Pt. ether	Fine needles	$C_{21}H_{27}O_2Cl$	72.71	72.90	7.85	8.12
62	-Cl	$-CH_2C_6H_5$	130–131	MeOH	Plates	$C_{17}H_{11}O_2Cl$	72.21	72.25	3.92	3.83

3-ethoxy-1,4-naphthoquinone (1.38 g., 58%) melted at 96–98°.

2-Methyl-3-alkoxy-1,4-naphthoquinones (Table III).—For preparation of the 3-methoxy compound (no. 42), 3 g. of the powdered silver salt of phthiocol was covered with 10 cc. of methyl iodide and allowed to stand at room temperature with occasional agitation for one hour. The product was extracted with 100 cc. of ether, the solution was washed three times with 3% ammonia solution, dried and evaporated. Crystallization of the residue from 15 cc. of methanol gave 0.93 g. (45%) of product, m. p. 93–94°.

The ethoxy compound was prepared in the same way in 47% yield (m. p. 72–74°); the silver salt failed to react with ethyl chloride. The alloxy, *n*-propoxy, *n*-butoxy, and benzyloxy derivatives (nos. 44–47) were obtained with use of allyl bromide, *n*-propyl iodide, *n*-butyl iodide and benzyl chloride in yields of 37, 53, 52 and 10%, respectively; the reaction of the silver salt with benzyl chloride was conducted for one-half hour on the steam-bath.

2,3-Dithioalkyl-1,4-naphthoquinones (Table IV).—The dithiomethyl derivative (no. 48) was prepared by treating a suspension of 5.7 g. of 2,3-dichloro-1,4-naphthoquinone in 20 cc. of methanol with a solution prepared from 2 g. of sodium hydroxide, 20 cc. of methanol, and 12 cc. of a solution of 25.3 g. of methyl mercaptan in 100 cc. of methanol. The mixture was refluxed for one-half hour and the resulting clear solution when cooled to 0° deposited 1.55 g. of yellow crystalline product, m. p. 90–100°. The solid was ground to a powder, shaken with 25 cc. of water, dried (1.33 g.) and crystallized from 95% ethanol (charcoal); the yield of long orange-red needles, m. p. 114–117°, was 0.74 g. (12%). 2,3-Dithioethyl-1,4-naphthoquinone (no. 49) was obtained similarly in 19% yield; the substance forms as an orange solution in ethanol, but the crystals that separate are extraordinary for their deep, almost black, purple color.

2,3-Dithioaryl-1,4-naphthoquinones (Table IV).—In a typical case a mixture of 2.27 g. of 2,3-dichloro-1,4-naphthoquinone and 2.48 g. of *p*-thiocresol in 100 cc. of 95% ethanol was refluxed for one hour and the solution cooled to 0°, when 3.68 g. (89%) of red crystals, m. p. 170–172°, separated. Two crystallizations from ethanol (80 cc./g.) gave pure 2,3-di-*p*-thiocresyl-1,4-naphthoquinone (no. 52), m. p. 173–174°. 2,3-Di-β-thionaphthyl-1,4-naphthoquinone was obtained in the same way in 95% yield (m. p. 192–195°).

2,3-Dithiophenyl-5-nitro-1,4-naphthoquinone was prepared by refluxing for one-half hour a mixture of 0.68 g. of 2,3-dichloro-5-nitro-1,4-naphthoquinone[22] in 25 cc. of 95% ethanol with 1.10 g. of thiophenol in 25 cc. of ethanol. A crystalline orange product separated (1.09 g., quantitative; m. p. 130–132°) and when crystallized from 75 cc. of ethanol formed red needles, m. p. 134–135°. A polymorphic form melts at 152°.

Anal. Calcd. for $C_{22}H_{12}O_4S_2N$: C, 63.00; H, 3.13. Found: C, 63.01; H, 3.28.

2-Thioalkyl-3-thioaryl-1,4-naphthoquinones (Table IV).—A solution of 0.25 g. of 2-thioethyl-3-chloro-1,4-naphthoquinone in 10 cc. of 95% ethanol was treated with 0.124 g. of *p*-thiocresol in 5 cc. of 95% ethanol and the mixture was heated gently for fifteen minutes and cooled to 80°, when 0.30 g. (89%) of long needles separated, m. p. 115–117° (no. 54). The homolog no. 55 was prepared similarly in 88% yield (m. p. 105–106°). The less soluble derivative no. 56 was prepared from 1.57 g. of the chloro compound in 20 cc. of 95% ethanol, treated with 0.162 g. of *p*-thiocresol in 25 cc. of 95% ethanol and 15 cc. of benzene; the yield of product, m. p. 98–100°, was 1.60 g. (80%).

2-Anilino-3-thio-*n*-amyl-1,4-naphthoquinone (no. 58) was prepared from a solution of 1.35 g. of 2-anilino-3-chloro-1,4-naphthoquinone[13] in 50 cc. of 95% ethanol mixed with a solution of 0.86 g. of *n*-amyl mercaptan and 0.2 g. of sodium hydroxide in methanol. The mixture was refluxed for two hours, diluted with 50 cc. of water, and the product that separated was crystallized from 20 cc. of methanol to give 1.44 g. (82%) of long, deep-red needles, m. p. 113–115°.

2,3-Disubstituted Naphthoquinones by Peroxide Alkylation

Diphenacetyl Peroxide.—Phenacetyl chloride (5.2 g. 0.0336 mole) was cooled well below 0° in Dry Ice–acetone and treated with 7.5 cc. of 30% hydrogen peroxide, cooled to 0° and added in one portion. The resulting semi-solid mass was treated with a solution of 7 g. of sodium hydroxide in 50 cc. of water that had been cooled almost to its freezing point and the mixture was shaken for ten minutes with intermittent cooling in Dry Ice–acetone, when the peroxide separated as a granular white solid. This was extracted with 100 cc. of ice-cold ether and the ether layer washed with cold saturated sodium chloride solution and used at once.

2-Methyl-3-benzyl-1,4-naphthoquinone.[19]—The above ethereal solution of peroxide was added to a solution of

(22) Fries, Pense and Pectus, *Ber.*, **61**, 1395 (1928).

TABLE V

6-ACYL-2-METHYL-1,4-NAPHTHOQUINONES

No.	Substituents: Position 6	Position 3	M. p., °C.	Solvent	Form	Formula	Analyses, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
63	$-COCH_3$		126–127	MeOH	Long prisms	$C_{13}H_{10}O_3$	72.90	72.98	4.71	4.82
64	$-COC_2H_5$		153–154	EtOH	Tiny prisms	$C_{14}H_{12}O_3$	73.60	73.45	5.30	5.26
	Hydroquinone		*ca.* 190	Aq. MeOH	Yel. needles	$C_{14}H_{14}O_3$	73.01	73.02	6.13	6.12
	Hydroq. dibenzoate		184–185	EtOH	White needles	$C_{28}H_{22}O_5$	76.40	76.52	4.75	5.09
65	$-COC_2H_5$	$-SC_6H_4CH_3$-*m*	107–108	MeOH	Orange leaves	$C_{21}H_{18}O_3S$	72.00	72.03	5.18	5.27
66	$-COC_3H_7$-*n*		153–154	EtOH	Tiny prisms	$C_{15}H_{14}O_3$	74.36	74.36	5.82	5.79
67	$-COC_3H_7$-*n*	$-SC_2H_5$	64–65	MeOH	Needles	$C_{17}H_{18}O_3S$	67.52	67.60	6.00	5.92
68	$-COC_3H_7$-*n*	$-C_{11}H_{23}$-*n*	73–74	MeOH	Fine needles	$C_{26}H_{36}O_3$	78.74	78.49	9.15	9.29
69	$-COC_4H_9$-*n*		86–87	MeOH	Prisms	$C_{16}H_{16}O_3$	74.98	74.88	6.29	6.20
70	$-COC_5H_{11}$-*n*		85–86	MeOH	Needles	$C_{17}H_{18}O_3$	75.53	75.41	6.71	6.93
71	$-CO(CH_2)_3$–Cyclohexyl		95–96	MeOH	Leaves	$C_{21}H_{24}O_3$	77.77	77.92	7.46	7.40
72	$-CO(CH_2)_2COOH$		198–199	EtOH	Needles	$C_{15}H_{12}O_5$	66.17	66.24	4.44	4.55
73	$-CO(CH_2)_2COOCH_3$		122–123	MeOH	Needles	$C_{16}H_{14}O_5$	67.11	66.90	4.93	4.77
74	$-CO(CH_2)_2COOCH_3$	$-SC_4H_9$-*n*	94–95	MeOH	Needles	$C_{20}H_{22}O_5S$	64.15	64.33	5.92	6.17

0.0167 mole of 2-methyl-1,4-naphthoquinone in 50 cc. of acetic acid and the mixture heated very gently on the steam-bath for one-half-hour and then heated more vigorously for an equal period. The resulting acetic acid solution was diluted and the precipitated product collected and dissolved in 100 cc. of ether. The solution was extracted repeatedly with 2% alkali, shaken for ten minutes with hydrosulfite solution, and starting material was removed by extraction of the ethereal hydroquinone solution with dilute alkali containing hydrosulfite. The solution was washed with brine, shaken for five minutes with 5 g. each of silver oxide and magnesium sulfate, filtered and evaporated. Crystallization of the residue from 20 cc. of methanol gave 0.7 g. (16% based on the acid chloride) of the substituted quinone, m. p. 106–108°, identical with an authentic sample.

Other Examples.—**2-Hydroxy-3-benzyl-1,4-naphthoquinone**[23] was prepared by the same method and the unchanged 2-hydroxy-1,4-naphthoquinone removed by extraction of an ethereal solution of the product with bicarbonate solution; the yield of material m. p. 175–176° was 31%, based on the acid chloride. **2-Chloro-3-methyl-1,4-naphthoquinone**[24] was obtained in 50% yield (m. p. 152–153°) by alkylation of the chloroquinone with diacetyl peroxide. The **ethyl** and ***n*-undecyl** and **benzyl** derivatives (Nos. 60–62) were prepared similarly in yields of 45, 37 and 36%, respectively.

Ethers from Chloroquinones

2,3-Dimethoxy-1,4-naphthoquinone[25] was prepared by refluxing a suspension of 2.27 g. of the dichloro compound and 1.08 g. of sodium methoxide in 50 cc. of absolute methanol for one-half hour. The bright yellow product that separated on cooling (1.8 g., 83%; m. p. 100–105°) on crystallization from methanol gave material m. p. 114–115°. **2-Methoxy-1,4-naphthoquinone** was obtained similarly from the 2-chloroquinone in 37% yield (recrystallized, m. p. 182–183°).

3,4-Benzo-8,11-β-brazanquinone.—A mixture of 9 g. of 2,3-dichloro-1,4-naphthoquinone and 6 g. of α-naphthol in 50 cc. of pyridine was refluxed for five hours and the sparingly soluble product was precipitated with alcohol and crystallized from benzene–alcohol; yield 6.8 g. (58%). The pure substance formed tiny orange needles, m. p. 229–230°.

Anal. Calcd. for $C_{20}H_{10}O_3$: C, 80.54; H, 3.35. Found: C, 80.28; H, 3.30.

6-Acyl-2-methyl-1,4-naphthoquinones (Table V)

The 6-acyl-2-methylnaphthalenes employed as starting materials were prepared by Friedel–Crafts acylation in nitrobenzene solution by the method of Haworth.[20] 6-Acyl derivatives purified to a condition suitable for oxidation have the following melting points: *n*-butyryl, 43–44°; *n*-valeryl, 53–55°; *n*-capryl, 66–68°; γ-cyclohexylbutyryl, 75–76°. Oxidation to the naphthoquinones listed in Table V was conducted with chromic acid in approximately 90% acetic acid solution[26]; the yields varied to 10–40%, depending upon the purity of the starting material. The 3-alkyl derivative No. 68 was prepared by peroxide alkylation; the 3-thioalkyl derivatives were prepared by mercaptan addition and oxidation.

Summary

The preparation of over seventy new naphthoquinones was undertaken in coöperation with investigators who have observed that 2-methyl-1,4-naphthoquinone possesses some power to inhibit the glycolytic enzyme of the schistosome and to inhibit choline esterase. A number of 3-thioalkyl and 6-acyl derivatives of the parent quinone are described, as well as various 2,3-disubstituted-1,4-naphthoquinones and related compounds. The results of assays will be reported elsewhere.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE 38, MASSACHUSETTS RECEIVED MAY 4, 1949

(23) Feiser, THIS JOURNAL, **48**, 3201 (1926).

(24) Fries and Lohmann, *Ber.*, **54**, 2920 (1921).

(25) Fieser, THIS JOURNAL, **50**, 461 (1928).

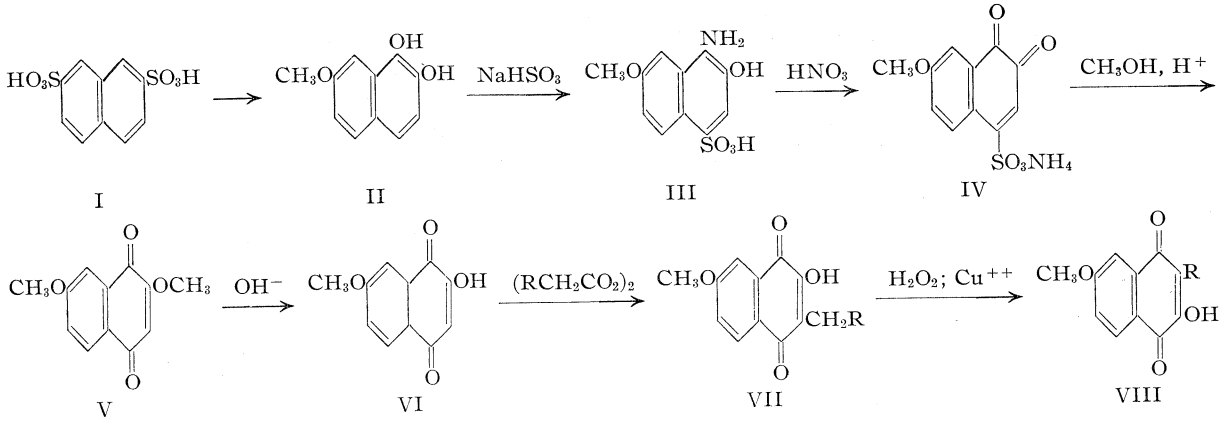
(26) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath Co., Boston, Mass., 1941, p. 233.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Naphthoquinone Antimalarials. XXIII. Bz-Substituted Derivatives[1]

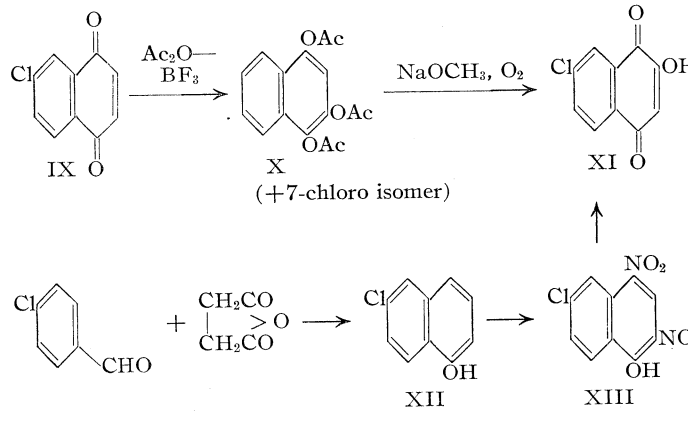
BY LOUIS F. FIESER AND RUSSELL H. BROWN[2]

In the few instances previously investigated the substitution of alkyl or hydroxyl groups in the benzenoid ring of a 2-hydroxy-3-alkyl-1,4-naphthoquinone has been found to practically obliterate antimalarial activity.[3] Since the case of atabrine would suggest the possibility of a more favorable result from the introduction of β-methoxy or β-chloro substituents into the aromatic ring, several new compounds of this type have been examined.



Two series of β-bz-methoxyquinones were prepared starting with 7-methoxy-1-nitroso-2-naphthol (II), available from naphthalene-2,7-disulfonic acid in three known steps. By procedures worked out for 1-nitroso-2-naphthol, II was converted through the aminonaphtholsulfonic acid III, the quinone sulfonate IV, and the dimethoxy quinone V into 2-hydroxy-7-methoxy-1,4-naphthoquinone (VI). By the peroxide alkylation reaction this was converted into 3-alkyl derivatives having from seven to eleven carbon atoms in the side-chain. These were converted by the modified Hooker oxidation[4] reaction into the next lower homologs in which, in consequence of the opening and reclosing of the quinone ring, the methoxy group is transposed to the 6-position (VIII). None of the compounds tested showed any antirespiratory activity,[5] whereas the corresponding methoxyl-free compounds are all active, even though the methoxyl substitution produces little change in the extraction constants.[6]

Related compounds carrying a chlorine atom at the 6- or 7-position were prepared starting with 6-chloro-1,4-naphthoquinone (IX), available from chloroprene and benzoquinone. The Thiele reaction afforded a separable mixture of the two hydroquinone triacetates, each of which was converted into the corresponding hydroxychloronaphthoquinone. One of these was identified as



the 2-hydroxy-6-chloro isomer by synthesis from the known 6-chloro-1-naphthol (XII) through the dinitro derivative XIII; this on reduction and oxidation afforded 6-chloro-2-amino-1,4-naphthoquinone-4-imine, which yielded XI on hydrolysis. The two hydroxychloroquinones were then alkylated with the peroxide from γ-cyclohexylbutyric acid, but neither product showed appreciable antirespiratory activity.

Experimental[7]

2-Hydroxy-3-alkyl-7(6)-methoxy-1,4-naphthoquinones

1-Nitroso-2-hydroxy-7-methoxynaphthalene.—Additional data on previously described procedures are as follows. Naphthalene (128 g.) was sulfonated with 95%

(1) This work was supported in part by grants from the Rockefeller Foundation and Research Corporation.

(2) Abbott Laboratories postwar Fellow, 1945–1948.

(3) Fieser and Richardson, THIS JOURNAL, **70**, 3156 (1948); Fieser, Leffler and co-workers, *ibid.*, **70**, 3212 (1948).

(4) Fieser and Fieser, *ibid.*, **70**, 3215 (1948).

(5) Heymann and Fieser, *J. Pharmacol. Exp. Therap.*, **94**, 97 (1948); Fieser and Heymann, *J. Biol. Chem.*, **176**, 1363 (1948).

(6) Fieser, Ettlinger and Fawaz, THIS JOURNAL, **70**, 3228 (1948).

(7) The melting points are all corrected,

TABLE I

1,4-NAPHTHOQUINONES

No.	Substituents	M. p., °C.	Solvent	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	2,7-$(OCH_3)_2$	214–215	EtOH	Orange needles	$C_{12}H_{10}O_4$	66.05	66.32	4.62	4.95
2	2-OH-7-OCH_3	220–222	EtOH	Orange needles	$C_{11}H_8O_4$	64.71	64.93	3.95	4.09
3	2-OH-7-OCH_3-3-$(CH_2)_3$-cyclohexyl	119–120	MeOH	Yellow needles	$C_{20}H_{24}O_4$	73.12	73.41	7.37	7.48
4	2-OH-7-OCH_3-3-CH_2-cyclohexyl	164–165	Pet. ether	Fine needles	$C_{18}H_{20}O_4$	72.00	72.36	6.71	7.03
5	2-OH-7-OCH_3-3-$C_{11}H_{23}$-*n*	94–95	MeOH	Leaves	$C_{22}H_{30}O_4$	73.70	73.86	8.44	8.28
6	2-OH-7-OCH_3-3-C_9H_{19}-*n*	97–98	MeOH	Leaves	$C_{20}H_{26}O_4$	72.71	72.97	7.93	8.07
7	2-OH-6-OCH_3-3-$(CH_2)_2$-cyclohexyl	137–138	MeOH	Large leaves	$C_{19}H_{22}O_4$	72.58	72.67	7.06	6.79
8	2-OH-6-OCH_3-3-cyclohexyl	142–143	MeOH	Fine blades	$C_{17}H_{18}O_4$	71.30	71.57	6.33	6.21
9	2-OH-6-OCH_3-3-$C_{10}H_{21}$-*n*	110–111	MeOH	Blades	$C_{21}H_{28}O_4$	73.23	73.15	8.19	8.32
10	2-OH-6-Cl	210–212	MeOH	Micro cryst.	$C_{10}H_5O_3Cl$	57.55	57.53	2.42	2.49
11	2-OH-6-Cl-3-$(CH_2)_3$-cyclohexyl	164–165	MeOH	Small leaves	$C_{19}H_{21}O_3Cl$	68.58	68.72	6.36	6.37
12	2-OH-7-Cl	205–207	MeOH	Micro cryst.	$C_{10}H_5O_3Cl$	57.55	57.57	2.42	2.40
13	2-OH-7-Cl-3-$(CH_2)_3$-cyclohexyl	132–133	MeOH	Leaflets	$C_{19}H_{21}O_3Cl$	68.58	68.39	6.36	6.20
14	2-OH-3-$(CH_2)_7CH{=}CH_2$	70–71	MeOH	Leaflets	$C_{19}H_{22}O_3$	76.47	76.60	7.43	7.61
15	2-OH-3-$(CH_2)_6CH{=}CH_2$	62–63	MeOH	Leaflets	$C_{18}H_{20}O_3$	76.01	75.95	7.09	7.39
16	2-OH-3-$(CH_2)_5CH{=}CH_2$	86–87	MeOH	Leaflets	$C_{17}H_{18}O_3$	75.54	75.35	6.71	6.98
17	2-OH-3-$(CH_2)_4CH{=}CH_2$	78–79	MeOH	Leaflets	$C_{16}H_{16}O_3$	74.99	75.00	6.29	6.77
18	2-OH-3-$(CH_2)_3CH{=}CH_2$	101–102	MeOH	Leaflets	$C_{15}H_{14}O_3$	74.35	74.52	5.82	6.05
19	2-OH-3-$(CH_2)_2CH{=}CH_2$	98–100	MeOH	Tiny plates	$C_{14}H_{12}O_3$	73.69	73.77	5.30	5.40

sulfuric acid (350 cc.) for four hours at 160°[8,9] and the cooled solution poured onto 500 g. of ice and 1.5 l. of water and neutralized with 450 g. of powdered calcium carbonate or 300 g. of quicklime. The mixture was filtered at 40° and the residual calcium sulfate extracted twice with 500-cc. portions of boiling water. The combined filtrates were evaporated to dryness and the mixture of 2,6- and 2,7-sulfonates was dried to constant weight at 200°; yield 263–285 g. Three parts of the crude calcium salt was treated with 5 parts of boiling water and the mixture was filtered by suction at the boiling point and the solid washed with a little hot water. Evaporation of the filtrate and dehydration as above gave 190 g. (58%) of **calcium 2,7-disulfonate.** Conversion to **2,7-dihydroxynaphthalene**[8] was effected by fusing 100 g. of calcium salt with 200 g. of crude potassium hydroxide flakes and 50 cc. of water for four hours at 250°. The granular mixture was added while hot in small portions with stirring to 800 cc. each of 36% hydrochloric acid and water and the granular 2,7-dihydroxynaphthalene that separated after cooling at 0° overnight was crystallized twice from water (100 cc.); yield 21.8–24.0 g. (44–49%), m. p. 189–190°.

2-Hydroxy-7-methoxynaphthalene[10] was prepared as outlined by Fischer and Hammerschmidt[11] by slowly adding 5.6 g. of potassium hydroxide in 100 cc. of water to a stirred mixture of 16 g. of 2,7-dihydroxynaphthalene; 150 cc. of water, and 20 cc. of dimethyl sulfate at 40°. After fifteen minutes 10% alkali was added to the point of distinct alkalinity, the solution was filtered by suction into dilute hydrochloric acid containing sodium sulfite and the residual diether washed repeatedly with warm alkali. The monomethyl ether separated as large white leaflets and was crystallized from ligroin; yield 9.76 g. (56%), m. p. 116–117°.

The 1-nitroso derivative[11] was prepared by slowly adding 20.3 g. of sodium nitrite in 150 cc. of water to a stirred solution at 0° of 51 g. of 2-hydroxy-7-methoxynaphthalene in 300 cc. of acetic acid containing 30 cc. of water. The resulting slurry was allowed to stand at room temperature for several hours, diluted with water, and the solid collected, washed, dried, and crystallized from 400 cc. of methanol. The yield of bright red needles, m. p. 124–125°, was 41 g. (69%).

7-Methoxy-1,2-naphthoquinone was obtained from the nitroso derivative by reduction and oxidation; it formed crimson microprisms from ethanol, m. p. 143–145°.

Anal. Calcd. for $C_{11}H_8O_3$: C, 70.20; H, 4.28. Found: C, 70.01; H, 4.18.

2,7-Dimethoxy-1,4-naphthoquinone (Table I).—By reaction with sodium bisulfite and acidification by a procedure worked out for the methoxyl-free compound,[12,13] 67 g. of 1-nitroso-2-hydroxy-7-methoxynaphthalene yielded 74 g. (84%) of 1-amino-7-methoxy-2-naphthol-4-sulfonic acid as a light gray granular solid. Oxidation of 83 g. of this material with nitric acid by the procedure of Fieser and Martin[14] gave 73 g. (83%) of ammonium 7-methoxy-1,2-naphthoquinone-4-sulfonate. Treatment of this substance with methanol and sulfuric acid according to Fieser and Martin afforded satisfactory 2,7-dimethoxy-1,4-naphthoquinone in 72% yield (No. 1, Table I).

The dimethoxy compound dissolved rapidly in hot dilute alkali, and acidification of the red solution gave **2-hydroxy-7-methoxy-1,4-naphthoquinone** in 82.5% yield (No. 2).

Alkyl Derivatives.—The 2-hydroxy-7-methoxy-3-cyclohexylpropyl and 3-undecyl derivatives Nos. 3 and 5 were prepared by peroxide alkylation in the usual manner.[15] A succession of Hooker oxidations[3] then gave, alternately, members of the 6-methoxy and the 7-methoxy series; thus: 3 → 7 → 4 → 8, and 5 → 9 → 6.

2-Hydroxy-3-alkyl-6(7)-chloro-1,4-naphthoquinones

6-Chloro-1,4-naphthoquinone[16] was prepared by the procedure described by Fieser for the parent quinone.[17] *p*-Benzoquinone (108 g.) was condensed with chloroprene[18] (89 g.) in acetic acid (500 cc.) at room temperature

(8) Weber, *Ber.*, **14**, 2206 (1881).

(9) Haller and Lynch, *Ind. Eng. Chem.*, **16**, 274 (1924).

(10) Büngly and Decker, *Ber.*, **38**, 3272 (1905).

(11) O. Fischer and Hammerschmidt, *J. prakt. Chem.*, **94**, 25 (1916).

(12) Fieser, *Org. Syn.*, Coll. Vol. II, 42 (1943).

(13) Fieser, THIS JOURNAL, **48**, 2929 (1926); Martin and Fieser, *Org. Syn.*, **21**, 91 (1941).

(14) Fieser and Martin, *Org. Syn.*, **21**, 56 (1941).

(15) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3175 (1948).

(16) Carothers and Collins, U. S. Patent 1,967,862 (1934) [*C. A.*, **28**, 5994 (1934)]; Koslov and Talybov, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 1827 (1939).

(17) Fieser, THIS JOURNAL, **70**, 3165 (1948).

(18) Obtained by fractionation of a stabilized chloroprene–xylene solution kindly supplied by the du Pont Company.

for forty-eight hours. Isomerization with hydrochloric acid–stannous chloride resulted in crystallization of 149 g. (76%) of light gray 6-chloro-5,8-dihydro-1,4-naphthoquinone (recrystallized sample, m. p. 197–198°). Oxidation in acetic acid with nitrous acid and then dichromate mixture gave bright yellow 6-chloro-1,4-naphthoquinone, m. p. 102–105°, in 77% yield from the dihydronaphthohydroquinone. Crystallization from ether raised the m. p. to 106–107°.

6- and 7-Chloro-1,2,4-triacetoxynaphthalene.—A suspension of 58 g. of 6-chloro-1,4-naphthoquinone in 120 cc. of acetic anhydride was cooled to 0° and treated with 6 cc. of boron fluoride etherate. After standing at room temperature for several hours, the mixture was warmed briefly on the steam-bath and again let stand. The suspension of crystals in dark brown liquor was poured into water and the product collected as a tan solid, m. p. 120–135°; yield 65 g. (63%). Fractionation from methanol was tedious but afforded substantial amounts of the less soluble 7-chloro compound, m. p. 163–164°, and of the more soluble 6-chloro isomer, m. p. 143–144°.

Anal. Calcd. for $C_{16}H_{13}O_6Cl$: C, 57.08; H, 3.89. Found: (164°) C, 57.34; H, 3.88; (144°) C, 57.31; H, 3.95.

6- and 7-Chloro-2-hydroxy-1,4-naphthoquinone (Table I) was prepared by the hydrolysis procedure of Fieser.[17] Thus 8.4 g. of 7-chloro-1,2,4-triacetoxynaphthalene was added in ten minutes to a suspension of 7 g. of sodium methoxide in 70 cc. of methanol, stirred in an ice-bath. After one hour the red salt was collected (more from mother liquor with air), dissolved in hot water, and the filtered solution acidified; yield of bright yellow microcrystalline product 4.5 g. (91%). The isomer was obtained in 81% yield.

The properties and analyses of the products of peroxide alkylation are listed in Table I.

Synthesis of 2-Hydroxy-7-chloro-1,4-naphthoquinone

7-Chloro-1-naphthol.—In the preparation of this substance according to Erdmann and Kirchhoff[19] the reaction mixture from 70 g. of *p*-chlorobenzaldehyde, 41 g. of fused sodium acetate and 50 g. of succinic anhydride was treated with water and 10 g. of the unchanged aldehyde was removed by steam distillation. The residue was diluted with water to about 2 liters, filtered, and acidified with hydrochloric acid. The crude precipitated *p*-chlorophenylparaconic acid [containing *p*-chlorobenzoic acid and β-(*p*-chlorobenzal)-propionic acid] weighing 40 g. was heated in a distilling flask until the evolution of carbon dioxide had subsided and distilled; the yellow, solidified distillate was dissolved in dilute alkali. The solution was extracted with ether to remove oily material and neutralized with carbon dioxide, when the 7-chloro-1-naphthol separated as almost colorless, fine needles, m. p. 125–130°; yield 8 g. (22%). One crystallization from water raised the m. p. to 130–131°.

2,4-Dinitro-7-chloro-1-naphthol was prepared by the exact procedure described for the chlorine-free substance[20] and obtained as the ammonium salt in 67% yield. The free phenol after several crystallizations from alcohol melted at 169–170°, dec.

Anal. Calcd. for $C_{10}H_5O_5N_2Cl$: C, 44.71; H, 1.88. Found: C, 44.70; H, 1.75.

2-Hydroxy-7-chloro-1,4-naphthoquinone.—By the procedure indicated,[20] 4 g. of the ammonium salt of the dinitro phenol yielded 2.0 g. (59%) of 2-amino-7-chloro-1,4-naphthoquinone-4-imine hydrochloride as deep red crystals. A suspension of 1.5 g. of this salt in 50 cc. of 5% aqueous potassium hydroxide solution was boiled for fifteen minutes and the resulting deep red solution was acidified. The amorphous precipitate of the hydroxyquinone (0.72 g.) was purified in the form of the hydroquinone triacetate, which crystallized from 40 cc. of methanol in the form of colorless needles, m. p. 140–143°. After five recrystallizations the analytical sample melted at 143–144° and gave no depression when mixed with the **7-chloro-1,2,4-triacetoxynaphthalene** described above.

Anal. Calcd. for $C_{16}H_{13}O_6Cl$: C, 57.08; H, 3.89. Found: C, 57.14; H, 3.73.

Other Observations

The **2-hydroxy-3-Δ$^{\omega}$-alkenyl-1,4-naphthoquinones** listed as Nos. 14–19 in Table I were all prepared from 2-hydroxy-3-Δ^{9}-decenyl-1,4-naphthoquinone[21] by the modified Hooker oxidation procedure.[4] We attempted to determine the nature of the water-soluble products obtainable[22] by the action of acetyl sulfuric acid in acetic acid solution on the homologs having 8, 7 and 6 methylene groups in the side-chain. The results were not fully conclusive but suggested that the products have the side-chain structure: $-(CH_2)_nCHOHCH_2SO_3H$. Thus the product from No. 7 yielded an aniline salt, m. p. 152–154°, and a *p*-toluidine salt, m. p. 163–165° (from alcohol–water) of the following analyses.

Anal. **Aniline salt.** Calcd. for $C_{25}H_{31}O_7NS$: C, 61.33; H, 6.38. Found: C, 61.61; H, 6.38. ***p*-Toluidine salt.** Calcd. for $C_{26}H_{33}O_7NS$: C, 62.00; H, 6.61. Found: C, 62.54; H, 6.67.

These substances were completely devoid of antirespiratory activity, as was a sulfonation product obtained in crude form from an oil resulting from alkylation of hydroxynaphthoquinone with the peroxide from oleic acid.

Oxidation of 3-Alkyl-1-tetralones with Selenium Dioxide.—The method of Weygand and Schröder[23] for the synthesis of 2-hydroxy-3-alkyl-1,4-naphthoquinones was briefly investigated with the following results. 3-Ethyl-1-tetralone, b. p. 112–114° at 2 mm., on reaction with selenium dioxide in ethanol afforded 2-hydroxy-3-ethyl-1,4-naphthoquinone, m. p. 137–138°, in 35% yield; the substance was compared with an authentic sample from the Hooker collection.[24]

2-Hydroxy-3-methyl-1,4-phenanthrenequinone was obtained by the same method in comparable yield; it formed bright orange needles from benzene, m. p. 215–217°.

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.61; H, 4.23. Found: C, 75.44; H, 4.25.

Summary

Substances related to actively antimalarial 2-hydroxy-3-alkyl-1,4-naphthoquinones but having methoxyl or chloro substituents in the β-positions of the benzenoid ring were synthesized and found to be devoid of activity.

Converse Memorial Laboratory
Cambridge 38, Massachusetts Received May 12, 1949

(19) Erdmann and Kirchhoff, *Ann.*, **247**, 366 (1888).

(20) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath Co., Boston, Mass., 1941.

(21) Fieser, Leffler and co-workers, This Journal, **70**, 3195 (1948).

(22) Fieser, *ibid.*, **70**, 3232 (1948).

(23) Weygand and Schröder, *Ber.*, **74**, 1844 (1941).

(24) Hooker, This Journal, **58**, 1174 (1936).

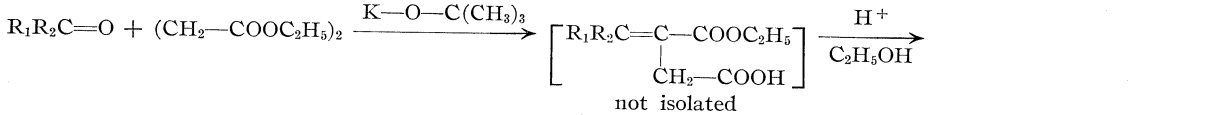
CONTRIBUTION FROM THE INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

The Preparation of 2-Alkyl-1,4-butanediols[1]

BY C. G. OVERBERGER AND CARLETON W. ROBERTS

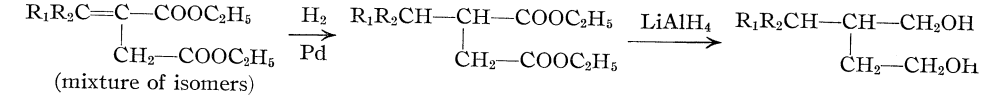
We have undertaken the preparation of a series of 2-alkylbutadienes in order to determine the reactivities of such dienes in the copolymerization reaction,[2] and to study the effects of side-chain alkyl groups, both straight and branched, upon the physical properties of diene polymers. Crystallization of the polymeric backbone and of the side chain are of special interest. Thus, the long alkyl side chains in a polymer of hexadecyl acrylate[3] results in crystallite formation in the side chain. Likewise, a branched alkyl group[4] or a long alkyl group may increase the amount of the 1,4-addition of the diene when forming the polymer, increasing the homogeneity and thus increasing the crystalline properties of the main polymer chain when the chains are oriented by stretching.

This paper will describe the preparation of some 2-alkyl-1,4-butanediols (II, also Table III), intermediates in the preparation of 2-alkylbutadienes. The synthetic route for preparing these diols was similar to that used by Wojcik and Adkins[5] and by Marvel, Myers and Saunders[6] to prepare 2-isopropyl-1,4-butanediol. Our improved procedure is experimentally different, and furnishes a good general method for the preparation of the 2-alkyl-1,4-butanediols. The procedure is outlined below.



not isolated
(mixture of isomers)

I



(mixture of isomers)

II

The crude half-esters (I) obtained by the general procedure of Johnson and co-workers[7] were not isolated by us but were esterified to give high yields of a mixture of isomeric unsaturated 2 alkyl succinate esters (Table I). The yield reported for the condensation of acetone and diethyl succinate to the unsaturated diester according to the original conditions of the Stobbe condensation with sodium ethoxide was 53%[6]; compare 92%, Table I. The unsaturated alkyl diesters were further characterized by saponification to the unsaturated 2-alkylsuccinic acids (Table I).

Hydrogenation of the unsaturated diethyl esters over palladium at low pressures gave the 2-alkylsuccinic esters (Table II), which were similarly characterized by conversion to the 2-alkylsuccinic acids (Table II). Reduction of the diethyl 2-alkylsuccinates to the 2-alkyl-1,4-butanediols (Table III) was accomplished in almost quantitative yields by means of lithium aluminum hydride.[8] The diacetates of these diols are described in Table IV. The preparation and characterization of the dienes will be described in a later paper.

Discussion of the Structure of the Unsaturated 2-Alkylsuccinate Diesters and Diacids.—On the assumption that the extinction coefficient of an α,β-unsaturated ester is similar to that of an α,β-unsaturated acid[9] and is between 11,000 and 13,000 depending on the solvent, between 2200 and 2100 Å., some of the compounds in Table I have the double bond largely in the α,β-position: R_1 = iso-C_3H_7, n-C_9H_{19}, n-$C_{11}H_{23}$ and n-C_6H_{13}; R_2 = H. Those that have a lower extinction coefficient between 2200 and 2100 Å. are the esterified conden-

(1) This work was supported by a contract from the Office of Naval Research.

(2) Alfrey and Goldfinger, *J. Chem. Phys.*, **12**, 205 (1944); Mayo and Lewis, THIS JOURNAL, **66**, 1594 (1944); Wall, *ibid.*, **66**, 2050 (1944).

(3) Kaufman, Sacher, Alfrey and Fankuchen, *ibid.*, **70**, 3146 (1948).

(4) However, it has recently been shown by Marvel, Williams and Baumgarten (*J. Polymer Sci.*, in press) that the isopropyl group in the 2-position has no effect on the amount of 1,4-addition in an emulsion polymer when compared with polyisoprene.

(5) Wojcik and Adkins, THIS JOURNAL, **55**, 4939 (1933); **56**, 2424 (1934).

(6) Marvel, Myers and Saunders, *ibid.*, **70**, 1694 (1948). Some of our work was done prior to this publication. Professor Marvel kindly furnished us with a copy of his manuscript before publication.

(7) (a) Johnson, Goldman and Schneider, THIS JOURNAL, **67**, 1357 (1945); (b) Johnson, Davis, Hunt and Stork, *ibid.*, **70**, 3021 (1948); (c) Johnson, Johnson and Peterson, *ibid.*, **67**, 1360 (1945).

(8) Nystrom and Brown, *ibid.*, **69**, 1197 (1947). Hydrogenation of diethyl 2-isopropylidenesuccinate at high pressures with a copper chromite catalyst (refs. 5, 6) gave low yields of 2-isopropyl-1,4-butanediol.

(9) (a) Braude, "Ann. Repts. on Progress Chem. (Chem. Soc., London)," 42, 111 (1945); (b) Dimroth, *Angew. Chem.*, **52**, 545 (1939); (c) Mohler and Lohr, *Helv. Chim. Acta*, **21**, 485 (1938); (d) for a comparison of carboxyl and carbalkoxy groups from a resonance viewpoint see Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 73; (e) thus Andrews, Cristol, Lindenbaum and Young, THIS JOURNAL, **67**, 715 (1945), have demonstrated the similarity between the absorption spectrum of α-cyanocrotonic acid, λ_{max}. 2150 Å., ϵ 9700 and methyl-α-cyanocrotonate, λ_{max}. 2200 Å., ϵ 8400.

TABLE I

UNSATURATED DIETHYL 2-ALKYLSUCCINATES

$$R_1-C(=)-C(R_2)-CH_2-COOC_2H_5 \quad (COOC_2H_5 \text{ on } C)$$

R_1, R_2	Reac. time, hr.	B. p., °C., mm.	Yield, %	$n^{25}D$	Percentage composition Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	$\lambda_{max.}$, Å.	ϵ[h]	M. p. of diacid[i]	Recryst. solvent of diacid
CH_3, CH_3	0.5[b]	76[d] (0.6)	92	1.4504	61.66	61.42[f]	8.47	8.37	2195	9200	161.5–162[j]	W[r]
CH_3, C_2H_5	0.5[b]	93–94 (1.0)	83	1.4500	63.13	62.87[g]	8.83	8.93	2180	6960	179–181[k]	W
C_5H_{10},[a] —	0.3[b]	120–121 (0.8)	72	1.4756	66.11	66.03[g]	8.72	8.85	2200	5050	179–180[l]	W
Iso-C_3H_7, H	1.5[b]	142–143[e] (11.0)	85	1.4410	63.13	62.92[f]	8.83	8.55	2130	11,400	189–189.5[m]	W
n-C_9H_{19}, H	2.0[c]	153 (1.1)	40	1.4530	69.19	69.00[f]	10.32	10.28	2135	10,200	140–140.5[n]	B[s]–PE[t]
n-$C_{11}H_{23}$, H	8.0[c]	164 (0.6)	58	1.4532	70.55	70.37[f]	10.66	10.41	2130	10,100	137–138[o]	B–PE
n-C_6H_{13}, H	14.0[c]	133–134 (1.5)	59	1.4508	66.63	66.64[f]	9.69	9.70	2135	11,200	127–127.5[p]	PE
Iso-C_3H_7, CH_3	7.0[b]	92.5–93 (0.8)	78	1.4490	64.44	64.18[f]	9.15	9.14	2195	7890	178.5–179.5[q]	A[u]–PE

[a] Prepared from cyclohexanone. [b] Prepared by procedure A. [c] Prepared by procedure B. [d] Ref. 6 reported b. p. 100–102° (2 mm.); $n^{20}D$ 1.4550; d^{20}_4 1.0304. [e] Fittig and Burwell, *Ann.*, **304,** 259 (1899) reported b. p. 282°. [f] Analyses by Mr. H. S. Clark. [g] Analyses by Dr. Francine Schwarzkopf. [h] Purified cyclohexane as solvent. [i] Prepared by saponification of the diester. [j] Fittig and Petkow, *Ann.*, **304,** 208 (1899), reported m. p. 160–161°; assigned α,β-structure because acid did not form lactone. Farmer, Ingold and Thorpe, *J. Chem. Soc.*, **121,** 128 (1921), reported m. p. 154–156° or 160° depending upon the rate of heating, and refers to Ssemenoff, *J. Russ. Phys.-Chem. Soc.*, **23,** 430 (1898), who reported m. p. 161–162°. Stobbe, *Ber.*, **26,** 2312 (1893); *ibid.*, **36,** 197 (1903), reported m. p. 160–161°; proved alleged α,β-structure by oxidation experiments. [k] Stobbe, *Ann.*, **321,** 105 (1902), reported m. p. 181°, presented evidence for α,β-structure by oxidation experiments; Stobbe, *ibid.*, **282,** 280 (1894), previously reported m. p. 165–167°; we found that heating at the rate of three degrees per minute gives m. p. 179–181°; slow heating, one degree per two minutes gives m. p. 164.5–166° dec. Ref. 10 reported m. p. 186° dec. [l] Ref. 7b reported m. p. 179–180°. [m] Fittig and Burwell, ref. [e], Table I, reported m. p. 189–192°; structure proof see [b]; λ_{max} 2135Å.; ϵ, 11,820, 95% ethanol. [n] *Anal.* Calcd.: C, 65.59; H, 9.44. Found: C, 65.42; H, 9.35; λ_{max}, 2140 Å.; ϵ, 12,340, 95% ethanol. [o] *Anal.* Calcd.: C, 67.57; H, 9.92. Found: C, 67.43; H, 9.89; $\lambda_{max.}$, 2130 Å.; ϵ, 12,130, 95% ethanol. [p] Fittig and Hoeffken, *Ann.*, **304,** 326 (1899), reported m. p. 129–130°. *Anal.* Calcd.: C, 61.66; H, 8.47. Found: C, 61.47; H, 8.37; $\lambda_{max.}$, 2130 Å.; ϵ, 11,587, 95% ethanol. [q] *Anal.* Calcd.: C, 58.05; H, 7.58. Found: C, 58.33; H, 7.47. Analyses by Mr. H. S. Clark. [r] W, water. [s] B, benzene. [t] PE, petroleum ether (90–100°). [u] A, acetone. Water may also be used.

TABLE II

DIETHYL 2-ALKYLSUCCINATES

$$R_1-CH(R_2)-CH(CH_2-COOEt)-COOEt$$

R_1, R_2	B. p., °C.	Mm.	Yield, %	$n^{25}D$	d^{25}_4	Mol. ref. diff.	Percentage composition Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	M. p. of diacid[f]	Recryst. solv. of diacid
CH_3, CH_3	105–106[b]	6.5	83	1.4237	0.9869	−0.25	....	...	...	...	115–115.5[g]	W[o]
CH_3, C_2H_5	75–76	0.2	94	1.4293	0.9745	+0.04	62.58[d]	62.86	9.63	9.38	130–130.5[h]	W
C_5H_{10},[a] —	103–104[c]	.5	88	1.4554	1.0284	−0.31	65.59[e]	65.72	9.44	9.39	145–145.5[i]	PE[p]
Iso-C_3H_7, H	84–85	.9	97	1.4259	0.9679	+0.01	62.58[d]	62.28	9.63	9.75	108–108.5[j]	B[q]–PE
n-C_9H_{19}, H	134	.3	91	1.4398	.9341	+ .01	68.75[d]	69.01	10.90	10.89	88.5–90[k]	B–PE
n-$C_{11}H_{23}$, H	159.5	.4	94	1.4412	.9237	+ .07	70.13[d]	70.19	11.18	10.91	96–97.5[l]	PE
n-C_6H_{13}, H	114–115	.7	92	1.4329	.9457	+ .03	66.14[d]	66.17	10.36	10.31	89.5–90.5[m]	W
Iso-C_3H_7, CH_3	86–87	.4	88	1.4400	.9838	+ .10	63.90[d]	64.01	9.90	9.61	90–91.5[n]	A[r]–PE

[a] From cyclohexanone. [b] B. p. also 94–95° (2.4 mm.) (86%). Ref. 6 reported b. p. 65° (10.5 mm.), $n^{20}D$ 1.4284, d^{20}_4 0.9925. [c] Swain, Todd and Waring, *J. Chem. Soc.*, 548 (1944), reported b. p. 110–120° (10^{-1} mm.). [d] Analysis by H. S. Clark. [e] Analysis by Dr. Francine Schwarzkopf. [f] Prepared by saponification of diesters. [g] Henry and Paget, *J. Chem. Soc.*, 78 (1928), reported m. p. 114°. [h] *Anal.* Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.02; H, 7.97. Analysis by R. Schachat. [i] Ref. C, Table II, reported m. p. 146–147°. [j] Bentley and Perkin, *J. Chem. Soc.*, **73,** 45 (1898), reported m. p. 109°. [k] Barry and Twomey, *Proc. Royal Irish Acad.*, **51B,** 137 (1947), reported m. p. 91–93°. [l] *Ibid.*, reported 97.5–98.5°. [m] Ref. *h*, Table II reported m. p. 90–91°. [n] *Anal.* Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.75; H, 8.29. Analysis by Mr. H. S. Clark. [o] W, water. [p] PE, petroleum ether (90–100°), [q] B, benzene. [r] A, acetone.

sates from methyl ethyl ketone (R_1 = CH_3, R_2 = C_2H_5) cyclohexanone, (R_1R_2 = C_5H_{10}), and methyl isopropyl ketone (R_1 = iso-C_3H_7, R_2 = CH_3). The condensate from acetone (R_1 = CH_3, R_2 = CH_3) has an extinction coefficient at the indicated range between the above two groups.

Separation of the unsaturated alkyl esters from unsymmetrical ketones or from aldehydes into possible *cis–trans* isomers has not been attempted. In general, there would only be slight displacements in the intensity and position of the absorption maxima for *cis* and *trans* forms in compounds of this type.

From the close agreement of the absorption spectra of the unsaturated alkyl diacids resulting from the diesters derived from aldehydes (R_1 = iso-C_3H_7, n-C_9H_{19} and n-C_6H_{13}; R_2 = H) it would appear that under the mild conditions of the saponification, no isomerization took place. The maximum absorption compares favorably with other α,β-unsaturated acids.[9b] Small increases of the extinction coefficients are noted, but this may be due to the small increase in resonance through a carboxyl group over the carbalkoxy group.[9e] Here again no attempt has been made to distinguish between *cis* and *trans* forms from aldehydes and unsymmetrical ketones.

The melting points of the diacids reported in

TABLE III

2-ALKYL-1,4-BUTANEDIOLS

$$R_1—CH(R_2)—CH(CH_2—CH_2OH)—CH_2OH$$

R_1, R_2	B. p., °C.	Mm.	Yield, %	$n^{25}D$	d^{25}_4	Molecular refraction Calcd.	Found	Formula	Percentage composition Carbon Calcd.	Found	Hydrogen Calcd.	Found
CH_3, CH_3	128–129	6.4[c]	96	1.4515	0.9533	37.58	37.41	$C_7H_{16}O_2$	...	...	...	...
CH_3, C_2H_5	143.5	8.9[d]	96	1.4582	0.9536	42.20	41.86	$C_8H_{18}O_2$	65.71	65.59[h]	12.41	12.83
C_5H_{10},[a] —	142.5	1.6[e]	90	1.4915	1.0211	49.24	49.24	$C_{10}H_{20}O_2$	69.72	69.44	11.70	11.52
Iso-C_3H_7, H	110	0.8	88	1.4510	0.9320	42.20	42.23	$C_8H_{18}O_2$	65.71	65.99	12.41	12.41
n-C_9H_{19}, H	161–163	1.1	94	1.4604	0.9018	69.92	70.01	$C_{14}H_{30}O_2$	72.98	73.28	13.13	13.13
n-$C_{11}H_{23}$, H	165[b]	0.4	95	....	....	...	...	$C_{16}H_{34}O_2$	74.36	74.63	13.26	12.98
n-C_6H_{13}, H	143	1.3[f]	93.3	1.4560	0.9164	56.06	55.86	$C_{11}H_{24}O_2$	70.16	70.08	12.85	12.61
Iso-C_3H_7, CH_3	108	0.5[g]	85	1.4688	0.9537	46.82	46.78	$C_9H_{20}O_2$	67.45	67.70	12.58	12.53

[a] From cyclohexanone. [b] M. p. from anhydrous ethyl ether, 40–41.5°. [c] B. p. also 100° (0.2 mm.). Ref. 6 reported b. p. 106° (4 mm.), 145–146° (18 mm.), $n^{20}D$ 1.4535, d^{20}_4 0.9672. [d] B. p. also 106° (0.6 mm.). [e] B. p. also 131.5–134° (0.5–0.6 mm.), 85%. [f] B. p. also 136° (0.7 mm.). [g] B. p. also 116–118° (1.0 mm.). [h] Analysis by H. S. Clark.

TABLE IV

2-ALKYL-1,4-BUTANEDIOL DIACETATES

$$R_1—CH(R_2)—CH(CH_2—CH_2—O—Ac)—CH_2—O—Ac$$

R_1, R_2	B. p. °C.	Mm.	Yield, %	$n^{25}D$	d^{25}_4	Molecular refraction Calcd.	Found	Formula	Percentage composition[e] Carbon Calcd.	Found	Hydrogen Calcd.	Found
CH_3, CH_3	85[b]	1.0	91	1.4331	1.0011	56.72	56.32	$C_{11}H_{20}O_4$	...	...	...	...
CH_3, C_2H_5	95.5–96[c]	0.9	86	1.4364	0.9886	60.94	60.96	$C_{12}H_{22}O_4$	62.58	62.28	9.63	9.71
C_5H_{10},[a] —	115.5	0.7	88	1.4599	1.0353	67.98	67.80	$C_{14}H_{24}O_4$	65.59	65.64	9.44	9.26
Iso-C_3H_7, H	96[d]	1.3	94	1.4303	0.9761	60.94	60.99	$C_{12}H_{22}O_4$	62.58	62.39	9.63	9.82
n-C_9H_{19}, H	155–156	1.1	86	1.4435	.9405	88.66	88.70	$C_{18}H_{34}O_4$	68.75	68.56	10.90	10.70
n-$C_{11}H_{23}$, H	154–155	0.3	92	1.4445	.9308	97.90	97.84	$C_{20}H_{38}O_4$	70.13	70.41	11.18	11.40
n-C_6H_{13}, H	123	0.7	86	1.4374	.9569	74.80	74.66	$C_{15}H_{28}O_4$	66.14	66.35	10.36	10.19
Iso-C_3H_7, CH_3	105–106	1.1	92	1.4417	.9859	65.55	65.51	$C_{13}H_{24}O_4$	63.90	64.16	9.90	9.72

[a] From cyclohexanone. [b] B. p. also 119° (6.9 mm.), 87%. Ref. 6 reported b. p. 96° (1.5 mm.), $n^{20}D$ 1.4349, d^{20}_4 1.0055. [c] B. p. also 132–133° (8.5 mm.), 82%. [d] B. p. also 88–90° (1.1 mm.). [e] Analysis by H. S. Clark.

Table I are dependent on the rate of heating. A sample of the diacid from the cyclohexanone condensate obtained from Professor W. S. Johnson[10] was identical with our acid, mixed m. p. 179–180°, if the rate of heating was 3° per minute whether immersion of the sample was at low temperature or 170°. Heating at the rate of one degree per minute gave a m. p. 164.5-166° dec., mixed m. p. 164–166° dec. This depression may be due to lactone formation or to other decomposition. We used a heating rate of a 2 or 3° rise per minute to obtain our melting points.

Experimental

Preparation of Diethyl 2-Alkyl Unsaturated Succinates. Procedure A.—The compounds listed in Table I were prepared according to modifications of the procedure described by Johnson and co-workers.[7a,7b] We have extended the preparative scheme to the direct preparation of the diethyl esters of 2-substituted unsaturated succinic acids. The following procedure was employed for the compounds in Table I indicated by superscript b.

A mixture of 0.8 mole of the carbonyl compound and 1.0 mole of diethyl succinate was added over fifteen minutes to a refluxing solution of 0.88 mole of potassium in 800 ml. of anhydrous t-butyl alcohol. The stirred reaction mixture was heated under reflux for a time depending upon the reactivity of the carbonyl compound (see Table I). The solvent was removed from the reaction mixture under reduced pressure, the residue was made slightly acid to litmus with dilute hydrochloric acid and the remainder of the solvent was removed. The organic layer was dissolved in 200 ml. of ethyl ether and the aqueous layer was separated and extracted with three 200-ml. portions of ether. The combined ether solutions were washed with water and then extracted completely with 10% aqueous carbonate. The ether washing of combined alkaline extracts was added to the original ether layer and the ether solution was dried over anhydrous magnesium sulfate. From this residue it was possible to recover unreacted and excess diethyl succinate.

The alkaline solution was made strongly acid with concentrated hydrochloric acid and chilled. The organic layer was separated, and the aqueous layer was extracted with four 150-ml. portions of ethyl ether. The ether layers were combined with the separated organic layer, washed with water, and dried over anhydrous magnesium sulfate. After removal of the ether from the "half-acid," a chilled solution of the residue in 10 volumes of anhydrous ethyl alcohol was treated with dry hydrogen chloride to give a 5% solution by weight. After twenty-four hours at room temperature, the alcohol was removed under reduced pressure. The residue was poured into an ice–ice-water mixture, and the ester layer was taken up in ethyl ether. The aqueous layer was extracted with four 200-ml. portions of ethyl ether, and the extracts, after combining with the original separation, were neutralized by washing with aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. The alkaline washes were saved and on subsequent saponification gave a small quantity of 2-alkenesuccinic acid. The residual diester was fractionated through a 30-cm., helices-packed column. The yields of the diesters and physical constants are found in Table I.

(10) We are indebted to Professor W. S. Johnson for a sample of the half-acid derived from the cyclohexanone condensate and the diacid from its saponification, m. p. 179–180°. Evidence was presented to show that this was the α,β-acid.

Procedure B.—The compounds listed in Table I (superscript c) were prepared by this modified procedure since by-products obtained in the initial condensation and difficulties due to emulsification made it impossible to completely separate the "half-acid" by the usual carbonate extraction. Therefore, the initially acidified reaction mixture was extracted with ether in the usual manner and dried over anhydrous magnesium sulfate. The entire ether-soluble reaction product was esterified as in the previous procedure, and the residue fractionated through a similar column. A typical experiment gave in the case of diethyl 2-*n*-decylidenesuccinate the following fractions: Fraction 1, 25 g., b. p. 80–90° (0.7 mm.); fraction 2, 75 g., b. p. 155–160° (0.6 mm.); fraction 3, 75 g., b. p. 210–220° (0.6 mm.). Fraction 2 was refractionated through the same column to give 60 g. (35%) of pure product.

Saponification of Unsaturated Diesters.—Five grams of the pure diethyl unsaturated 2-alkylsuccinates were saponified in 50 ml. of a refluxing 10% aqueous sodium hydroxide. Acidification of the decolorized and filtered reaction mixtures with concentrated hydrochloric acid gave crystalline succinic acids. The products were air-dried and recrystallized from the appropriate solvent as noted in Table I.

Preparation of Diethyl 2-Alkylsuccinates.—One-tenth mole of our initial condensation product (Table I) was dissolved in 50 ml. of 95% ethyl alcohol containing 0.5 g. of suspended 5% palladium-on-charcoal catalyst, and the mixture shaken in an atmosphere of hydrogen at 55–60 p. s. i. pressure. In all experiments between 95 and 100% of the theoretical quantity of hydrogen was absorbed. The reaction mixture was filtered to remove the catalyst, and the solvent was removed by distillation at atmospheric pressure. The residual ester was distilled under reduced pressure. The data are summarized in Table II.

Preparation of 2-Alkylsuccinic Acids.—Five grams of the diethyl 2-alkylsuccinates was saponified as described for the treatment of the unsaturated esters. The data are summarized in Table II.

Preparation of 2-Alkyl-1,4-butanediols.—Following the general procedure of Nystrom and Brown,[8] 0.1 mole of the diethyl 2-alkylsuccinate was added dropwise to a chilled, stirred anhydrous ether solution of 0.12 mole of lithium aluminum hydride. The reaction mixture was stirred for one hour after the addition was completed and the excess hydride was decomposed by the careful addition of the required amount of water. The reaction mixture was then poured into a mixture of ice and water containing 10% sulfuric acid. The ether layer was separated after the complex had been completely decomposed and the aqueous layer was extracted with five 100-ml. portions of ethyl ether. The combined ether layers were washed with a minimum of water containing bicarbonate and dried over anhydrous magnesium sulfate. The residual diol was fractionated through a 30-cm., helices-packed column. There was usually a forerun of lower boiling material. The data on each of the diols are summarized in Table III.

Preparation of the 2-Alkyl-1,4-butanediol Diacetate.—Each diol was suspended in a threefold excess by weight of acetic anhydride and boiled under reflux for from six to ten hours. The excess anhydride was removed by distillation under reduced pressures, the residue taken up in ethyl ether and the ether solution washed with bicarbonate solution until neutral. The ether solution was dried over anhydrous magnesium sulfate, and the residue was fractionated through a 30-mm., helices-packed column. The data are summarized in Table IV.

Ultraviolet Absorption Spectra.—Ultraviolet absorption spectra were determined with a Beckman quartz ultraviolet spectrophotometer in purified cyclohexane[11] and 95% ethanol as solvents. The cell length used in all experiments was 1 cm. Figure 1 describes the spectra for the esterified condensation product of diethyl succinate and *n*-decylaldehyde and the analogous diacid.

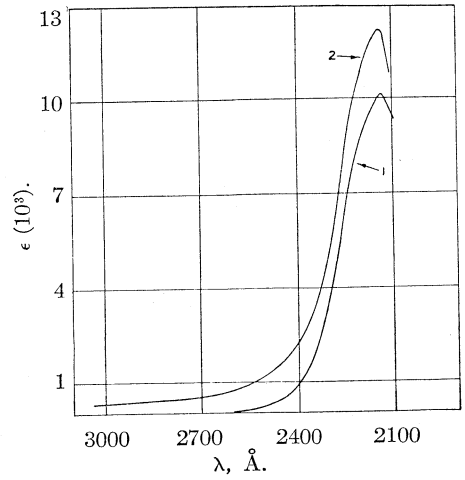


Fig. 1.—Ultraviolet absorption spectrum of: (1) diethyl-2-decylidenesuccinate in cyclohexane; (2) 2-decylidenesuccinic acid in 95% ethanol.

Summary

1. A convenient preparation of 2-alkyl-1,4-butanediols, intermediates in the synthesis of 2-alkyl-1,3-butadienes has been described.

2. Seven new 2-alkyl-1,4-butanediols have been prepared and characterized [OH–CH_2–$CH(CHR_1R_2)$–CH_2–CH_2OH] R_1 = CH_3, R_2 = C_2H_5; R_1R_2CH = C_5H_{10}; R_1 = iso-C_3H_7, R_2 = H; R_1 = *n*-C_9H_{19}, R_2 = H; R_1 = *n*-$C_{11}H_{23}$, R_2 = H; R_1 = *n*-C_6H_{13}, R_2 = H; R_1 = iso-C_3H_7, R_2 = CH_3. The diacetates of these diols have likewise been prepared and characterized.

3. Seven new diethyl 2-alkylsuccinates intermediate in the diol synthesis have been prepared and characterized [EtOOCCH(CHR_1R_2)CH_2–COOEt]. Likewise the diacid (R_1 = iso-C_3H_7, R_2 = CH_3) derived from the corresponding diester is described.

4. The absorption spectra of eight unsaturated 2-alkylsuccinates (see above R_1R_2, also R_1 = CH_3, R_2 = CH_3) have been measured. The isomeric structures surmised from these data are briefly discussed. Likewise, absorption spectra have been obtained for four new unsaturated 2-alkylsuccinic acids. On the basis of existing data for the absorption spectrum of an α,β-unsaturated acid, the results indicate that the double bond is in the α,β-position.

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(11) Maclean, Jencks and Acree, *J. Research Natl. Bur. Standards*, **34**, 271 (1945).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Oxidation Potentials of Aldehydes and Ketones

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The relative strengths of ninety carbonyl compounds as oxidizing agents have been ascertained by determining the concentrations at equilibrium in systems of the type

$$R_2CO + R'_2CHOH \underset{\longleftarrow}{\xrightarrow{Al(OC_4H_9\text{-}t)_3}} R_2CHOH + R_2'CO.$$

The experimental observations on which the data in the table are based were made by F. W. Cox,[2] Robert H. Baker,[3,4] A. G. Rossow,[5] C. C. Robinson[6] and Richard M. Elofson.[7] The last named has calculated all the values given herewith, and has concluded[7] that except for benzaldehyde, the values previously published are high by 33 m.v.

The oxidation potentials were calculated on the basis of the oxidation potentials of certain quinones. Three quinones of known oxidation potentials[8] were included in the series, *i. e.*, 9,10-anthraquinone, 154 mv., 1-chloroanthraquinone, 174 mv. and isopropyl 9,10-anthraquinone-2-carboxylate, 222 mv. One ketone, 2,7-dichlorofluorenone, was equilibrated against each of the three quinones. The oxidation potential, E_0, of 2,7-dichlorofluorenone was calculated from the oxidation potential of a quinone E_0' using the expression $E_0 = E_0' + RT/NF \ln K$ where K is the equilibrium constant for the reaction given above. For 25° the expression becomes $E_0 = E_0' + 0.0296 \log K$.

The oxidation potential of the ketone was found to be 157, 156 or 160 mv. depending upon the quinone used in comparison. Fluorenone and benzophenone have also been equilibrated against each other and against 9,10-anthraquinone. These ketones were in turn equilibrated against cyclohexanone and the latter against 2,7-dichlorofluorenone. The values of E_0 for 2,7-dichlorofluorenone, calculated from these series of comparisons, were 154 and 159 mv. The average of the five values for 2,7-dichlorofluorenone is 157 mv. This figure has been used as the basis for calculating the oxidation potential of most of the carbonyl compounds listed in the Table I, since 2,7-dichlorofluorenone was equilibrated directly or indirectly against all the other ketones and aldehydes except chloral and the alpha-keto esters. These keto esters and chloral were equilibrated against isopropyl benzoylformate and the latter against isopropyl 9,10-anthraquinone-2-carboxylate.

Limitations and Reliability of Data

There are several factors which determine and limit the reliability of the procedures on which the data in Table I are based. The method for the determination of the concentration of the reactants at equilibrium depends upon at least one of the two carbonyl compounds in a reaction mixture showing a depolarization potential on a polarograph. Thus direct comparisons must include an aldehyde, or a quinone, or a ketone with unsaturation in the 2,3-position. The concentration of such carbonyl compounds can be determined so accurately with a polarograph[4] that if the analytical determination were the only source of error the calculated oxidation potential would in general be reliable within 1 or 2 mv.

The greater the difference in oxidation potential between the two carbonyl compounds in the reaction mixture, the less accurate is the calculated oxidation potential. Small errors in the analytical determination will cause relatively large errors in the calculated oxidation potential when the difference between E_0 and E_0' is more than about 50 mv. This follows from the fact that if two carbonyl compounds A and B differ in potential by 100 mv. then at equilibrium there will be only 2% of the ketone A having the higher potential and 98% of B. If the difference in potential is 80 mv. there will be 4.2% of A, for 60 mv. 8.8% A, for 50 mv. 12.5% A, for 30 mv. 23.5% A, for 20 mv. 31.5% A and for 10 mv. 40.5% A. In order to minimize errors arising from this source, fluorenone, 119 mv., 2,7-dichlorofluorenone, 157 mv., and isopropyl benzoylformate, 282 mv., were preferred for the measurement of carbonyl compounds having potentials in the three ranges. Cyclohexanone, 162 mv., has been used in equilibrations where the polarographic curve for 2,7-dichlorofluorenone was obscured by that of the other carbonyl compound in the reaction mixture. Benzaldehyde, 192 mv., and trimethylacetaldehyde, 211 mv., were also useful in determining the oxidation potential of other aldehydes in the range of 186 to 270 mv.

The most serious limitation upon the accurate determination of the oxidation potential of a carbonyl compound, by the procedures described herewith, is imposed by side reactions. These are particularly serious with carbonyl compounds which react slowly as oxidizing agents and yet are capable of undergoing the aldol or Tischenko types of condensation. The more rapid the oxidation by the reference compound the less

(1) Wisconsin Alumni Research Foundation Fellow (a) 1941–1944; (b) 1939–1942.

(2) Adkins and Cox, THIS JOURNAL, **60**, 1151 (1938); **61**, 3364 (1939).

(3) Baker and Adkins, *ibid.*, **62**, 3305 (1940).

(4) Baker and Schafer, *ibid.*, **65**, 1675 (1943).

(5) A. G. Rossow, Ph.D. Thesis, Univ. of Wisconsin, 1942.

(6) C. C. Robinson, Ph.D. Thesis, Univ. of Wisconsin, 1943.

(7) R. M. Elofson, Ph.D. Thesis, Univ. of Wisconsin, 1944.

(8) Conant and Fieser, THIS JOURNAL, **46**, 1858 (1924).

TABLE I

SUMMARY OF OXIDATION POTENTIALS

No.	Compound	E_0, mv.	$-\Delta F^0$ 25°, cal.	Equilibrated against[a]	M. p., °C. or $n^{25}D$ Carbinol	Carbonyl	Dep. pot. (−)
1	Δ^4-Cholestenone	63	2.9	20E	140.5–141	80–81[c]	1.30[b]
2	α-Hydrindone	73	3.4	20Rb	66–68	41–42[d]	1.55
3	α-Tetralone	80	3.7	20Rs	1.5643	1.5662	1.67
4	Camphor	82	3.7	20B			
5	Δ^2-Cyclohexenone	85	3.9	20E	1.4828	1.4853	1.55[b]
6	*p*-Methoxyacetophenone	99	4.6	20Rb	1.5330	1.5310[e]	1.70
7	Di-isopropyl ketone	100	4.6	39C			
8	Di-*n*-butyl ketone	101	4.6	39C			
9	Di-*n*-propyl ketone	101	4.6	39C			
10	Di-isobutyl ketone	102	4.7	39C			
11	Di-ethyl ketone	110	5.1	39C			
12	Acenaphthenone	110	5.1	20Rb	144.5–145.5	120.5–121.5	
13	*n*-Propyl phenyl ketone	113	5.2	39C			
14	3,5-Dimethoxyphenyl *n*-butyl ketone	114	5.3	20Rb	1.5166	42–43[c]	1.56
15	1,4-Diphenylbutanone-1	115	5.3	20E	47.5–48	56–57[c]	
16	*p*-Methylacetophenone	115	5.3	20Rb	1.5186	1.5310[d]	1.66
17	Methyl cyclohexyl ketone	116	5.4	20B			
18	*n*-Butyl phenyl ketone	116	5.4	39C			
19	*n*-Amyl phenyl ketone	117	5.4	39C			
20	Fluorenone	117	5.4	58B	151–152	83–84	1.07[b]
	Fluorenone	119	5.5	55E			
21	Methyl phenyl ketone	118	5.4	20B			
22	Ethyl phenyl ketone	118	5.4	39C			
23	2-Fluorenyl methyl ketone	119	5.5	20Rb	137–138	128–129	1.51[b]
24	β-Acetonaphthone	120	5.5	20E	73–73.5	54.5–55[c]	1.65
25	*m*-Methoxyacetophenone	120	5.5	20Rb	1.5316	1.5383	1.65
26	1,3-Diphenylpropanone-1	121	5.6	20E	1.5685	72.5–73	1.61
27	Isopropyl 9-fluorenone-4-carboxylate	121	5.6	58Rb	93.5–95	89–90.5[c]	1.04[b]
28	Ethyl 9-fluorenone-4-carboxylate	121	5.6	58Rb		103	
29	Methyl *t*-butyl ketone	121	5.6	20B			
30	α-Furyl methyl ketone	122	5.6	20Rs	1.4763	1.5043	1.63
31	Ethyl methyl ketone	123	5.7	20B			
32	Methyl isopropyl ketone	123	5.7	20B			
33	Cyclopentanone	123	5.7	20B			
34	Xanthone	124	5.7	20B			
35	Isopropyl phenyl ketone	125	5.8	39C			
36	1-Naphthyl phenyl ketone	128	5.9	20Rb	86–87	76	1.46[b]
37	*m*-Tolyl phenyl ketone	128	5.9	20Rb	54–55	1.5965	1.57[b]
38	Dimethyl ketone	129	6.0	20B			
39	Diphenyl ketone	129	6.0	20B			
	Diphenyl ketone	126	5.8	55E			
40	*p*-Bromoacetophenone	129	6.0	20Rb	1.5689	49–51[c]	1.57
41	Phenyl benzyl ketone	136	6.3	20Rs	67–68	55.5–56	1.60[b]
42	Ethyl *p*-acetylbenzoate	136	6.3	20Rb	1.5062	54–56	1.35[b]
43	β-Hydrindone	139	6.4	20Rb	70–70.3	57–57.5	
44	Benzyl methyl ketone	140	6.5	20Rs	1.5187	1.5139	
45	Methyl 9-fluorenone-2-carboxylate	140	6.5	58Rb	118–119.5	184–185[c]	1.02[b]
46	2-Chlorofluorenone	141	6.5	58Rs	142–143	122–123	1.06[b]
47	*o*-Methoxyacetophenone	141	6.5	20Rb	1.5312	1.5378[c]	1.63
48	Ethyl benzoylacetate	147	6.8	20Rb	1.5107	102–3/1[f]	1.49[b]
49	Isopropyl *m*-benzoylbenzoate	149	6.9	58Rb	180–1/2[f]	1.5723[c]	1.38
50	*m*-Nitroacetophenone	152	7.0	20Rb	63	79.5–81[c]	0.80–1.67
51	Ethyl *p*-benzoylbenzoate	152	7.0	58E		54.5–55.5	1.27[b]
52	Isopropyl *p*-benzoylbenzoate	153	7.1	58E	51–52	55.5–56	1.26[b]
53	*t*-Butyl *p*-benzoylbenzoate	152	7.0	58E		49–50	1.27[b]
54	Δ^5-Cholestenone-3	153	7.1	20E	148		
55	9,10-Anthraquinone	154	7.1	Ref. 8			
56	β-Tetralone	155	7.2	20Rs	1.5632	1.5557	

TABLE I (*Continued*)

No.	Compound	E_0, mv.	$-\Delta F^0$ 25°, cal.	Equilibrated against	M. p., °C. or $n^{25}D$ Carbinol	Carbonyl	Dep. pot. (−)
57	2,7-Dichlorofluorenone	157	7.2	58Rs	161–162	192–193	0.84[b]–1.07
	2,7-Dichlorofluorenone	157	7.2	55E			
58	Cyclohexanone	162	7.5	20B			
59	Δ^3-Cyclohexenone	162	7.5	20E			
60	3-Methoxycyclohexanone	167	7.7	20Rs	1.4638	1.4558[d]	
61	4-Methoxycyclohexanone	167	7.7	20Rs	1.4661	1.4530	
62	β-Pyridyl phenyl ketone	167	7.7	58E	67.5–69	1.6060[c]	1.22[b]
63	*t*-Butyl phenyl ketone	169	7.8	20B			
64	*p*-Nitrobenzophenone	171	7.9	57E	73–74	136–137[c]	1.42
65	1-Chloroanthraquinone	175	8.1	57E		161–161.5	
	1-Chloroanthraquinone	174	8.0	Ref. 8			
66	Benzhydryl methyl ketone	182	8.4	20Rs	57.5–58.5	58–60	
67	Cinnamaldehyde	186	8.6	74E	1.5772	1.6120	1.08[b]
68	Methoxyacetone	189	8.8	57Rs	1.4010	1.3955	
69	α-Tetrahydrofuryl methyl ketone	195	9.0	57Rs	1.4461	1.4361	
70	Crotonaldehyde	194	9.0	74E	1.4262	1.4355[c]	1.37
71	Benzaldehyde	197	9.1	57E			1.34
72	Benzoin methyl ether	199	9.2	58Rs	54–61	47–48	1.52[b]
73	ω-Piperidinoacetophenone	203	9.4	58Rs	70.5–71.5	1.5396	1.25
74	Trimethylacetaldehyde	211	9.8	71E	54–55	1.3765	
75	Phenylglyoxal dimethyl acetal	212	9.8	58Rs	1.5097	1.5102[d]	
76	ω-Methoxyacetophenone	213	9.8	58Rs	1.5190	1.5319[c]	1.43
77	Furfuraldehyde	214	9.9	74E	1.4868	1.5248	
78	Dibenzyl ketone	216	10.0	57Rs	1.5691	35	
79	2-Methoxycyclohexanone	218	10.1	57Rs	1.4571	1.4519[d]	
80	Isobutyraldehyde	220	10.2	71E	1.3953	1.3713	
81	Isopropyl anthraquinone-2-carboxylate	219	10.2	57E	125 (*ca.*)	138–139[c]	0.55
	Isopropyl anthraquinone-2-carboxylate	222	10.2	Ref. 8			
82	Acetaldehyde	226	10.4	71E			1.87
83	*t*-Butylglyoxal	245	11.3	71E	1.4297	85	
84	Formaldehyde	270	12.5	71E			1.38
	Formaldehyde	257	11.9	Ref. 9			
85	Chloral	277	12.8	86E	55.5/13[f]	96.5/74.0[f,c]	
86	Isopropyl benzoyl formate	282	13.0	81E	1.4969	1.5035	1.05[b]
87	Ethyl pyruvate	297	13.8	86Rs	1.4110	1.4042	1.35
88	Isopropyl pyruvate	299	13.8	86E	1.4078	1.4036	1.45[b]
89	Ethyl oxomalonate	298	13.8	86E	1.4283	1.4190	
90	1,3-Dimethoxyacetone	350[g]	..	57Rs	1.4177	1.4161	
				86E			

[a] The carbonyl compound against which Cox (C), Baker (B), Rossow (Rs), Robinson (Rb), or Elofson (E) equilibrated a given compound is indicated in the fifth column of the table, by using the number of the carbonyl compound as given for the compound in the first column of the table. The values for the methoxyacetophenones, given by Baker and Schafer,[4b] are in agreement with the potentials listed in the table for these compounds, if they are based upon a potential for fluorenone of 117 mv., rather than upon the value 150 mv. reported earlier.[4a] [b] These depolarization potentials were observed in a 0.1 *N* ammonium chloride solution, while the others reported were in a 0.05 *N* tetramethylammonium hydroxide solution. [c], [d] and [e] These ketones were reduced to the corresponding alcohols with aluminum isopropoxide[c] or by catalytic hydrogenation over Raney nickel[d] or copper chromium oxide[e]. [f] Boiling points. [g] This is a minimum value.

chance there is for a significant amount of a side reaction. Fluorenone is outstanding in giving rapid reactions. 2,7-Dichlorofluorenone is less reactive while isopropyl benzoylformate reacts quite slowly. Cyclohexanone reacts rapidly but is itself subject to condensation.

The determination of the oxidation potentials of Δ^4-cholestenone-3, Δ^5-cholestenone-3, Δ^2-cyclohexenone and Δ^3-cyclohexenone involves certain peculiar difficulties and uncertainties. In the classical Oppenauer oxidation of cholesterol by acetone to Δ^4-cholestenone-3 there is an intramolecular as well as an intermolecular oxidation–reduction. The latter ketone may be isolated in a yield of about 80% from such a reaction mixture. The reactions may be represented by the scheme

$$\begin{array}{ccc} \Delta^5\text{-cholestenol-3} + K & \rightleftharpoons & \Delta^5\text{-cholestenone-3} + A \\ \uparrow\downarrow & & \uparrow\downarrow \\ \Delta^4\text{-cholestenol-3} + K & \rightleftharpoons & \Delta^4\text{-cholestenone-3} + A \end{array}$$

where K represents a ketone and A the alcohol corresponding to it.

Cholesterol (Δ^5-cholestenol-3) is oxidized by

fluorenone, under our standard conditions of reaction, until at equilibrium the concentration of fluorenone is 80%. The conversion at equilibrium corresponds to a value of 153 mv. for Δ^5-cholestenone-3. The concentration of fluorenone at equilibrium with Δ^4-cholestenone-3, *i. e.*, 11%, corresponds with an oxidation potential of 63 mv. for the Δ^4-cholestenone-3, but the equilibrium then shifts in the direction of increasing fluorenone concentration. These facts are compatible with the hypothesis that in the oxidation of cholesterol to Δ^4-cholestenone-3 by ketones such as acetone and fluorenone, the Δ^5-cholestenone-3 is first formed and then undergoes intramolecular oxidation–reduction and the formation of the isomeric Δ^4-cholestenone-3.

Δ^2-Cyclohexenone and fluorenol or Δ^2-cyclohexenol and fluorenone give a similar series of changes which presumably involved the formation of Δ^3-cyclohexenol and Δ^3-cyclohexenone, *i. e.*

$$\Delta^3\text{-cyclohexenol} + K \rightleftarrows \Delta^3\text{-cyclohexenone} + A$$

$$\Delta^2\text{-cyclohexenol} + K \rightleftarrows \Delta^2\text{-cyclohexenone} + A$$

These intramolecular changes will be discussed in a subsequent paper; however, it should be pointed out that the conclusions as to the potential of the four ketones just discussed did not involve the isolation of Δ^5-cholestenone-3, Δ^3-cyclohexenone nor Δ^3-cyclohexenol.

Many of the ketones react so slowly that it was necessary to approach equilibrium concentrations by a series of approximations. After the probable ratio of the two ketones at equilibrium had been estimated, several reaction mixtures of the two ketones, R_2CO and $R_2'CO$, and the corresponding alcohols were made up. The ratios of reactants were varied so that in some mixtures there was slightly more and in some slightly less of R_2CO than at equilibrium. Determination of the direction and extent of shift could then be made after relatively short periods of reaction that minimized the effect of any side reactions.

Due to uncertainty as to the precise concentrations at equilibrium, the oxidation potentials given for formaldehyde, Δ^3-cyclohexenone, cinnamaldehyde, the α-methoxy ketones, ω-piperidinoacetophenone, *t*-butylglyoxal, chloral, isopropyl and ethyl pyruvates, Δ^4- and Δ^5-cholestenone-3 and ethyl oxomalonate may be in error by as much as ± 10 mv. Only a minimum value can be given for 1,3-dimethoxyacetone. The values for other equilibria, except as noted below, may be considered as accurate to within ±5 mv. Relative to each other, the potentials of most of the ketones having values from about 110 to 170 mv. are probably reliable to within ±3 mv. All equilibria except as noted were approached from both directions.

The equilibrium between formaldehyde and benzaldehyde could only be approached from one direction, *i. e.*, through the reaction of methanol and benzaldehyde. However, the value determined, 270 mv., is in fair agreement with the value of 257 mv. calculated from thermal data.[9] The earlier data in Parks and Huffman[10] indicate an oxidation potential of 277 mv.

The oxidation potentials of acetaldehyde, acetone and pyruvic acid have been reported, or may be calculated from data in the literature, and so compared with the potentials determined in this Laboratory. The oxidation potential of acetone, calculated from the data of Parks and Huffman,[10] is 126 mv. Later measurements by Dolliver, Gresham, Kistiakowsky and Vaughan[11] indicate that the value should be lower, *i. e.*, 121 mv. From Conant's[12] work it can be concluded that the oxidation potential of 9,10-anthraquinone in the gas phase is not more than 10–20 mv. lower than in solution. Thus the value of 129 mv. reported here for acetone is in agreement with those calculated from thermal data.

The free energy of reduction of acetaldehyde in the gas phase reported by Parks and Huffman is only 7,320 calories. However, they state that this value leads to an inconsistency of 2,230 calories in the free energy of formation, calculated for gaseous acetaldehyde. If such a correction is made, we find that $\Delta F^\circ_{298} = -9550$ cal., and $E_0 = 207$ mv. for acetaldehyde. The data given by Kistiakowsky and associates indicate that $\Delta F^\circ_{298} \approx -9400$ cal., assuming an entropy of 60 e. u. for acetaldehyde. However, until the entropy of gaseous acetaldehyde is measured, an accurate estimate of the free energy of reduction of gaseous acetaldehyde is not available. The oxidation potential measured by equilibration is 226 mv., which is in satisfactory agreement with the approximate values calculated above, since the values in solution are presumably 10 or 20 mv. higher than in the gas phase reaction.[12]

Three groups of investigators[13,14,15] have reported the oxidation potential of pyruvic acid in solution to be 288 mv. while two other groups[16,17] give higher values of 316 and 325 mv. The value reported here is 297–299 mv. for two esters of pyruvic acid. Conant and Fieser[8] have shown that in the quinone series the potential of an acid is about 10 mv. lower than for the ester. Thus the value for pyruvic acid would be 287–289 mv. which is in perfect agreement with that reported by three groups of investigators.

(9) Thompson, *Trans. Faraday Soc.*, **37**, 249 (1941).

(10) Parks and Huffman, "Free Energies of Some Organic Compounds," The Chemical Catalog Co., New York, N. Y., 1932.

(11) Dolliver, Gresham, Kistiakowsky and Vaughan, THIS JOURNAL, **59**, 831 (1937).

(12) Conant, *ibid.*, **54**, 2881 (1932).

(13) Barron and Hastings, *J. Biol. Chem.*, **107**, 567 (1933).

(14) Banga, Laki and Szent-Györgi, *Z. physiol. Chem.*, **217**, 43 (1933).

(15) Wurmser and Meyer, *J. chim. phys.*, **30**, 429 (1933).

(16) Baumberger, Jurgens and Bardwell, *J. Gen. Physiol.*, **16**, 961 (1933).

(17) Ganguli, *J. Indian Chem. Soc.*, **14**, 656 (1937).

Attention should be called to two assumptions made in the calculations of the potentials given in the table. The oxidation potentials for the quinones used for reference were determined in an alcohol–water solution,[8] while the equilibria were measured in toluene solution in the presence of aluminum alkoxides. The equilibria were in most instances established at 60 to 70°. In the calculations it is assumed that the value of K is the same at these temperatures as at 25°. The heat of the oxidation–reduction reaction is small and measurements with the aldehydes showed that the concentrations at equilibrium at 25° were the same as at 60°. Neither of these assumptions would affect the relative values of the oxidation potentials given herewith, but might distort the absolute values. However, the agreement between the values of E_0 calculated from physical chemical data and those from our experimental results supports the thesis that the absolute as well as the relative values of E_0 as given are reliable for the carbonyl compounds reported.

Relations of Structure and Oxidation Potential

There is a wide difference in oxidation potentials of carbonyl compounds depending upon the associated structures. The oxidation potential, or the free energy of reduction, is approximately five times as large for the highest as for the lowest member of the group of compounds reported here. The magnitude of this variation from a practical standpoint may be illustrated by a comparison of Δ^4-cholestenone-3 63 mv., cyclohexanone 162 mv., formaldehyde 270 mv., and dimethoxyacetone 350 mv. *Each* of these compounds would oxidize the alcohol corresponding to the *preceding* member of the series in a conversion of about 98%.

However, the potentials of the majority of ketones apparently lie within the range of 110 to 160 mv. The potentials of about half the ketones determined lie within this range despite the fact that compounds of lower and particularly of higher potentials were being sought. The potentials of the aldehydes lie somewhat higher, *i. e.*, in the range 220 to 270 mv.

Replacement of Hydrogen by Alkyl or Aryl Groups.—The replacement of hydrogen on a carbonyl by an alkyl or aryl group lowers the oxidation potential of a carbonyl compound. This is illustrated by the series H_2CO 260 mv., CH_3CHO 226 mv. and $(CH_3)_2CO$ 129 mv. Replacement of a hydrogen on a carbon adjacent to the carbonyl has a similar but much less marked effect, *e. g.*, CH_3CHO 226 mv., $(CH_3)_2CHCHO$ 220 mv. and $(CH_3)_3CCHO$ 211 mv. There is a similar effect in a series of open-chain ketones, which may be considered as related to acetone.

There are many alkyl and aryl groups which compared with methyl manifest little difference in effect upon the potential of the carbonyl group. There are perhaps twenty-five ketones listed in the table which show relatively little difference in potential as compared with acetone. Yet among this group of ketones are such diverse structures as in acetophenone, cyclopentanone, xanthone, benzophenone, fluorenone and the acetylnaphthalenes. No doubt there are among this group of ketones counterbalancing effects where one group tends to raise while another tends to lower the potential of the carbonyl group.

Four ketones have surprisingly high potentials, *i. e.*, cyclohexanone 162 mv., *t*-butyl phenyl ketone 169 mv., benzhydryl methyl ketone 182 mv. and dibenzyl ketone 216 mv. The high oxidation potentials of at least two of the ketones just mentioned, as well as many other observations reported in this paper, have been rationalized in the electronic terms of the English school.[7]

Effect of Unsaturation.—The presence of carbon-to-carbon double bonds in the 2,3-position with respect to a carbonyl brings about a distinct lowering of the oxidation potential. A comparison of benzaldehyde 197 mv., crotonaldehyde 194 mv. and cinnamaldehyde 186 mv., with a saturated aldehyde, acetaldehyde 226 mv. or isobutyraldehyde 220 mv., shows a lowering of 20 to 40 mv. An even more marked lowering of potential as compared with acetone 129 mv., is shown by Δ^4-cholestenone 63 mv., α-hydrindone 73 mv., α-tetralone 80 mv. and Δ^2-cyclohexenone 85 mv. α-Furyl methyl ketone 122 mv., is 73 mv. lower than the corresponding saturated ketone.

Carbon-to-carbon unsaturation in the 3,4-position with respect to the carbonyl has little or no effect upon the potential. Apparently Δ^3-cyclohexenone and cyclohexanone have the same potential of 162 mv. β-Tetralone 155 mv., and β-hydrindone 139 mv., have potentials similar to the corresponding alkyl aryl ketones. Δ^5-Cholestenone has a potential 90 mv. higher than the Δ^4-isomer. The unsaturation of the phenyl group does not in many instances have any marked effect on the potential when it replaces a methyl group in a methyl ketone. Acetone, benzophenone and acetophenone all have potentials in the range of 118–129 mv. However, in α-tetralone and benzaldehyde the potentials are considerably lower than for similar saturated cyclic compounds.

Effect of Ring Structures.—The very low oxidation potentials of certain cyclic ketones such as camphor, Δ^4-cholestenone, α-hydrindone and α-tetralone would not be anticipated from a knowledge of open-chain and aryl ketones. The high oxidation potential of cyclohexanone must result from the ring structure. However, the potential of cyclopentanone is in accord with that of open-chain compounds.

Effect of Alkoxy, Carbonyl and Carbalkoxy Groups.—The replacement of hydrogen by oxygen in the alpha position in a ketone results in a marked increase in the oxidation potential of the

carbonyl. This is shown by a comparison of acetone 129 mv., methoxyacetone 189 mv. and dimethoxyacetone of more than 350 mv. The ω-mono- and dimethoxyacetophenones, $C_6H_5COCH_2OCH_3$ and $C_6H_5COCH(OCH_3)_2$ show potentials of 212–213 mv., about 95 mv. higher than the corresponding non-oxygenated ketone acetophenone. α-Tetrahydrofuryl methyl ketone 195 mv., is 60–70 mv. higher than ketones without oxygen α to the carbonyl.

The α-methoxy ketone $C_6H_5CH(OCH_3)COC_6H_5$ 199 mv. is 59 mv. higher than the corresponding benzyl phenyl ketone 140 mv. 2-Methoxycyclohexanone 218 mv. is 56 mv. higher than cyclohexanone.

If the series of compounds $C_6H_5COCH_3$ 118 mv., $C_6H_5COCH_2OCH_3$ 213 mv., $C_6H_5COCH(OCH_3)_2$ 212 mv. and $C_6H_5COCO_2C_3H_7$ 282 mv. be considered to involve a progressive oxidation of the carbon atom α to the carbonyl to the alcohol, aldehyde and carboxylic acid stages, then it may be considered that the first step in oxidation of methylene increases the potential of the ketone by 95 mv. The second step in oxidation to the aldehyde or ketone is without effect, while the third step of oxidation to the acid raises the potential of the ketone group almost as much as the first. A similar effect is evident in the series CH_3COCH_3 129 mv., $CH_3COCH_2OCH_3$ 189 mv., and $CH_3COCO_2C_3H_7$ 299 mv. although in this series the third step in oxidation is more effective than the first. In both series the difference in potential between the simple ketone and the α-keto ester is quite large, *i. e.*, 164–170 mv.

Alkoxy and carbalkoxy groups more distant from a carbonyl than in the α-substituted compounds just considered, are considerably less effective in raising the oxidation potential. *m*-Methoxyacetophenone had a potential almost identical with acetophenone, while *o*-methoxyacetophenone was 22 mv. higher and *p*-methoxyacetophenone 19 mv. lower than acetophenone. The 3- and 4-methoxycyclohexanones had potentials little different from cyclohexanone. The carbalkoxy substituted ketones such as items 42, 45, 48, 49, 51, 52 and 53 in the table show potentials 18 to 29 mv. higher than the corresponding unsubstituted ketones.

The potential of an α-keto aldehyde was found to be considerably higher than for an aldehyde of somewhat similar structure but without an α-carbonyl group, *i. e.*, *t*-butylglyoxal was 34 mv. higher than trimethylacetaldehyde. The effect of free hydroxyl or carbonyl groups on the oxidation potential of a carbonyl group cannot in general be determined because of the multiplicity of equilibria which would be involved. However, the potential of *t*-butylglyoxal could be evaluated since the *t*-butyl group served to inactivate the adjacent carbonyl toward reduction.

Effect of Amino and Nitro Groups and of Halogens.—The substitution of a nitrogen for hydrogen α to carbonyl, like the substitution of an oxygen, gave a marked increase in potential. ω-Piperidinoacetophenone with a potential of 203 mv. is 85 mv. higher than acetophenone. Nitrogen in the β-position with respect to the carbonyl also enhances the potential. β-Pyridyl phenyl ketone with a potential of 167 mv. is about 40 mv. above benzophenone. The introduction of a nitro group in the meta position of acetophenone and in the para position in benzophenone also raised the potentials by 34 and 42 mv., respectively.

The substitution of a chlorine for a hydrogen in a ketone has given in certain instances a marked increase in oxidation potential. The 2-chlorofluorenone and 2,7-dichlorofluorenone were prepared and tested because Conant and Fieser[8] had noted that certain chloroquinones had higher oxidation potentials than the parent compounds. The discovery[5] of the relatively high potential of the dichlorofluorenone, 157 mv., as compared to 117 mv. for fluorenone, was one of the important steps in making possible the determination of the potential of ketones high in the series. The effectiveness of chlorine substitution in raising the oxidation potential is very evident in a comparison of chloral 277 mv., with acetaldehyde 226 mv.

Rate of Reaction.—There is a very considerable difference in the rate with which equilibrium is established with different carbonyl compounds. Quantitative data on the rates of reaction are not available and in many cases significant numerical values are not obtainable because of side reactions. However, it may be significant to note some of the facts encountered.

Aldehydes such as acetaldehyde, trimethylacetaldehyde, isobutyraldehyde, furfural and benzaldehyde reach equilibrium within an hour or less at 60°. Certain ketones such as cyclohexanone and acetone react with fluorenol almost as rapidly as the aldehydes mentioned. The cyclic ketones β-hydrindone, the two tetralones and the 3- and 4-methoxy cyclohexanones react rather rapidly, only a few hours being required for the attainment of equilibrium. Many ketones such as acetophenone, furyl methyl ketone and benzophenone require twelve to forty-eight hours to reach equilibrium even with fluorenol. The α-oxygenated ketones and aldehydes, chloral, β-pyridyl phenyl ketone, ω-piperidinoacetophenone, tetrahydrofuryl methyl ketone and the carbethoxy ketones react very slowly indeed so that one hundred to one thousand hours would be required for the attainment of equilibrium.

Depolarization Potentials of Carbonyl Compounds.—The oxidation potential of a quinone may be calculated from its depolarization potential at a dropping mercury electrode.[18,19,20]

(18) Miller and Baumberger, *Trans. Electrochem. Soc.*, **71**, 169 (1937).

(19) Smith, Kolthoff, Wawzonek and Ruoff, THIS JOURNAL, **63**, 1018 (1941).

(20) Arnold and Zaugg, *ibid.*, **63**, 1317 (1941).

TABLE II

ANALYSES OF COMPOUNDS

Name of compound	B. p. °C.	Mm.	Formula	Calcd., % Carbon	Calcd., % Hydrogen	Found, % Carbon	Found, % Hydrogen
Mandelaldehyde dimethyl acetal	126.5–127.5	10	$C_{10}H_{14}O_3$	65.9	7.7	65.7	7.8
3-Methoxycyclohexanone	76.5–77	9	$C_7H_{12}O_2$	65.6	9.4	65.3	9.3
Isopropyl 9-fluorenol-2-carboxylate	M. 118–119.5		$C_{17}H_{16}O_3$	76.1	6.0	75.9	5.9
Isopropyl *p*-benzoylbenzoate	190–192	2	$C_{17}H_{16}O_3$	76.1	6.0	76.1	5.9
t-Butyl *p*-benzoylbenzoate	190–192	2	$C_{18}H_{18}O_3$	76.6	6.4	76.7	6.2
4-Carbisopropoxy benzhydrol	209	4	$C_{17}H_{18}O_3$	75.5	6.7	75.2	6.8
Isopropyl benzoylformate	153.5–154.4	12	$C_{11}H_{12}O_3$	68.6	6.2	68.5	6.1
Isopropyl pyruvate	50.5–51	13	$C_6H_{10}O_3$	55.4	7.7	55.5	7.6
β-Pyridylphenylcarbinol	M. 67.5–69		$C_{12}H_{11}ON$	77.8	5.9	77.7	5.9
1-Chloro-10-oxanthrol	M. 135–137		$C_{14}H_9O_2Cl$	68.7	3.7	69.0	3.7
Isopropyl anthraquinone-2-carboxylate	M. 138–139		$C_{18}H_{14}O_4$	73.6	4.8	73.5	4.7
Methyl-*p*-carbethoxyphenylcarbinol	131	2	$C_{11}H_{14}O_3$	68.0	7.3	68.4	7.4
3-Carbisopropoxybenzohydrol	180–181	2	$C_{17}H_{18}O_3$	75.5	6.7	75.7	6.6

There has been no similar correlation observed between the oxidation potentials of aldehydes and ketones and their depolarization potentials.[4] The depolarization potential of many carbonyl compounds was determined at the dropping mercury electrode, incidental to the analytical procedure used in determining the concentration of carbonyl compounds at equilibrium. These values are given in the last column of Table I. The potential recorded is that applied between the falling droplets of mercury and the quiet pool of mercury at the bottom of the polarograph cell, when the diffusion current had attained one-half of its limiting value. A comparison of the depolarization potentials with the oxidation potentials of the carbonyl compounds in column three of Table I lends further support to the conclusion expressed above as to the lack of correlation between the two characteristics of a carbonyl compound. For example Δ^4-cholestenone-3 and ethyl pyruvate have similar depolarization potentials yet the oxidation potentials of the two carbonyl compounds lie almost at the extremes of the compounds listed in the table.

Procedures and Preparations of Reactants.—The procedures followed in equilibrating a quartet of carbonyl compounds and alcohols, and in determining the relative concentration of the compounds at equilibrium, were essentially those described earlier.[4] Since many of the sets of reactants reacted very slowly and gave side reactions it was usually necessary to make up many mixtures and carefully bracket the equilibrium mixture before drawing the final conclusion as to the true concentration at equilibrium. These data, even in abstract form, are so voluminous that they are not submitted for publication.

A few minor improvements in the procedures were introduced in order to avoid difficulties encountered from time to time. The addition of a drop of 0.25 *N* ammonium chloride solution facilitated the complete precipitation of aluminum hydroxide in the hydrolysis step. Care was taken to avoid the exposure of the alcohols or the reaction mixtures to strong sunlight at any stage of the procedure. An electrode of the type described by Kolthoff and Lingane[21] is more satisfactory than that used in earlier work. A stopcock without grease was inserted just above the flat-bottom capillary. The intervals between droplets of mercury were 2 ± 0.5 seconds.

Most of the carbonyl and carbinol compounds used in this investigation have been prepared earlier by others. Space was not available for publication of references to the earlier papers, however the references have been assembled.[5,6,7] Analytical data for compounds not previously described are given in Table II. The melting points or refractive indices of the alcohols and ketones used in the determinations, reported for the first time in this paper, are given in Table I. Several of the alcohols were prepared for the first time through the reduction of a ketone to the corresponding alcohol with aluminum isopropoxide or by catalytic hydrogenation over Raney nickel or copper-chromium oxide. These cases have been noted in Table I. Procedures for the preparation of a few compounds are given below.

2,7-Dichlorofluorenone and 2,7-Dichlorofluorenol.—Ten grams of pure, white, distilled fluorene, m. p. 110–112°, was chlorinated in 90 ml. of chloroform during one and one-half hours. The temperature of the mixture rose somewhat above room temperature due to heat of reaction but fell again to room temperature during the period of reaction. The solvent was blown off on a steam-bath and the residue recrystallized two or three times from petroleum ether (b. p. 90–100°). The yield was 5.4 g. (38%) of 2,7-dichlorofluorene, m. p. 123–124.5°. The compound (21 g.) was dissolved in 100 ml. of hot acetic acid and 65 g. of sodium dichromate in 100 ml. of acetic acid added slowly. The mixture was refluxed for thirty minutes and then poured into cold water. The product was separated by filtration and crystallized from a 1:4 mixture of benzene and petroleum ether (b. p. 90–100°). The yield of 2,7-dichlorofluorenone, m. p. 190–191° was 17.5 g. The ketone (9 g.) was reduced with zinc in an ammoniacal solution[22] to give 2,7-dichlorofluorenol (7.4 g.), m. p. 161–162°.

(21) Kolthoff and Lingane, *Chem. Revs.*, **24**, 1 (1939).

(22) Courtot, *Ann. chim.*, **14**, 5 (1930).

2-Chlorofluorenone and 2-Chlorofluorenol.—2-Aminofluorene[23] (15.8 g., m. p. 127–128°) was made into a paste on a steam-bath with 90 ml. of water. Concd. hydrochloric acid (16.5 ml.) in 185 ml. of water was added to the paste and the mixture allowed to cool to room temperature. The amine was diazotized with a solution of 6.1 g. of sodium nitrite in 45 ml. of water. The mixture, in which the diazonium salt had crystallized out, was poured with shaking into a solution of 25 g. of cuprous chloride in 125 ml. of concd. hydrochloric acid and refluxed for thirty minutes. After cooling, the solid material was filtered off, dried, pulverized and extracted with 500 ml. of ether. The ether solution was washed with a 5% solution of sodium hydroxide and dried over potassium carbonate. The ether was distilled off and the residue distilled 140–150° (2 mm.). The white solid product (10.5 g.) was recrystallized from 30 ml. of hot 95% alcohol giving 8.7 g. white 2-chlorofluorene m. p. 93–94°. The product was converted to 2-chlorofluorenone (8.0 g., m. p. 113–116° or 6.3 g., m. p. 122–123°) by oxidation as described for 2,7-dichlorofluorenone. The ketone (3.5 g.) was reduced to 2-chlorofluorenol (3.2 g., m. p. 142–143°) as by Courtot.

sym-Dimethoxyacetone.—Methyl methoxyacetate (101 g., b. p. 128–130° (740 mm.), $n^{25}D$ 1.3940) was prepared from methanol and chloroacetic acid (157 g.) as by Schreiner.[24] The ester was added to sodium methoxide (from 17 g. of sodium) and stirred for four hours on a steam-bath. The reaction mixture was then cooled, diluted with water and neutralized with acetic acid. The solution was extracted twice with ether and the latter washed with a sodium carbonate solution and dried over sodium sulfate. After removing the ether the desired dimethoxy keto ester was distilled at 114–115° (10 mm.). The yield was 31.8 g. having $n^{25}D$ of 1.4358. The ester was hydrolyzed in 200 ml. of a 5% sodium hydroxide solution for three hours on the steam-bath. The reaction mixture was acidified with sulfuric acid in the cold. About three-fourths of the solution was distilled; the distillate was saturated with potassium carbonate. The solution and oil was extracted with ether and dried over sodium sulfate. After removal of the ether the product was distilled through a short column giving 2.2 g. of crude ketone b. p. 58–65° (10 mm.). Redistillation gave 1.6 g. of 1,3-dimethoxyacetone b. p. 62.5–63° (10 mm.).

3-Methoxycyclohexanol.—Resorcinol (110 g.) was methylated at room temperature during two hours with dimethyl sulfate (100 ml.) in 600 ml. of water containing 100 g. of potassium hydroxide. The solution was acidified and extracted three times with benzene. The benzene solution was washed with 40 g. of sodium hydroxide in 600 ml. of water in three equal portions, in order to separate the desired product from the dimethylated material. The alkaline extract was acidified with hydrochloric acid, extracted with benzene, the solution dried, and the benzene distilled. Resorcinol monomethyl ether (59 g.) was distilled 115–119° (7.5 mm.). The product was hydrogenated over 5 g. of Raney nickel at 150° during forty-five minutes under 3000 p. s. i. of hydrogen. 3-Methoxycyclohexanol (36 g.) was obtained by fractionation of the product at 88–89° (8 mm.).

2- and 3-Methoxycyclohexanones.—These ketones were prepared by the oxidation of the corresponding alcohols, which had been prepared by hydrogenation of the corresponding phenols over Raney nickel as described for 3-methoxycyclohexanol. For example, 2-methoxycyclohexanol (28 g.) was added to a cool solution of 43 g. of potassium dichromate in 31 ml. of concentrated sulfuric acid and 190 ml. of water. The temperature rose from 12 to 65° and then slowly dropped to room temperature. The solution was extracted with 600 ml. of ether in three portions. The ether solution was washed with a carbonate solution and dried over sodium sulfate. Fractionation of the product gave 13 g. of 2-methoxycyclohexanone b. p. 58–59° (8 mm.), $n^{25}D$ 1.4519. The yield of 3-methoxycyclohexanone (3.8 g.) b. p. 76.5–77° (9 mm.), from 3-methoxycyclohexanol (22 g.) was rather low.

Dibenzyl Ketone.—A solution of 155 g. of benzyl cyanide in 200 ml. of ether was added to a solution of benzylmagnesium chloride, prepared from 37.7 g. of magnesium and 196 g. of benzyl chloride in 750 ml. of ether. The mixture was refluxed for two hours and the addition product hydrolyzed in ice-water and then with dilute sulfuric acid. The crude ketone (48 g.) was distilled at 138–140° (3 mm.). The ketone solidified and was crystallized from petroleum ether (b. p. 40–60°) to give 32 g., m. p. 32.5–34°, and 25 g., m. p. 35° after recrystallization.

α-Tetrahydrofuryl Methyl Ketone.—Ethyl tetrahydrofuroate (b. p. 73–74° (11 mm.), $n^{25}D$ 1.4328) was prepared by the hydrogenation of ethyl furoate (220 g.) over Raney nickel at 100° in 88% yield. Ethyl α-tetrahydrofuroylacetate was prepared through the reaction of the sodium salt of ethyl acetoacetate (0.63 mole) with ethyl tetrahydrofuroate (1.25 moles) at 150–155°, for four hours by the method of McElvain and Weber.[25] The desired keto ester 15.5 g., b. p. 115–116° (8 mm.), $n^{25}D$ 1.4530 was obtained by fractionation of the crude distillate. The keto ester (15 g.) was hydrolyzed in a 5% sodium hydroxide solution during four hours on a steam-bath. The cold solution was acidified with dilute sulfuric acid and two-thirds of the solution distilled. The distillate was made slightly alkaline and two-thirds of it again distilled. The distillate was saturated with potassium carbonate and extracted twice with ether. The ether solution was dried and the desired ketone (4.9 g., b. p. 160.5–161.5° (740 mm.)) distilled through a short Vigreux column.

Benzhydryl Methyl Ketone.—Lead diphenylacetate was prepared by the reaction of lead nitrate in a slightly acid water solution of sodium diphenylacetate. Dry lead diphenylacetate (31 g.) was intimately mixed with dry lead acetate (62 g.) in a mortar and the mixture heated under reduced pressure in a 250-ml. distilling flask held in a Woods metal bath at 280°. A yellow distillate (6 g.) was obtained and redistilled at 155–157° (8 mm.) to give 3.7 g. of crude ketone. The product solidified when kept overnight in a refrigerator, and was then crystallized from 40 ml. of petroleum ether (b. p. 40–60°). In different experiments both the stable form m. p. 58–60° and the unstable form m. p. 45–46° of the ketone were obtained in beautiful white crystals.[26,27]

Summary

The oxidation potentials of eighty-seven ketones and aldehydes have been determined by equilibrating them against each other and against three quinones of known oxidation potentials. The data are summarized in Table I. The limitations and reliability of the data and some of the relationships of structure to oxidation potentials have been discussed.

MADISON, WISCONSIN RECEIVED NOVEMBER 6, 1948

(23) "Organic Syntheses," **13**, 74, John Wiley and Sons, Inc., New York, N. Y., 1933.

(24) Schreiner, *Ann.*, **197**, 8 (1879).

(25) McElvain and Weber, THIS JOURNAL, **63**, 2192 (1941).

(26) Kenner and Morton, *Ber.*, **72**, 452 (1939).

(27) Stoermer and Riebel, *ibid.*, **39**, 2302 (1906).

[CONTRIBUTION FROM THE RESEARCH LABORATORY AND THE KNOLLS ATOMIC POWER LABORATORY,[1a] GENERAL ELECTRIC COMPANY]

A Spectrophotometric Study of Three Zirconium Lakes

BY JOHN F. FLAGG, HERMAN A. LIEBHAFSKY AND EARL H. WINSLOW

Surprisingly enough, Beer's law holds over a considerable concentration range in the complex systems of alcohol–hydroxyanthraquinone–suspended zirconium (or hafnium) lake, and this fact forms the basis for a spectrophotometric determination of either metal in microgram amounts.[1] Furthermore, spectrophotometric evidence[2] has indicated that the hafnium–alizarin lake is a definite chemical compound, the combining ratio being unity. Similar evidence is given here for the lakes that zirconium forms with alizarin, with purpurin and with quinalizarin.

As for hafnium, lake formation was studied with zirconium in excess, and with zirconium and dye in stoichiometrically comparable amounts. In the former (limiting) case, all the dye is assumed to be combined so that the lake is the only colored substance present; in the latter (intermediate) case, there is free dye also. The experimental results are interpreted with the aid of data for the other limit, where dye is in excess and zirconium can be determined spectrophotometrically. The procedures for all cases have been fully described, and detailed references will consequently make repetition unnecessary.

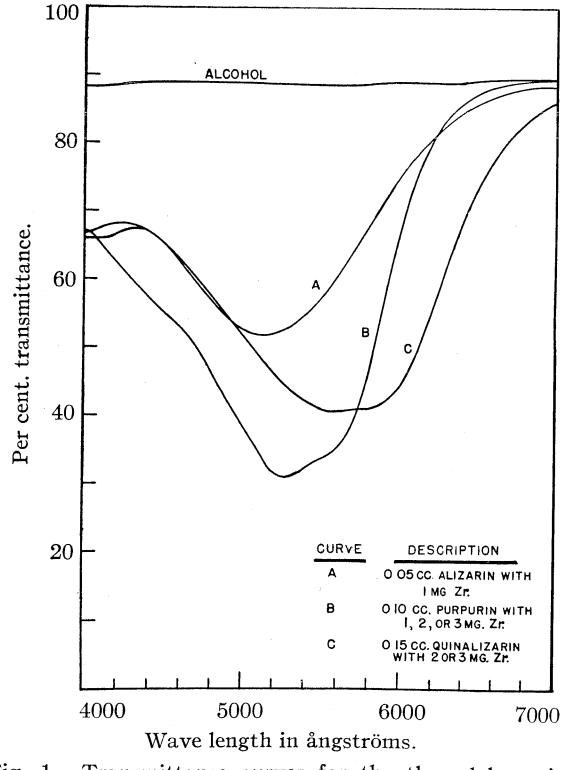

Fig. 1.—Transmittance curves for the three lakes, zirconium being in excess.

Experimental Results

Zirconium in Excess.—Transmittancies[3] were measured on a General Electric recording spectrophotometer for a series of suspensions prepared in the standard way by adding varying excess amounts of standard zirconium solution each to the same amount of dye. When increasing the excess of zirconium did not further increase the transmittance at the minimum in the curve for the dye (near 4360 Å. for alizarin; *cf.* ref. 2, Fig. 1), it was assumed that all the dye had combined to form a lake of formula $Zr_m(Dye)_n$. From the number of moles of dye added and the number of moles of zirconium combined (as obtained from Beer's law plots[1b]), values of the combining ratio n/m (Table I) were calculated (see ref. 2, Fig. 4, and the second paragraph beginning on p. 1131). Typical transmittance curves for the lakes are given in Fig. 1.

TABLE I

RATIO OF DYE TO ZIRCONIUM IN LAKES

Dye	Moles of dye taken × 10^7	Moles of Zr taken × 10^7	Moles of Zr combined × 10^7	n/m
Alizarin	2.88	37.2	2.58	1.1
Alizarin	4.03	37.2	3.77	1.1
Alizarin	5.75	74.4	5.06	1.1
Alizarin	5.32	74.4	5.14	1.0
Alizarin	7.83	330	5.72	1.4
Alizarin	7.87	55.8	8.10	1.0
Alizarin	8.62	37.2	7.73	1.1
Quinalizarin	1.81	330	1.26	1.4
Purpurin	2.94	330	2.68	1.1

Within the range of concentrations chosen, the combining ratio is essentially one for the alizarin lakes. As in the case of the hafnium lake, these ratios tend to exceed unity, perhaps owing to experimental error or to the incomplete realization of a fundamental assumption; *e. g.*, the absorption of dye by the lake may explain the value 1.4 found for the quinalizarin lake.

(1a) The Knolls Atomic Power Laboratory is operated by the General Electric Research Laboratory for the Atomic Energy Commission. Part of the work reported here was carried out under Contract No. W-31-109 Eng.-52.

(1b) Liebhafsky and Winslow, THIS JOURNAL, **60**, 1776 (1938); (c) see also Green, *Anal. Chem.*, **20**, 370 (1948).

(2) Liebhafsky and Winslow, THIS JOURNAL, **69**, 1130 (1947).

(3) National Bureau of Standards Letter Circular LC857 attempts to standardize the confused nomenclature in the field of absorptometry. The recommendations given there will be followed so far as is possible without complicating the references to previous work. Let I_1 and I_2 represent the radiant energy incident upon, and that leaving the filled cell. Then $T = I_2/I_1$ is the (over-all) *transmittance*. The transmittancy, T_S, is the ratio Tsoln./Tsolv., where "soln." in our case refers to a colored system and "solv." to alcohol. $A_S = \log 1/T_S$ is the *absorbancy*.

Zirconium and Dye in Comparable Amounts.—Lake and uncombined dye are both present, so that the absorbancy for a cell of unit length is given by

$$A_S = \epsilon_1(\Sigma[\text{Dye}] - n[\text{L}]) + \epsilon_2[\text{L}] \qquad (1)$$

in which ϵ_1 and ϵ_2 are, respectively, the molar absorbancy indexes of dye and lake, the brackets denote moles/l., Σ[Dye] represents dye added, and L the lake. Given a series of transmittance curves (*cf.* ref. 2, Fig. 2) for suspensions each prepared from a constant amount of dye and a different, comparable amount of zirconium, n/m at a suitable wave length can be obtained graphically from a plot of absorbancy against *combined* zirconium provided ϵ_2/m and ϵ_1 are known; see ref. 2, eq. 2 and 3, Fig. 5, and the neighboring text. The values of ϵ_2/m required for this evaluation were calculated from curves like those of Fig. 1 and are listed in Table II along with the molar absorbancy indexes (ϵ_1's) for the dyes.

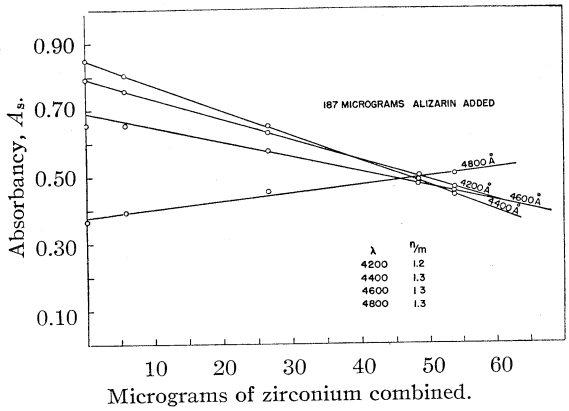

Fig. 2.—Determination of combining ratio, n/m, for the zirconium–alizarin lake at a higher amount of added alizarin.

TABLE II

1. MOLAR ABSORBANCY INDEXES OF THE DYES IN ETHYL ALCOHOL

Wave length, Å.	ϵ_1 of dye: Alizarin	Quinalizarin	Purpurin
4060	4350	3595	2360
4200	5170	4610	3260
4400	5420	6240	5180
4600	4270	7720	7070
4800	2410	8880	8020
5000	960	8760	6070

2. ABSORBANCY INDEXES OF THE LAKES[a]

Wave length, Å.	ϵ_2/m of lake prepared from: Alizarin[b]	Quinalizarin[c]	Purpurin[c]
4060	3280	4950	2350
4200	3260	4725	2890
4400	3190	5170	3630
4600	3580	6270	4300
4800	4310	7990	5460
5000	5030	9930	6910

[a] If m is (plausibly) taken as unity, then ϵ_2/m values are the molar absorbancy indexes. [b] Averaged values from seven curves. [c] Values from a single curve.

The results of the graphical evaluation of the combining ratios are given in Figs. 2–5. As in the case of the hafnium–alizarin lake, n/m tends to increase with wave length; possible reasons for this have been considered previously.[2] In general, these data support the conclusion drawn from the experiments with zirconium in excess—namely, that $n/m = 1$.

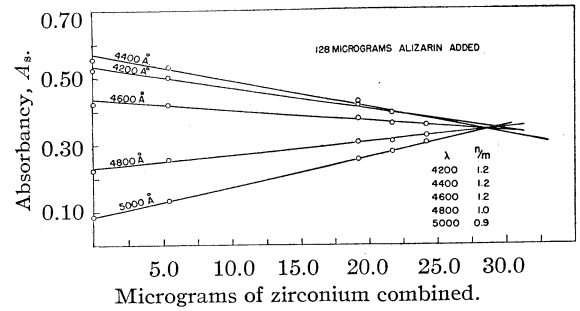

Fig. 3.—Determination of combining ratio, n/m, for the zirconium–alizarin lake at a lower amount of added alizarin.

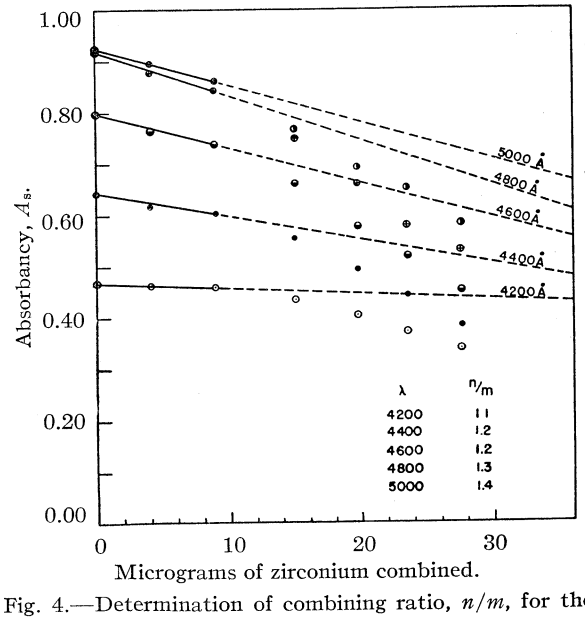

Fig. 4.—Determination of combining ratio, n/m, for the zirconium–quinalizarin lake.

Incomplete Lake Formation.—When a lake was formed from comparable amounts of zirconium and dye, the zirconium combined was less in each case than the zirconium added. Some of the complex situations that could lead to this result have been mentioned for the hafnium–alizarin case, where lake formation was incomplete also (see ref. 2, especially p. 1132). Of these situations, the following seems the most likely. When the lakes are formed in alkaline solution, equilibrium is reached (or at least approached) although the time allowed (two minutes) is short. Because acidification and dilution follow rapidly, these equilibria are "frozen" so that the concen-

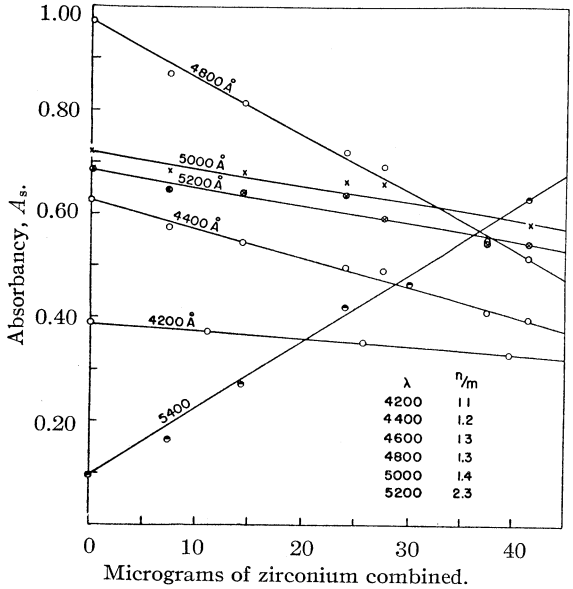

Fig. 5.—Determination of combining ratio, n/m, for the zirconium–purpurin lake.

trations of lake, dye and zirconium remain at the equilibrium values for the alkaline medium. To test this explanation, the "equilibrium quotients" (Q = moles of lake divided by the product of moles uncombined zirconium and moles free alizarin) in Table III were calculated, $n/m = 1$ being assumed. The constancy of the Q's, especially of those for the alizarin lake, makes the explanation seem reasonable.

In parallel experiments at different temperatures, lake formation from comparable amounts of zirconium and alizarin was found to be 67% complete at room temperature and 83% complete at 75°.

Summary

Spectrophotometric evidence indicates that the lakes formed by zirconium with each of the dyes, alizarin, purpurin and quinalizarin, are definite compounds, the two constituents being combined in equimolal amounts.

The spectrophotometric behavior, and the incomplete lake formation observed under some conditions, resemble closely experimental results obtained on the hafnium–alizarin lake. On this basis, it is logical to assign the three lakes studied here a chelate-ring formula analogous to that given the lake formed by hafnium and alizarin.

TABLE III

EQUILIBRIUM QUOTIENTS AT ROOM TEMPERATURE

Moles dye added × 10^7	Moles Zr added × 10^7	Moles lake × 10^7	Moles Zr uncombined × 10^7	Moles dye uncombined × 10^7	$Q \times 10^{-6}$
5.32	0.93	0.59	0.34	4.73	3.7
(Alizarin)	3.72	2.10	1.62	3.22	4.0
	4.65	2.37	2.28	2.95	3.5
	6.50	2.66	3.84	2.66	2.6
7.80	0.93	0.646	0.284	7.15	3.2
(Alizarin)	4.65	2.92	1.73	4.88	3.5
	9.30	5.32	3.98	2.48	5.4
	12.10	5.91	6.20	1.90	5.0
5.58	0.11	0.058	0.052	5.52	2.0
(Quin-	0.55	0.397	0.153	5.18	5.0
alizarin)	1.10	0.954	0.145	4.63	14.2
	2.20	1.65	0.055	3.93	7.6
	3.30	2.19	1.10	3.39	5.9
	4.40	2.61	1.79	2.97	4.9
	6.60	3.08	3.51	2.50	3.5
5.89	1.10	0.814	0.286	5.08	5.6
(Purpurin)	2.20	1.57	0.626	4.32	5.8
	4.40	2.65	1.75	3.24	4.7
	5.50	3.02	2.47	2.87	4.3
	7.70	4.13	3.57	1.76	6.6
	8.80	4.56	4.22	1.33	8.1

SCHENECTADY, NEW YORK RECEIVED MARCH 10, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

The Partial Pressure of Hydrogen Chloride from Its Solutions in Aprotic Solvents: Comparison of Solubility and Infrared Absorption Studies[1]

BY S. JAMES O'BRIEN[2] AND CECIL V. KING

Data were presented in previous papers[3] which indicated that the entropy of solution of hydrogen chloride in aprotic solvents is related linearly to the shift produced by the various solvents in the position of the 3.46 μ absorption band as measured by Gordy and co-workers.[4] In further work along these lines, measurements have been made at two or more temperatures of the partial pressure of hydrogen chloride above its solutions in four more aprotic solvents for which infrared absorption values are available. These determinations provide additional facts pertinent to the relationships between the entropy of solution of hydrogen chloride and the shift of its 3.46 μ absorption band. It is the purpose of this paper to

(1) Abstracted from a dissertation submitted by S. James O'Brien in December, 1946, to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: American Cyanamid Co., Calco Chemical Division, Bound Brook, New Jersey.

(3) S. J. O'Brien, THIS JOURNAL, **63**, 2709 (1941); **64**, 951 (1942).

(4) W. Gordy and P. C. Martin, *J. Chem. Phys.*, **7**, 99 (1939); W. Gordy, *ibid.*, **9**, 215 (1941).

report the new measurements which were made in phenetole, *n*-butyl phenyl ether, diphenyl ether and *m*-nitrotoluene and to consider them in connection with the relationship between the partial molal entropy of solution and the shift of the infrared absorption band of the solute.

Experimental

The apparatus and procedure used were the same as in the earlier work.[3,5] The phenetole, *n*-butyl phenyl ether, diphenyl ether and *m*-nitrotoluene were all Eastman Kodak Co. products which were carefully dried and redistilled before using. The index of refraction, or in the case of *m*-nitrotoluene the melting point, was taken as the criterion of purity.

Results

As in the earlier studies, it was found that hydrogen chloride agreed with the law of Henry in the four solvents employed in the present work. The results of the partial pressure measurements are summarized in Table I.

TABLE I

HENRY LAW CONSTANTS AND THE MOLE FRACTION SOLUBILITY OF HYDROGEN CHLORIDE AT 1 ATM.

Solvent	Temp., °C.	Detns.	k	Dev. ±	N
Phenetole	25	6	1.02	0.04	0.107
Phenetole	20	2	0.90	.01	.120
Phenetole	10	2	0.70	.03	.151
n-Butyl phenyl ether	25	4	1.37	.05	.100
n-Butyl phenyl ether	20	4	1.21	.04	.110
Diphenyl ether	30	4	3.52	.01	.0442
Diphenyl ether	25	4	3.33	.07	.0494
m-Nitrotoluene	35	4	2.08	.04	.0614
m-Nitroltoluene	25[a]	7	1.65	.05	.0768

[a] Reported previously: S. J. O'Brien and C. L. Kenny, THIS JOURNAL, 62, 1189 (1940).

In Table I, the first column gives the solvent; the second, the temperature at which the measurements were made; the third, the number of individual determinations; the fourth column gives the Henry law constant, k, in the form

$$k = p/m$$

where p is the partial pressure in atmospheres and m is the molal concentration of hydrogen chloride in the solution; the fifth column contains the average deviation from the mean of the individual Henry law constants; the last column gives the mole fraction solubility of hydrogen chloride at a partial pressure of 1 atmosphere calculated by means of the equation

$$N = 1/(1 + km_s)$$

N being the mole fraction solubility and m_s the number of moles of solvent in 1000 g.

Discussion

In the earlier work,[3] it was found that the change of mole fraction solubility of hydrogen chloride with temperature could be represented by an equation of the form

$$\log N = A/T + B \quad (1)$$

where T is the absolute temperature and A and B are constants which may be identified with the heat and entropy of solution.[6] That is

$$A = \Delta H/2.303R \quad (2)$$
$$B = \Delta S/2.303R \quad (3)$$

where ΔH is the partial molal heat of solution of the solute, ΔS is the partial molal entropy of solution and R is the molar gas constant. The data presented above for phenetole solutions also fit an equation of this type, and it has been assumed that a similar relationship between the temperatures and the solubility of hydrogen chloride is valid in the other solvents. On this basis, the heats and entropies of solution were derived from the mole fraction solubilities given in Table I. These calculated thermodynamic values are shown in the second and third columns of Table II.

TABLE II

THE HEAT AND ENTROPY OF SOLUTION

Solvent	$-\Delta H$, cal.	$-\Delta S$, eq. 3, e. u.	$-\Delta S$, eq. 4, e. u.
Phenetole	3950	17.6	17.7
n-Butyl phenyl ether	3780	17.2	17.3
Diphenyl ether	3800	18.9	19.0
m-Nitrotoluene	3900	18.8	18.7

The connection between the entropy of solution of hydrogen chloride and the shift of its 3.46 μ absorption band in solution, which was suggested by the data given in a prior paper,[3] could be expressed by the linear equation

$$\Delta S = 10.0\,\Delta\mu - 21.1 \quad (4)$$

in which ΔS is the partial molal entropy of solution of hydrogen chloride and $\Delta\mu$ is the shift of the infrared absorption band. The data reported in this paper are also in agreement with this equation. This is demonstrated in Table II where the last column contains entropy values calculated by means of equation (4) using the infrared absorption data of Gordy.[4] All of the available data relative to this proportionality between the entropy of solution and the shift of the absorption band are summarized graphically in Fig. 1. The line drawn in this diagram is a plot of equation (4); the circles define values obtained from the experimental data as presented in this and the earlier papers.[3] The agreement between the experimental points with equation (4) is quite good; the values assigned to the slope and intercept are adequate. This linear correlation of the shift of the infrared absorption band with the entropy of solution makes it evident that a good straight line connection is not to be expected between the shift of the infrared band

(5) J. H. Saylor, THIS JOURNAL, **59**, 1712 (1937).

(6) Compare J. H. de Boer, *Chem. Weekblad*, **35**, 839 (1938), and V. A. Kireev, *Acta Physicochim. (U. R. S. S.)*, **13**, 531 (1940).

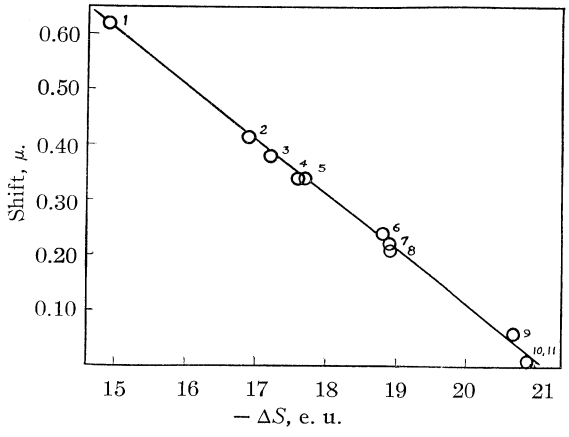

Fig. 1.—A plot of the shift of the 3.46μ absorption band of hydrogen chloride against its entropy of solution in: (1) diethyl ether, (2) β,β'-dichlorodiethyl ether, (3) *n*-butyl phenyl ether, (4) phenetole, (5) anisole, (6) *m*-nitrotoluene, (7) nitrobenzene, (8) diphenyl ether, (9) chlorobenzene, (10) bromobenzene and (11) benzene. The spectroscopic data are taken from the papers of Gordy[4] except those for chlorobenzene and bromobenzene [W. West and P. Arthur, *J. Chem. Phys.*, **2**, 215 (1934)] and for benzene [E. K. Plyler and D. Williams, *Phys. Rev.*, **49**, 215 (1936)]. The entropy values not presented in Table II were taken from the earlier papers.[3]

and the deviation of hydrogen chloride from the law of Raoult.[7] Differences in the heat of solution in the various solvents would lead to deviations from such a relationship. It is, of course, interesting that the increase in the partial molal entropy of the solute is greatest in the more basic solvents in which the infrared absorption band is shifted to the greatest extent.

Summary

1. The partial pressure of hydrogen chloride from its solutions in phenetole, *n*-butyl phenyl ether, diphenyl ether and *m*-nitrotoluene have been determined at two or more temperatures. From these data, the mole fraction solubilities at 1 atm., the partial molal heats and the partial molal entropies of solution of hydrogen chloride have been calculated.

2. A linear relationship between the entropy of solution and the shift of the 3.46 μ absorption band of hydrogen chloride reported previously is further substantiated by a comparison of the calculated entropies of solution with the spectroscopic data available in the literature.

(7) Compare W. Gordy and S. C. Stanford, *J. Chem. Phys.*, **8**, 170 (1940).

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Importance of Interatomic Spacing in Catalysis. A Correlation between Hydrogen Overvoltage on Metals and the Distance between Atoms[1]

BY HENRY LEIDHEISER, JR.

Introduction

It is of great importance to the theories of surface phenomena to understand the importance of the distance between surface atoms in controlling the rates of reactions. A few studies indicate the importance of this distance in catalytic reactions.[2] Recent measurements of the hydrogen overvoltage offer a series of values which may be utilized to compare the relative catalytic activities of a number of metals under similar experimental conditions. Hydrogen overvoltage may be considered as a numerical value representing the ability relative to platinized platinum with which a material catalyzes the over-all reaction, $2H^+ + 2e = H_2(gas)$, in an acid solution. The greater the numerical value of the hydrogen overvoltage, the greater the difficulty with which the reaction occurs.

Correlations of the results of hydrogen overvoltage studies on different metals have been made previously with position in the periodic table, melting point, catalytic activity for the combination of hydrogen atoms, and thermionic work functions,[3] but no one has pointed out the interesting correlation between hydrogen overvoltage and the distance between atoms in the surface.

Results

In Fig. 1 values for the hydrogen overvoltage at 10^{-3} amp./sq. cm. are plotted *versus* the distance of closest approach of atoms for all the body-centered cubic and face-centered cubic metals for which reliable values are available. The values for nickel, copper, molybdenum, tantalum and columbium were taken from Bokris,[4] the values for lead, aluminum, silver, chromium (estimated from the value at 10^{-1} amp./sq. cm.), iron, tungsten, plati-

(1) This paper was written during the author's residence at the University of Virginia under a grant from the Research Corporation. Present address: Virginia Institute for Scientific Research, Richmond 20, Virginia.

(2) See for example: O. Beeck, *Revs. Modern Physics*, **17**, 61 (1945); J. Turkevich and R. K. Smith, *Nature*, **157**, 874 (1946); H. Leidheiser, Jr., and A. T. Gwathmey, THIS JOURNAL, **70**, 1200, 1206 (1948); H. Leidheiser, Jr., and R. Meelheim, *ibid.*, **71**, 1122 (1949).

(3) See J. O'M. Bokris, *Chem. Revs.*, **43**, 525 (1948), for a recent comprehensive discussion of the theories of hydrogen overvoltage and a critical evaluation of the data.

(4) J. O'M. Bokris, *Trans. Faraday Soc.*, **43**, 417 (1947).

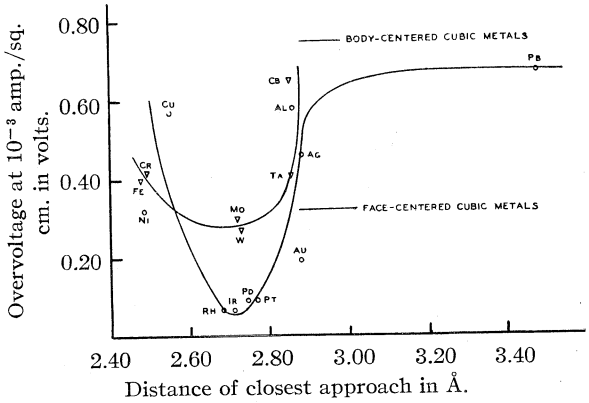


Fig. 1.—The relation between the hydrogen overvoltage at 10^{-3} amp./sq. cm. and the distance of closest approach of atoms for sixteen metals of the body-centered cubic and face-centered cubic structures.

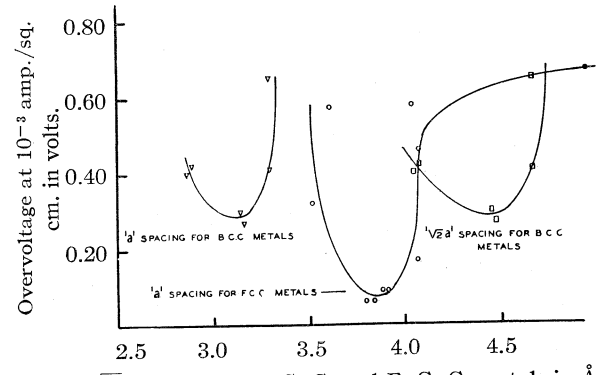


Fig. 2.—The relation between the hydrogen overvoltage at 10^{-3} amp./sq. cm. and the a and $\sqrt{2}a$ spacings for sixteen metals of the body-centered cubic and face-centered cubic structures.

num, gold and rhodium from Hickling and Salt,[5] and values comparative to these were estimated for palladium and iridium from the combined data of Newbery,[6] Volmer and Wick,[7] and Frumkin and Aladzhalova.[8] It should be pointed out that Bokris and Hickling and Salt obtained similar values for the hydrogen overvoltage using different methods for nickel, copper and lead, the only metals that were studied in common. The choice of values obtained at 10^{-3} amp./sq. cm. for plotting is purely arbitrary but curves of comparable shape would be obtained if the hydrogen overvoltage at 10^{-2} or 10^{-1} amp./sq. cm. were plotted. These three current densities are the only ones that have been extensively studied with a number of different metals.

With the exception of vanadium and barium, for which no data are available, and the alkali metals, which cannot be studied in aqueous solution because of their reactivity, all the metals of body-centered cubic structure that are stable at room temperature are included. In the case of the face-centered cubic metals ten different metals are included. It can be seen that the interatomic spacing of approximately 2.7 Å. in the case of both body-centered cubic and face-centered cubic metals corresponds to the minimum overvoltage. The hydrogen overvoltage values for the hexagonal close-packed metals are not complete enough to prepare a similar plot for metals of this structure. However, the values at 10^{-3} amp./sq. cm. for beryllium, cadmium and thallium, the only hexagonal close-packed metals for which reliable values are available, are not inconsistent with a plot of the same general shape as those for the body-centered cubic and face-centered cubic metals.

As shown in Fig. 2 equally good curves can be drawn for the a spacing of the face-centered cubic metals and for the a and $\sqrt{2}a$[9] spacing of the body-centered cubic metals. However, as can readily be seen from Fig. 2 the minimum overvoltage does not occur at the same spacing for these two different metallic structures when plotted in this manner. It is felt that the approximate coincidence of the minima for both types of structure at 2.7 Å. is evidence that this spacing is the important one in hydrogen overvoltage phenomena.

The exact manner in which the curves are drawn in Figs. 1 and 2 is subject to considerable latitude. In the case of the body-centered cubic metals it is impossible to decide on the exact position of the minimum. The reason for this is the small number of body-centered cubic metals which are stable at room temperature. In the case of the face-centered cubic metals the exact position of the minimum depends on a more critical determination of the relative values for the hydrogen overvoltage of rhodium, iridium, palladium and platinum. However, the presence of minima at approximately 2.7 Å. is very definite. Two points occur to the left of the minimum and two occur to the right of the minimum for the body-centered cubic metals. For the face-centered cubic metals two points occur to the left of the minimum and 4 points occur to the right of the minimum. The fact that all of the 16 points plotted are consistent with minima at the 2.7 Å. spacing is strong statistical evidence that the effect is a valid one.

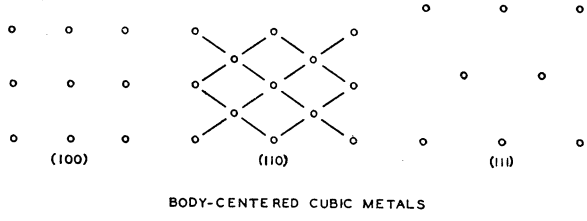
Discussion

The results reported herein furnish evidence that the spacing between atoms in the surface is an important consideration in the rates of catalytic reactions. An interesting observation which shows up in Fig. 1 is the fact that not only is spacing important but also the crystal structure in which the metal crystallizes. The face-centered

(5) A. Hickling and F. W. Salt, *Trans. Faraday Soc.*, **36**, 1226 (1940).
(6) E. Newbery, *J. Chem. Soc.*, **109**, 1051, 1107 (1916).
(7) M. Volmer and H. Wick, *Z. physik. Chem.*, **172**, 429 (1935).
(8) A. Frumkin and N. Aladzhalova, *Acta Physicochim. U. R. S. S.*, **19**, 1 (1944).

(9) The a spacing refers to the distance along the cube edge and the $\sqrt{2}a$ spacing refers to the distance along the diagonal of the cube face.

cubic metals and body-centered cubic metals fall in two distinct classes. Although the data are incomplete for the hexagonal close-packed metals it also appears that these metals fall into a third class. The structure can play a part in the geometry of the surface and in the frequency with which a certain type of spacing occurs in the surface. It is impossible at present to decide between the relative importance of these two possibilities. Figure 3 represents a schematic drawing of the arrangement of atoms on the 3 major faces, (100), (110) and (111), of the body-centered and face-centered cubic metals. The solid lines represent the distance of closest approach of the atoms. It will be noticed that the arrangement of atoms, or geometry, is different on each of these 6 faces and that the distance of closest approach occurs more often in the face-centered cubic structure than in the body-centered cubic structure.



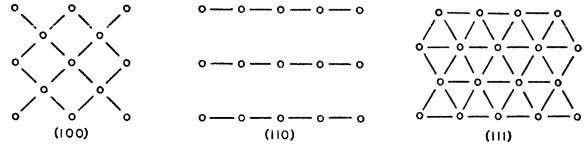


Fig. 3.—The arrangement of atoms and the frequency with which the distance of closest approach of atoms occurs on the major faces of the body-centered cubic and face-centered cubic metals. The solid lines represent the distance of closest approach.

It is of interest in terms of the correlation between hydrogen overvoltage and thermionic work function[4] that there is no relation similar to that of Fig. 1 for thermionic work function and interatomic distances. Thermionic work function is very roughly a linear function of interatomic distance in the case of the high-melting body-centered cubic metals, the low-melting body-centered cubic metals, and the face-centered cubic metals (the linear relation here is very poor—platinum is a bad exception).

Weeks[10] has previously pointed out the qualitative correlation between hydrogen overvoltage and the melting point of metals. As shown in Fig. 4 there is also a correlation between melting point and the distance of closest approach of atoms in the case of the face-centered cubic and body-centered cubic metals. A comparison of Figs. 1 and 4 indicates that the maximum in melting point and the minimum in hydrogen overvoltage occur at approximately 2.7 Å. Although the shapes of the curves are drawn slightly differently in Figs. 1 and 4, it can be seen that there is a semi-quantitative similarity of the relative positions of the metals in both figures.

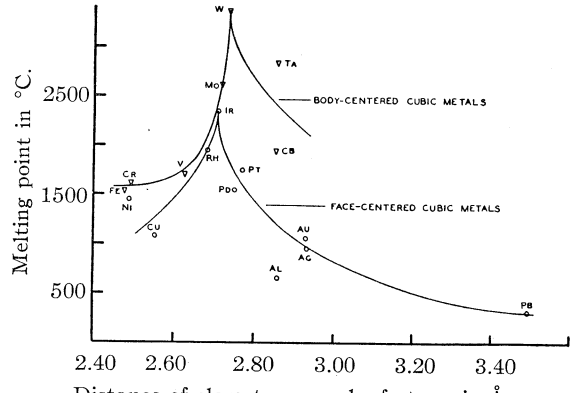


Fig. 4.—The relation between the melting point and the distance of closest approach of atoms for seventeen metals of the body-centered cubic and face-centered cubic structures.

The correlation between hydrogen overvoltage and the spacing between atoms in the surface as reported in this paper does not in itself enable one to choose between the numerous theories developed to account for the phenomenon of hydrogen overvoltage. It is hoped, however, that these results will stimulate theoretical investigations of the significance of the 2.7 Å. spacing in hydrogen overvoltage.

Summary

Evidence was presented which indicated that the spacing between atoms is an important factor in catalysis. Values of the hydrogen overvoltage were shown to be a minimum at a distance of closest approach of atoms of approximately 2.7 Å. for both the body-centered cubic and face-centered cubic metals.

CHARLOTTESVILLE, VA. RECEIVED MAY 12, 1949

(10) E. J. Weeks, *Chem. News*, **129**, 17 (1924).

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

The Surface Area and Catalytic Activity of Aluminum Oxide[1]

BY WALLACE S. BREY, JR.,[2] AND K. A. KRIEGER

The ability of a solid catalyst to promote a gaseous reaction depends upon the amount of surface which the solid possesses as well as upon the specific activity of the surface. Methods of surface area measurement, such as that based on the theory of Brunauer, Emmett and Teller,[3] afford a means of distinguishing between changes in quality and in extent of a catalyst surface. Aluminum oxide is known to undergo changes on thermal treatment, and the purpose of this investigation was the determination of how the resulting variations in its effectiveness as a catalyst for the dehydration of ethanol are related to the two aspects of surface alteration.

Experimental

Alumina catalysts were prepared from $^{8}/_{14}$ mesh Alorco Activated Alumina by heating at temperatures between 500 and 1000°, both in vacuum and in the presence of water vapor. Surface areas of the catalysts before use were measured by the BET method using nitrogen,[3] following outgassing of the samples at 400°.

The catalytic reaction was carried out at 350 and 400° in an electrically heated, vertical tube, of 25 mm. inside diameter. The 200-proof ethanol was pumped at constant rate into an electrically heated evaporator and then passed as vapor into the reactor. The upper part of the reactor tube contained a preheater section packed with quartz chips and provided with manual temperature control; the middle section of the tube contained the catalyst bed of 49 cc. volume, and the temperature of this part was controlled to about ±1° by means of a Micromax potentiometer controller. The liquid products of the reaction were condensed in receivers cooled in ice and in dry ice and were analyzed by distillation. The uncondensed gas was measured in a wet-test meter and analyzed for ethylene by absorption in $HgSO_4$–H_2SO_4 solution.[4] Before the reaction was begun the catalyst tube was brought up to temperature under vacuum and then filled with nitrogen; the first portion of the products was discarded while the system was reaching a steady state.

Results and Discussion

Surface Areas.—Catalysts prepared by evacuation at 600 to 900° show an approximately linear decrease of area with increasing temperature (Table I). The areas of aluminas treated with water vapor are always lower than are those of the aluminas vacuum-treated at corresponding temperatures; the magnitude of the difference depends somewhat upon the pressure of water vapor as well as upon the duration of vapor treatment.

All materials prepared by heating at temperatures between 500 and 900°, either in vacuum or in the presence of water vapor, were shown by X-ray diffraction powder photographs to consist of gamma alumina. Increasing treatment temperature, as well as the presence of water, caused the sharpening of the gamma alumina lines, indicating growth of the crystallites composing the solid. A parallel increase in particle size[5] would, of course, explain the reduction in area. Between 900 and 1000° a sharp decrease in area was found as the result of both methods of treatment; the diffraction patterns indicated that the 1000° samples had been partially converted to corundum.

The surface area values here cited may be compared with the measurements made earlier in this laboratory on portions of the same large quantity of alumina.[6] For samples outgassed between 400 and 500°, the present area values are about 15% larger than the previous results, while areas of samples evacuated at 600° and above are closely coincident in the two sets of measurements. We interpret these facts as evidence that interaction with water took place during the intervening period in a manner so that removal of water by heating disrupted the crystal; this effect was eliminated by higher evacuation temperatures at which crystallite growth and sintering occurred, and where, in the absence of water vapor, the area is a function of temperature of preparation only.

Changes of Catalyst Activity with Use.—Runs employing one catalyst under similar conditions in general gave results which were in satisfactory agreement; ethylene conversion at a reaction temperature of 400° was reproducible within 3%. For certain catalysts, however, there was a consistent trend in activity with use for the first few runs: catalysts heated in vacuum at 800 and 900° became more active, while those heated at 600° in vacuum or in steam were deactivated.

That these changes were not due to changes in surface area is evidenced by the complete restoration, after use, of the activity of catalyst D, originally steam-treated at 600°, by heating in vacuum at 525°, and by the observed lack of increase in area with use of catalyst K, originally heated in vacuum at 900°. Rather, they are associated with the existence of an optimum surface water content for the reaction, and with the slow activated adsorption of water by the catalyst during use. The 600° catalysts thus have at the outset a water content in excess of the optimum; as they are used, adsorption of more water reduces activity. The 800 and 900° vacuum-treated catalysts have initially less than the optimum water

(1) Based on the thesis of Wallace S. Brey, Jr., presented to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: St. Joseph's College, Philadelphia, Pa.

(3) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

(4) Francis and Lukasiewicz, *Ind. Eng. Chem., Anal. Ed.*, **17**, 703 (1945).

(5) Jellinek and Fankuchen, *Ind. Eng. Chem.*, **37**, 158 (1945).

(6) Krieger, THIS JOURNAL, **63**, 2712 (1941).

TABLE I

AREAS AND RATE CONSTANTS OF ALUMINA CATALYSTS

Batch	Treatment: Method	Treatment: Temp., °C.	Treatment: Time, hr.	Area, millimoles N_2/g.	Ignited wt., g.	Reaction temp. 400°: k_1	Reaction temp. 400°: k_1'	Reaction temp. 350°: k_1	Reaction temp. 350°: k_1'	$100k_1$ at 400°/total area of batch
A	Vacuum	500	19	2.49	33.1	0.55	2.0	0.052	1.0	0.67
A-2	[a]			1.86	33.1	.37[f]				.60
B	Steam[b]	500	5	1.30	33.4	.25	1.6	.025	0.9	.58
C	Vacuum	600	19	2.29	33.7	.45	2.1	.040[f]		.58
D	Steam[c]	600	6	1.32	34.5	.27	1.3	.0241	0.46	.59
D-2	Vacuum[d]	525	3		34.5	.35[f]				
E	Vacuum	700	9	1.82	35.9	.32[f]				.49
F	Vacuum	700	20	1.87	34.0	.31	1.7	.030[f]		.48
G	Steam[b]	700	5	0.80	34.7	.12[f]				.43
H	Vacuum	800	19	1.49	34.4	.25	1.6	.0221	0.7	.49
J	Steam[c]	800	8	0.75	33.0	.067	0.8	.008[f]		.27
K	Vacuum	900	19	1.24	34.7	.13	2.0	.0122	1.9	.30
L	Steam[c]	900	5	0.87	36.0	.10[f]				.32
M	Steam[c]	900	5	0.83	[e]					
N	Vacuum	1000	5	0.64	[e]					
O	Steam[c]	1000	5	0.48	35.8	.04[f]				.23

[a] Following several runs in which it was used with aqueous feed, catalyst batch A was designated A-2; the area cited for A-2 was determined after use. [b] In flowing stream of water vapor at 1 atm. pressure. [c] Water vapor pressure about 25 mm. [d] Catalyst D, after use, was evacuated to produce this batch. [e] Activity not determined. [f] Estimated from relatively few runs.

content; adsorption of more water causes the surface to become more efficient as a catalyst.[7]

Reaction Products and Mechanism.—In Figs. 1 and 2 are plotted representative conversion curves for the formation of ether and ethylene in runs using several of the catalysts. The reaction rate is given by the slope of these curves.[8] The trend of the curves with increasing extent of reaction is similar to the results of earlier workers.[9] For every catalyst studied at a reaction temperature of 400° and for the more active catalysts at 350° the ether conversion passes through a maximum while the ethylene conversion steadily increases. For the less active catalysts at 350° the alcohol feed rate was not in all cases sufficiently reduced for the ether maximum to be reached but there seems no doubt that it could have been observed.

In order to evaluate quantitatively the catalyst activity, it is necessary to relate the observed rates of ethylene formation to a velocity constant of the rate-determining step in the reaction. Diffusion is not rate-controlling, in view of the large temperature coefficient of the reaction and the dependence of rate upon surface area. The problem of establishing the rate constant is thus that of the choice of the direct precursor or precursors of ethylene.

If alcohol is assumed to be the sole immediate source of ethylene, then, since ether is produced initially quite rapidly and subsequently disappears, the ether must be formed from alcohol and then reconverted to alcohol to maintain equilibrium with the latter as it is converted to ethylene

$$C_2H_5OH \longrightarrow CH_2{=}CH_2 + H_2O$$
$$\uparrow\downarrow$$
$$H_2O + C_2H_5OC_2H_5$$

This mechanism, with the assumptions that the surface reaction is rate-determining, that ethanol and water are strongly adsorbed while ethylene and ether are not, that only one active site is involved in the reaction and that the reverse reaction may be neglected because of the magnitude of the equilibrium constant, leads to the equation

$$22{,}400R = \frac{kLK_aP_a}{K_aP_a + K_wP_w} = \frac{k_1P_a}{P_a + k_1'P_w} \quad (1)$$

where R is the rate in moles ethylene formed per cc. of catalyst bed per sec., k is the rate constant, L is the number of active sites per cc., the K's are adsorption equilibrium constants, the P's are partial pressures, and the subscripts a and w refer to alcohol and water, respectively.[8] Equation (1) fits the experimental data, while similar equations for the cases in which adsorption or desorption are rate-determining do not. The curves of conversion to ethylene in Figs. 1 and 2 have been calculated from equation (1), employing the values of the constants shown in Table I, while the points shown represent experimental results. The constants in equation (1) were evaluated by the method described in reference (8), pages 958–959.

If, on the other hand, ether is formed from alcohol and is the sole source of ethylene, the initial

(7) (a) Eucken and Wicke, *Naturwissenschaften*, **32**, 161 (1945); (b) Munro and co-workers, *Can. J. Research*, **10**, 321 (1934); **12**, 707 (1935); **21B**, 21 (1943).

(8) Hougen and Watson, "Chemical Process Principles," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1947.

(9) (a) Engelder, *J. Phys. Chem.*, **21**, 676 (1917); (b) Pease and Yung, THIS JOURNAL, **46**, 390, 2397 (1924); (c) Clark, Graham and Winter, *ibid.*, **47**, 2748 (1925); (d) Alvarado, *ibid.*, **50**, 790 (1928); (e) Parravano, *Mem. accad. Italia, Classe sci. fis. mat. e. nat.*, **1**, *Chim.* No. 1, 1 (1930); (f) Kearby and Swann, *Ind. Eng. Chem.*, **32**, 1607 (1940).

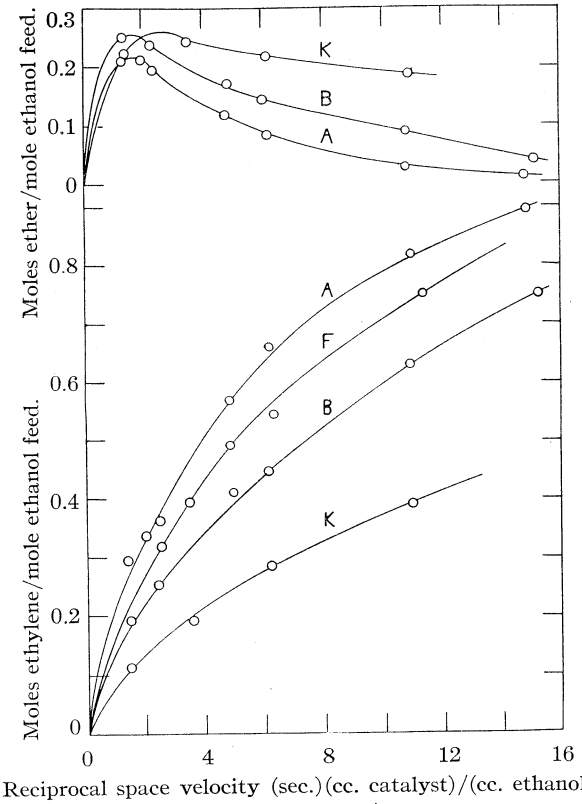


Fig. 1.—Conversion of ethanol to ethylene and ether at 400° reaction temperature for representative catalyst batches.

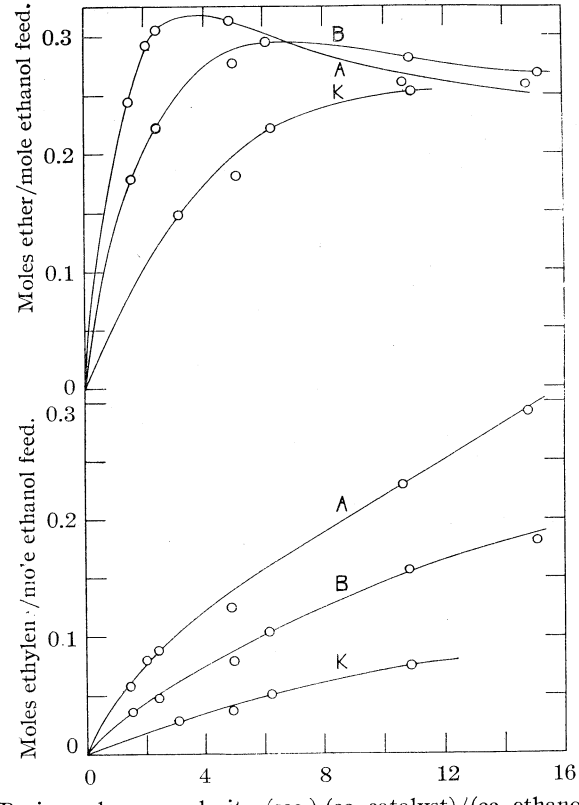


Fig. 2.—Conversion of ethanol to ethylene and ether at 350° reaction temperature.

rate of ethylene production should be zero, since the initial ether concentration is zero. There is no indication of this in the present work or in the results reported by others, except in those of Alvarado.[9d]

It is possible that ethylene is produced by parallel paths, with a fraction coming directly from alcohol and the remainder from ether. In fact, ethylene is formed quite rapidly when ether is passed over the catalyst. From 0.52 mole of ether fed during sixty minutes, 0.39 mole of ethylene and 0.05 mole of alcohol were obtained, at a reaction temperature of 400°. This is roughly 50% more ethylene than would have been obtained from one mole of alcohol under the same conditions. However, the circumstance that the rate of ethylene formation is given satisfactorily by equation (1) and seems, on examination of the conversion curves, not to be directly affected by the changing ether pressure during the course of the reaction, indicates that if ethylene is produced by two paths, the effect of the presence of ether is not exerted independently of the alcohol concentration.

To account for this situation, it seems necessary to assume that a common intermediate such as a carbonium ion may be formed from either alcohol or ether and can then react to form either ethylene or ether

$$C_2H_5OH \underset{+OH^-}{\overset{-OH^-}{\rightleftharpoons}} C_2H_5^+ \xrightarrow{-H^+} C_2H_4$$

$$-C_2H_5O^- \uparrow\downarrow +C_2H_5O^-$$

$$C_2H_5OC_2H_5$$

The appearance of this type of intermediate is indicated by the products formed when higher alcohols are dehydrated over alumina.[10] This mechanism also explains the important role of a water molecule in the reaction as the result of its ability to supply a hydrogen atom to form a hydrogen bridge between the catalyst and an alcohol or ether oxygen atom, thus weakening a carbon to oxygen bond in the organic molecule and creating a favorable situation for carbonium ion formation.[7a] If the carbonium ion concentration is proportional to the surface concentration of alcohol, and the rate-determining step is the conversion of the ion to ethylene, then the rate of ethylene production is proportional to the surface concentration of alcohol and the use of equation (1) is justified.

Specific Activity of the Catalyst.—In Table I are given the values of k_1 and k_1', from equation (1), for the reaction temperatures of 350° and 400°, as well as the ratio of k_1 at 400° to the total

(10) Henne and Matuszak, THIS JOURNAL, **66**, 1649 (1944).

surface area of the catalyst batch. This ratio represents the activity of unit area of surface. For catalysts for which activity changed with use, the values are for the final, stable level of activity.

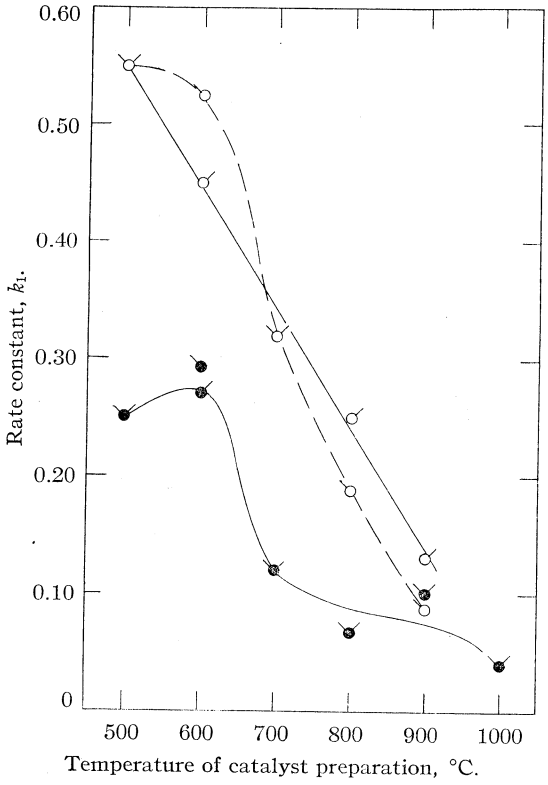


Fig. 3.—Rate constants at 400°: ◔, initial activity of vacuum-treated alumina; ◑, stable (final) activity, vacuum-treated; ◔, initial activity, steam-treated; ◑, stable (final) activity, steam-treated.

In Fig 3 are plotted the values of k_1 at 400°, along with estimates of the original activities for the catalysts showing changing activity. It is clear from Fig. 3 that the effect of steam treatment is markedly to reduce total activity below that resulting from vacuum activation at the same temperature, except perhaps at the highest temperatures where all catalysts show very small activities. That this decrease in activity is not, however, a matter of quality, but only of quantity of surface is illustrated in the plot of specific activity presented in Fig. 4, which demonstrates that the activity per unit area of remaining surface is substantially independent of method of treatment except at 800°, where the vacuum activated surface is distinguished by ability to improve its activity upon use. Further evidence that the effect of water vapor is exercised largely through a change in surface area is given by the data in Table I for catalyst A. Following reaction runs with pure alcohol, this catalyst was employed several times with a feed containing approximately 75 mole per cent. water, at a temperature of 350°. When the catalyst was then again used with pure alcohol feed, the total activity had been reduced, during the runs with high water content, by 33%, while the specific activity had decreased only 10%.

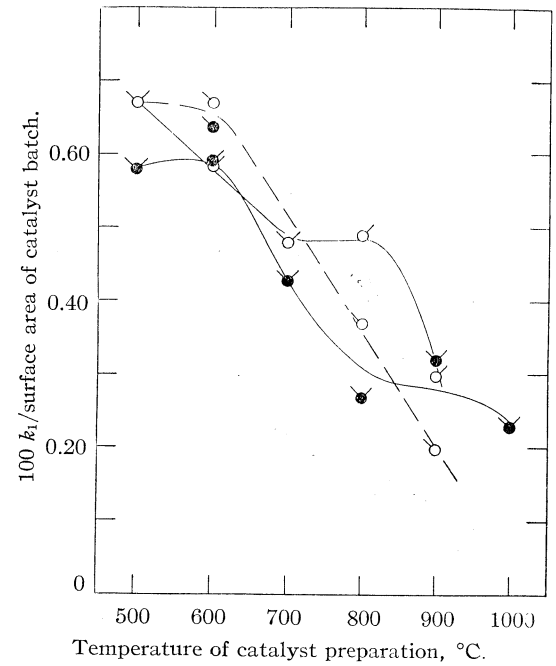


Fig. 4.—Specific activity of catalysts for 400° reaction temperature: ◔, initial activity, vacuum-treated; ◑, stable activity, vacuum-treated; ◔, initial activity, steam-treated; ◑, stable activity, steam-treated.

The specific activity of the catalyst decreases as the temperature of preparation is increased above 600°. This is probably a consequence of increased perfection of the crystal lattice, leading to a decrease in the number of sites at which there exist unsatisfied valence forces. However, it appears from the values of k_1 for 350° and for 400° in Table I that the temperature coefficient of the reaction is very nearly constant, within the experimental error, for all the catalysts studied, and consequently the active sites have approximately the same nature in all the materials.

Summary

1. The catalytic activity of samples of aluminum oxide prepared by heating in vacuum and in water vapor at temperatures between 500 and 1000° has been measured for the dehydration of ethanol at reaction temperatures of 350 and 400°.

2. Both total activity and specific activity decrease as the preparation temperature increases above 600°. Heating with water vapor induces an additional loss of area and activity as compared with heating in vacuum, but the specific activity of the surface is nearly independent of the presence of water.

3. Crystallite growth is a concomitant of the reduction in area produced by high temperatures

and by the presence of water vapor; under the more severe conditions of treatment, this change is accompanied by a decrease in the number of catalytic centers without substantial change in their nature.

4. Some possible mechanisms for the formation of ethylene have been considered in the light of the reaction kinetics, and the ether intermediate theory in its simplest form has been shown to be inapplicable.

5. Changes of activity with use have been explained as the result of changes in the water content of the surface, rather than in surface area.

RECEIVED FEBRUARY 2, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

Copper(II) and Nickel(II) Complex Ions of Hydroxyethylethylenediamine

BY JEAN L. HARVEY,[1] CHARLES I. TEWKSBURY AND HELMUT M. HAENDLER

Complex ions formed by the action of multidentate amines on metal ions are of considerable interest structurally. In a previous article Haendler[2] reported the formation of copper(II) and nickel(II) complex ions with diethylenetriamine, $H_2N(CH_2)_2NH(CH_2)_2NH_2$. Subsequently, Breckenridge[3] isolated specific complexes of this amine and of hydroxyethylethylenediamine (2-(2-aminoethylamine)-ethanol), $H_2N(CH_2)_2NH(CH_2)_2OH$ (abbreviated "hn"). The work on diethylenetriamine led to the conclusion that it probably behaved as a tridentate ligand, a conclusion supported by polarographic studies by Laitinen, *et al.*,[3a] and that the copper and nickel complexes were structurally similar.

Using hydroxyethylethylenediamine, however, Breckenridge was able to isolate copper complexes with a copper:hn ratio of 1:1 and 1:2 from 95% ethanol and a single nickel complex with a nickel:hn ratio of 1:3 from absolute ethanol. Spectrophotometric methods have now been applied to the study of the ions formed in water solution by copper(II) and nickel(II) ions and this amine. It has been found that copper forms the complex ions $[Cu(hn)]^{++}$, $[Cu(hn)_2]^{++}$ and $[Cu(hn)_4]^{++}$, and that nickel forms the ions $[Ni(hn)]^{++}$ and $[Ni(hn)_2]^{++}$.

The results for copper are compatible with the structures suggested by Breckenridge. In $[Cu(hn)]^{++}$ and $[Cu(hn)_2]^{++}$, the amine probably acts as a bidentate ligand, the coördinating power of the hydroxyl group being slight. The shape of the spectral curves for $[Cu(hn)_4]^{++}$ indicates low stability of the ion, consistent with a nonchelated structure involving four primary amine groups. The complex is apparently stable only in solution.

Attempts to identify the ions formed between copper(II) and diethanolamine (2,2′-dihydroxydiethylamine), $HO(CH_2)_2NH(CH_2)_2OH$ (abbreviated "den"), indicate that there are ions with copper:den ratios of both less than 1:3 and greater than 1:3. If the amine were coördinated through both the amine and hydroxyl groups, a ratio of 1:2 would be the maximum expected. No ratio greater than 1:3 could be expected if coördination were through the hydroxyl groups only. It is thus probable that the diethanolamine is coordinated only through the secondary amine group. The ions are stable only in the presence of excess amine, indicating lower coördinating power than with primary amine groups. This supports the proposal that only primary amine groups are involved in the 1:4 ion of hydroxyethylethylenediamine and that both amine groups participate in the formation of 1:1 and 1:2 ions.

The $[Ni(hn)]^{++}$ and $[Ni(hn)_2]^{++}$ are assumed to be similar in structure. No evidence could be found of an ion corresponding to $[Ni(hn)_3]Cl_2$ isolated by Breckenridge. There is evidence, however, that the solvent affects the coördinating power of the amine. Mann[4] reported that only two moles of diaminopropanol would coördinate to nickel in water solution. The compound $[Ni(hn)_2]HgI_4$ has been prepared by reaction in

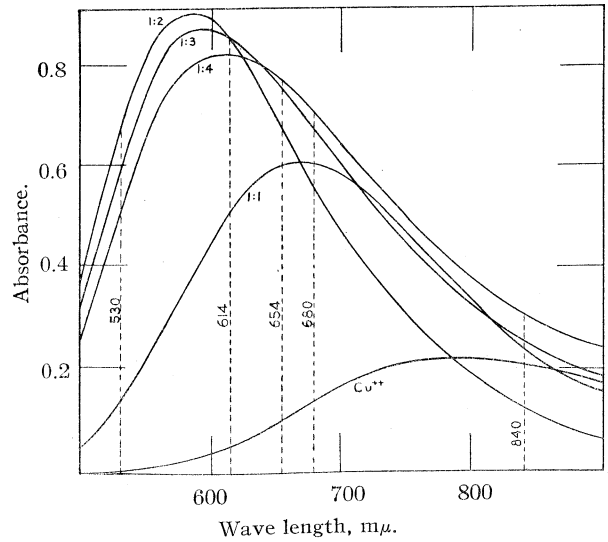


Fig. 1.—The absorption spectra of solutions of Cu^{++} and hn.

(1) This paper represents in part a thesis presented by J. L. Harvey to the University of New Hampshire in partial fulfillment of the requirements for the degree of Master of Science.

(2) Haendler, THIS JOURNAL, **64**, 686 (1942).

(3) Breckenridge, *Can. J. Research*, **B26**, 11 (1948).

(3a) Laitinen, *et al.*, THIS JOURNAL, **71**, 1550 (1949).

(4) Mann, *J. Chem. Soc.*, 2904 (1927).

water solution, using an amount of amine in excess of that needed for the 1:3 compound.

Experimental

Determination of composition was made by the method of continuous variations, as described by Vosburgh and Cooper.[5] Maxima of curves obtained by plotting the amount of ligand solution (x) against the difference (Y) between observed absorbance and that calculated for no reaction give directly the compositions of the ions present, if both components are in solutions of equimolar concentration.

All absorption spectra were measured with the Beckman DU Spectrophotometer, using 1-cm. Corex cells. Measurements were made directly in terms of absorbance.[6]

Hydroxyethylethylenediamine was purified by vacuum distillation, b. p. 130.5° at 11 mm. Solutions of the amine were standardized against hydrochloric acid, using brom thymol blue. Diethanolamine was also distilled, b. p. 155–157° at 12 mm.

Copper(II) Complex Ions.—A 0.100 M copper(II) ion solution was prepared from copper(II) acetate monohydrate, used without further purification. Five drops of 6 M acetic acid per liter was added to prevent hydrolysis. The absorption spectra were measured for solutions 0.010 M in copper ion and, in addition, 0.010, 0.020, 0.030, 0.040 and 0.060 M in hydroxyethylethylenediamine, corresponding to molar ratios of 1:1, 1:2, 1:3, 1:4 and 1:6. The spectra are shown in Fig. 1. The 1:6 curve closely resembled the 1:4 curve.

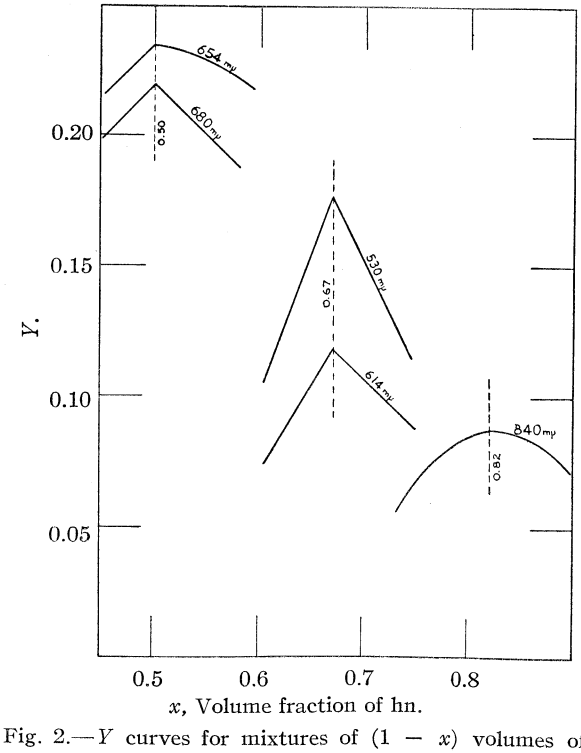


Fig. 2.—Y curves for mixtures of $(1 - x)$ volumes of 0.010 M Cu^{++} and x volumes of 0.010 M hn solutions.

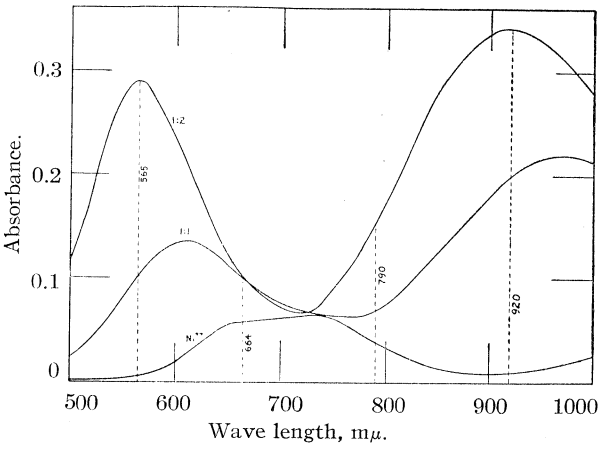


Fig. 3.—The absorption spectra of solutions of Ni^{++} and hn.

Further measurements were made at 530, 614, 654, 668, 680 and 840 mμ, using variable amounts of 0.010 M solutions. The Y curves are shown in Fig. 2. The maxima indicate the presence of the ions $[Cu(hn)]^{++}$, $[Cu(hn)_2]^{++}$ and $[Cu(hn)_4]^{++}$.

Nickel(II) Complex Ions.—A 0.667 M nickel (II) sulfate solution was prepared from the hexahydrate, which had been treated for removal of cobalt.[7] Five drops of 3 M sulfuric acid per

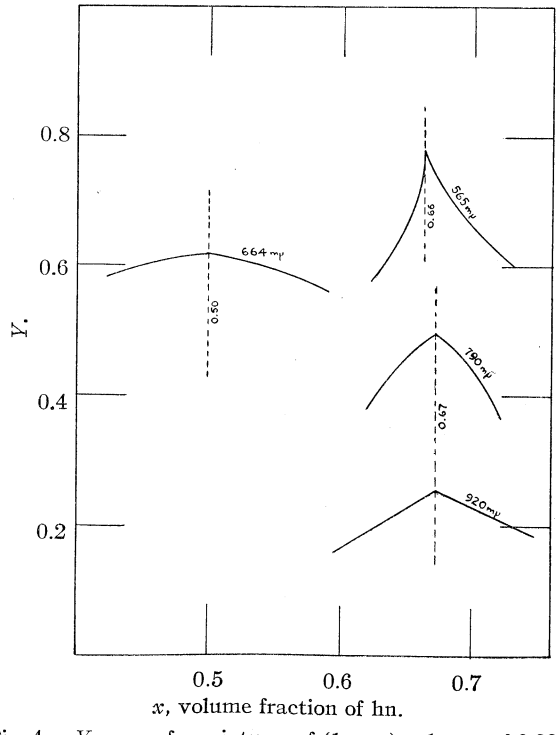


Fig. 4.—Y curves for mixtures of $(1 - x)$ volumes of 0.334 M Ni^{++} and x volumes of 0.334 M hn solutions.

(5) Vosburgh and Cooper, THIS JOURNAL, **63**, 437 (1941).

(6) Mellon, *Anal. Chem.*, **21**, 3 (1949).

(7) Deakin, Scott and Steele, *Z. physik. Chem.*, **69**, 126 (1909).

liter was added. A 0.667 *M* amine solution was used. By dilution, solutions 0.067 *M* in nickel ion and of the proper amine concentration for ratios of 1:1, 1:2, 1:3, 1:4 and 1:6 were prepared. The absorption spectra of these solutions are shown in Fig. 3. The spectra of the 1:3, 1:4 and 1:6 ratios are almost identical to the 1:2 curve.

The *Y* curves were obtained from measurements at 565, 664, 790 and 920 mμ, using 0.334 *M* solutions. These curves, Fig. 4, show the presence of the ions $[Ni(hn)]^{++}$ and $[Ni(hn)_2]^{++}$.

The compound $[Ni(hn)_2]HgI_4$ was prepared by adding an excess of a solution of mercury(II) iodide in excess potassium iodide to a mixture of nickel sulfate and hydroxyethylethylenediamine. The pale blue-violet precipitate was washed with dilute amine solution and with ethanol. Nickel was determined as anthranilate, after removal of mercury with hydrogen sulfide, and mercury was determined as $[Cu(en)_2]HgI_4$.[8]

Anal. Calcd. for $[Ni(hn)_2]HgI_4$: Ni, 6.02; Hg, 20.6. Found: Ni, 6.09, 5.92; Hg, 20.1, 20.2.

Copper(II) Complex Ions of Diethanolamine.—The absorption spectra were measured for solutions 0.010 *M* in copper ion and containing diethanolamine in ratios of 1:3, 1:4, 1:6 and 1:8. The spectra are shown in Fig. 5. The 1:8 curve resembled the 1:6. Solutions of lower ratio could not be prepared because of precipitation of hydroxide. The 1:3 solution hydrolyzed slowly. Uncorrected *Y* curves for the higher values of *x* are shown in Fig. 6. The maximum at 0.82 suggests the 1:4 ion for the measurement at 530 mμ. At the other wave lengths the absence of maxima indicate that the ions formed are less than 1:3.

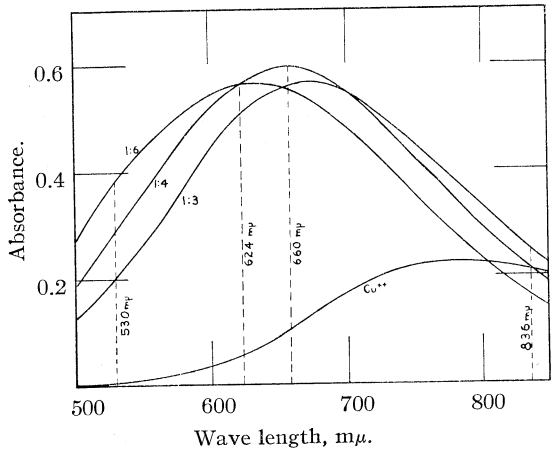


Fig. 5.—Absorption spectra of solution of Cu^{++} and diethanolamine.

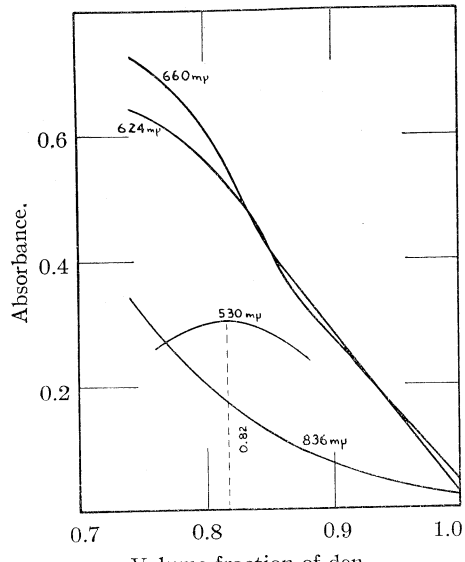


Fig. 6.—Absorption spectra for mixtures of $(1 - x)$ volumes of 0.010 *M* Cu^{++} and *x* volumes of 0.010 *M* diethanolamine.

Summary

Complex formation between copper(II) and nickel(II) ions and hydroxyethylethylenediamine has been studied spectrophotometrically.

The presence of the ions $[Cu(hn)]^{++}$, $[Cu(hn)_2]^{++}$, $[Cu(hn)_4]^{++}$, $[Ni(hn)]^{++}$ and $[Ni(hn)_2]^{++}$ has been shown.

DURHAM, NEW HAMPSHIRE RECEIVED JUNE 18, 1949

(8) Spacu and Suciu, *Z. anal. Chem.*, **77**, 334 (1929).

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF CALIFORNIA]

Cation Complexes of Compounds Containing Carbon–Carbon Double Bonds. IV. The Argentation of Aromatic Hydrocarbons[1]

BY L. J. ANDREWS AND R. M. KEEFER

Detailed information concerning the argentation of aromatic hydrocarbons is lacking. The results of studies of the phase relationships in the systems silver perchlorate–benzene–water and silver perchlorate–toluene–water[2] suggest that the tendency for such complex formation is appreciable.

In the present investigation, which represents an extension of the work reported previously,[3] the solubilities of several aromatic hydrocarbons in aqueous silver nitrate solutions have been measured. The data have been interpreted on the assumption that from each hydrocarbon two water-soluble complexes, $AgAr^+$ and Ag_2Ar^{++}, are formed.[4] Equilibrium constants for reactions leading to their formation have been calculated.

Experimental

The Aromatic Hydrocarbons.—All of the hydrocarbons used were of the best grade obtainable from Eastman Kodak Co. The benzene and toluene were washed successively with concentrated sulfuric acid, water and dilute sodium hydroxide and, after drying, were fractionated. Cuts of b. p. 80.1° (benzene) and 110.4° (toluene) were used in the solubility experiments. The xylenes were fractionated and samples of the following b. p. used: *o*-xylene (144.3–144.5°), *m*-xylene (139.5°), *p*-xylene (138.5°). The naphthalene was recrystallized from ethanol, m. p. 80.5°. The biphenyl was used directly, m. p. 70.0–70.5°. The diphenylmethane was purified by fractional freezing,[5] m. p. 25.0°. Phenanthrene was recrystallized twice from ethanol, m. p. 101.0°.

The Solubility Measurements.—To aqueous silver nitrate solutions of varying silver ion concentration contained in glass-stoppered Erlenmeyer flasks were added 0.1–1.0-g. samples of aromatic hydrocarbon. In all cases sufficient potassium nitrate was contained in the aqueous solution to maintain an ionic strength of unity. The mixtures were rotated twenty hours in a constant temperature bath at 25.0° to saturate the aqueous phase with hydrocarbon.

Pipet samples (5–20 ml.) of the aqueous phase were then removed and extracted with measured volumes of hexane (10–50 ml.) by shaking in glass-stoppered Erlenmeyer flasks. The optical density of the hexane phase was measured against a hexane blank on the Beckman spectrophotometer at a wave length and slit width setting for each particular hydrocarbon for which values of the molecular extinction coefficient of such solutions had previously been determined. In all cases investigated one extraction with hexane removed all of the hydrocarbon, both free and complexed, from the aqueous phase, as was indicated by the fact that hexane samples used in a second extraction of the aqueous phase gave negligible optical density readings. The volumes of the aqueous and hexane phases were adjusted insofar as possible to obtain optical density readings between 0.200 and 0.800. Thus the data were available to calculate the aromatic hydrocarbon content of the saturated aqueous solutions.

Samples of aqueous silver nitrate and potassium nitrate were extracted with hexane. The hexane phase contained no light absorbing materials as evidenced by measurement of its spectrum against a hexane blank.

The hexane was Skellysolve B rendered optically pure for purposes of the experiments by two washings with fuming sulfuric acid, followed by washings with water and dilute sodium hydroxide solution, drying and distillation.

The wave lengths and slit width settings used in the optical density measurements of the hexane solutions of the hydrocarbons with corresponding values of the molecular extinction coefficients are given in Table I. In each case the solutions obeyed Beer's law. Included in this table are values of the water solubilities of the hydrocarbons at 25.0°, determined by the method described above as a check on the extraction procedure, with corresponding data from the literature.

Attempts at a determination of the argentation constants for anthracene by this method were unsuccessful. Reproducible results were not obtainable, since difficulty was encountered with contamination during sampling of the saturated solutions.

To check on the possibility that silver nitrate may have distributed to the aromatic hydrocarbon phase in the solubility experiments, equal volumes of benzene and 1 *N* silver nitrate solution were shaken for several hours. Samples of the benzene were removed and shaken with dilute aqueous potassium chloride. No silver chloride was formed.

Results

The solubility of the several hydrocarbons in aqueous solutions increased with increasing silver ion concentration to a greater degree than was consistent with the supposition that only a 1–1 complex, $AgAr^+$, was formed. Accordingly the data were interpreted on the assumption that equilibria (1) and (2) were established in these solutions.

$$Ag^+ + Ar = AgAr^+ \quad K_1 = (AgAr^+)/(Ag^+)(Ar) \quad (1)$$

$$Ag^+ + AgAr^+ = Ag_2Ar^{++} \quad K_2 = (Ag_2Ar^{++})/(Ag^+)(AgAr^+) \quad (2)$$

An additional constant K was defined in terms of the several species postulated as present in the saturated aqueous solutions as follows

$$K = \frac{(Ar_c)}{[(Ag_t^+) - (Ar_c) - (Ag_2Ar^{++})](Ar)} = \frac{(AgAr^+) + (Ag_2Ar^{++})}{[(Ag_t^+) - (AgAr^+) - 2(Ag_2Ar^{++})](Ar)} \quad (3)$$

$$= K_1 + K_1K_2(Ag^+)$$

where

(Ar_c) = the molar concentration of complexed hydrocarbon = $(Ar_t) - (Ar)$

(Ar_t) = the molar concentration of all hydrocarbon-containing species

(Ar) = the molar concentration of free hydrocarbon = the concentration of hydrocarbon in its saturated solution in 1 *N* potassium nitrate

(Ag^+_t) = the molar concentration of silver ion in free and complexed form

(1) Presented before the Organic Division of the American Chemical Society, San Francisco, California, March, 1949.

(2) Summarized in Seidell, "Solubilities of Inorganic and Metal-Organic Compounds," Third Edition, Vol. I, D. Van Nostrand Company, Inc., New York, N. Y., 1940.

(3) For the preceding paper in this series see Keefer, Andrews and Kepner, THIS JOURNAL, **71**, 2381 (1949).

(4) The symbol Ar is used to represent the aromatic hydrocarbon molecule.

(5) DeVries and Stow, THIS JOURNAL, **61**, 1797 (1939).

TABLE I

EXTINCTION COEFFICIENTS OF HEXANE SOLUTIONS AND WATER SOLUBILITIES AT 25.0° OF THE HYDROCARBONS

Hydrocarbon	Optical properties: λ, mμ	Slit width, mm.	ε	Solubility: Measured g./100 cc. satd. soln.	Literature values[a] g./100 cc. H_2O
Benzene	250 or 262	0.40 or 1.425	106 or 28.5	0.174	0.180
Toluene	260	1.27	183	.053	.054
o-Xylene	263	0.36	267	.0204	.013[b]
m-Xylene	265	.36	268	.0173	
p-Xylene	275	.35	554	.0200	
Naphthalene	275	.34	5.50×10^3	.00315	.0030
Biphenyl	252	.48	1.58×10^4	5.94×10^{-4}	.....
Diphenylmethane	222	1.10	7.69×10^3	1.41×10^{-4}	.....
Phenanthrene	252	0.42	7.16×10^4	9.94×10^{-5}	1.6×10^{-4} (27°)[c]

[a] Values, except as noted, from Seidell, "Solubilities of Organic Compounds," Third Edition, Volume II. [b] For a xylene mixture of unrecorded composition. [c] Results of Davis, Krake and Clowes, THIS JOURNAL, **64**, 108 (1942), as based on the nephelometric method.

To calculate K the concentrations of substances as defined above were substituted in the left-hand expression of equation (3). It was assumed that (Ag_2Ar^{++}) was sufficiently small as compared to the concentration of uncomplexed silver ion so that it could be neglected in calculating K. In every case the K_2 values obtained as described below indicated that (Ag_2Ar^{++}) was very small as compared to uncomplexed silver ion concentration, so that the values of K needed no correction.

Values of K calculated from the data recorded for each compound are summarized in Table II.

TABLE II

THE SOLUBILITY OF THE HYDROCARBONS IN AQUEOUS SILVER NITRATE AT 25.0°

(Ag^+) mole/liter	(Ar) mole/liter × 10^3	K	(Ar) mole/liter × 10^3	K	(Ar) mole/liter × 10^6	K
	Benzene		Toluene		Phenanthrene	
0.000	16.5	..	4.30	..	4.05	...
.100	20.5	2.52	5.55	2.94	....	...
.200	24.3	2.46	6.93	3.10	8.10	5.00
.400	33.3	2.66	9.68	3.18	14.52	6.45
.600	42.1	2.70	12.8	3.34	22.5	7.57
.800	51.0	2.82	...	..	33.0	8.94
1.000	62.0	2.90	19.4	3.57	45.6	10.27
	o-Xylene		*m*-Xylene		*p*-Xylene × 10^3	
0.000	1.48	..	1.12	..	1.29	...
.100	1.92	2.99	1.48	3.16	1.64	2.72
.200	2.35	2.96	1.86	3.28	2.02	2.86
.400	3.40	3.26	2.66	3.42	2.81	2.96
.600	4.51	3.43	3.52	3.57	3.72	3.15
.800	5.75	3.62	4.52	3.79	4.71	3.32
1.000	7.06	3.79	5.60	4.00	5.78	3.50
	Naphthalene		Biphenyl × 10^5		Diphenylmethane × 10^4	
0.000	0.191	..	2.46	..	0.781	...
.200	.328	3.58	4.82	4.80	1.43	4.20
.400	.514	4.23	7.90	5.53	2.32	4.93
.600	.746	4.85	11.56	6.17	3.41	5.61
.800	.986	5.20	16.58	7.18	4.75	6.35
1.000	1.31	5.86	21.97	7.94	6.30	7.06

If reaction (1) were the only one contributing appreciably to complex formation, K should equal K_1 and values of K for any particular hydrocarbon should be independent of silver ion concentration of the medium. The marked increase in K values observed indicates an appreciable contribution of reaction (2). As would be expected, if equations (1) and (2) account for all complexes formed, plots of K against the silver ion concentration in the saturated solutions should give straight lines. This was found to be true for all the compounds investigated. In such plots the ordinate intercept is K_1, and K_2 may be obtained from the slope of the lines which is equal to K_1K_2. The values of K_1 and K_2 obtained are given in Table III.

TABLE III

THE EQUILIBRIUM CONSTANTS FOR ARGENTATION OF THE HYDROCARBONS AT 25.0°

Hydrocarbon	K_1	K_2
Benzene	2.41	0.212
Toluene	2.95	.214
o-Xylene	2.89	.315
m-Xylene	3.03	.320
p-Xylene	2.63	.331
Naphthalene	3.08	.909
Biphenyl	3.94	1.01
Diphenylmethane	3.46	1.04
Phenanthrene	3.67	1.80

The Structures of the Complexes.—The complex formed between silver ion and a molecule containing an unconjugated double bond has been described[6] in terms of resonance formulas

$$>C\overset{+}{-}C< \qquad >\overset{+}{C}-C< \qquad >C{=}C<$$
$$\diagdown\ \diagup \qquad\qquad \diagup\ \diagdown \qquad\qquad\qquad \diagdown$$
$$Ag \qquad\qquad Ag \qquad\qquad\qquad Ag^+$$

A similar structure in which silver ion is bonded to one particular double bond of a ring might be postulated for aromatic systems. This seems unattractive since such a structure would entail the loss of considerable ring resonance energy within the aromatic system itself. An attractive

(6) Winstein and Lucas, THIS JOURNAL, **60**, 836 (1938).

modification of the above structure, as applied to the singly argentated benzene molecule, pictures the silver ion as being located above the plane of the ring at a position equidistant from the six-ring carbon atoms. This silver ion would be in a position to utilize the π-electrons of the ring to form covalent bonds of the type indicated above with any of the six ring carbons. The structure of the complex would then be represented by eighteen equivalent single-bonded structures in addition to two no-bond structures as contributors to a resonance hybrid.[6,7] The loss of ring-resonance energy when such a complex is formed would be compensated to a large degree by the resonance energy associated with the complex itself. In the doubly argentated benzene complex the second silver ion could bond to the plane of the ring from the side opposite to which the first silver ion is attached. A synchronized resonance[8] in which two silver–carbon bonds resonate among six equivalent positions might then exist. One can calculate, using the tetrahedral covalent radii for the ring-carbon atoms and for silver,[9] that the silver ion in the complex would not penetrate the plane of the ring, thus eliminating the possibility of steric interference between two silver ions in the doubly argentated complex. It is interesting to note that the covalent radius of silver is sufficiently large so that the silver ion would overlap the perimeter of the carbon–carbon bond skeleton of the ring. With these postulates as to structure in mind it is interesting to consider the tendencies for complex formation of the several hydrocarbons.

It appears that a methyl substituent enhances slightly the basic strength of the benzene ring, as reflected in the values of the equilibrium constants for benzene and toluene. The presence of two methyl groups on the ring (see the data for the xylenes) apparently causes no marked increases in basicity over that for toluene, which suggests that a steric effect opposing complex formation may be present in these molecules.[10]

In the case of the multiple ring systems the K_1 values are higher than those for benzene. One might expect for biphenyl, in which the two phenyl groups are on the average in the same plane,[11] a K_1 value approximately double that for benzene. The interaction between rings in biphenyl is at least partially responsible for the fact that K_1 observed is less than the predicted value.

For diphenylmethane, in which the two rings are not coplanar, steric influences should effectively eliminate one of the four positions of attack available to silver ion. On this basis K_1 should be approximately $^3/_2$ K_1 for benzene, and the observed value is only slightly less than the predicted value.

A lower value of K_1 is obtained for naphthalene than for biphenyl. Since there are only five double bonds in naphthalene as compared to six in biphenyl, naphthalene might be expected to be less basic than biphenyl.

The K_1 value for phenanthrene is greater than that for naphthalene but less than that for biphenyl. In addition to the possibility that silver ion may coördinate with any of the three rings in this molecule, the possibility that it may coördinate with the carbon–carbon bond at the 9,10-position should be considered. This bond has a high degree of double bond character, and in other reactions preferential substitution or addition occurs at this point.[12]

The K_2 values for the single ring compounds are small as compared to those for multiple-ring systems. This seems reasonable since the presence of a silver ion in $AgAr^+$ must considerably reduce the basicity of the ring with respect to addition of a second silver ion. This effect would be much less pronounced in the multiple-ring systems since the second silver may bond to a ring other than that to which the first silver ion is attached.

Assuming that the first silver ion attached to benzene does not alter the ability of a molecule to coördinate a second silver ion, the predicted value of K_2 for benzene (on a statistical basis) would be $^1/_4$ K_1. The observed value is about $^1/_3$ the predicted value.

There are three positions at which a silver ion might add to the $AgAr^+$ complex of biphenyl. The position on the side of the ring opposite to that at which the first silver ion is attached might be expected to be roughly equivalent in base strength to the $AgAr^+$ complex of benzene. Two alternate bonding positions are available on the other ring, each of which should be roughly equivalent in basicity to one of the four positions available when silver ion coördinates with biphenyl. The ease of loss of a silver ion should be twice as great from Ag_2Ar^{++} as from $AgAr^+$. Combining the above observations one might predict that K_2 for biphenyl would be $^1/_4$ K_1 for biphenyl plus K_2 for benzene. The observed value of 1.01 is less than the value of 1.2 predicted on the above basis.[13]

(7) Taufen, Murray and Cleveland, THIS JOURNAL, **63**, 3500 (1941).

(8) Pauling, *J. Chem. Soc.*, 1461 (1948).

(9) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1940.

(10) Benesi and Hildebrand, THIS JOURNAL, **70**, 2832 (1948), have described a 1-1 complex for certain aromatic hydrocarbons and iodine and report evidence that increasing methyl substitution on the benzene ring appears to result in an increased tendency for complex formation. Undoubtedly these iodine complexes are closely associated structurally with those under consideration in this report. It is further interesting in this connection to note that if benzene solutions of iodine are treated with anhydrous silver salts, reaction occurs to yield iodobenzene and silver iodide; *cf.* Birckenbach and Goubeau, *Ber.*, **66B**, 1280 (1933). One cannot overlook the possibility that these silver complexes may be very closely related structurally to the transition state intermediates in certain aromatic substitution reactions; *cf.* Dewar, *J. Chem. Soc.*, 777 (1946); 463 (1949).

(11) Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 160.

(12) Price, THIS JOURNAL, **58**, 2101 (1936).

(13) This treatment assumes that the front and rear faces of the free ring in the $AgAr^+$ complex of biphenyl offer equivalent bonding positions for the second silver ion. Considering the coplanarity of biphenyl this assumption is open to question insofar as the silver–silver repulsions would be different for the two possible forms of

A maximum value of K_2 for diphenylmethane of $^1/_3$ K_1 (for diphenylmethane) is predicted if it is assumed that the position sterically prohibited is the other side of the ring containing the first silver ion. The observed value of K_2 is 1.04 as compared to a maximum calculated value of 1.15.

In attempting to predict K_2 values for the fused ring systems, as represented by naphthalene and phenanthrene one cannot overlook the possibility that structures for Ag_2Ar^{++} in which two silver ions are coördinated with adjacent rings on the same side of the plane of the molecule are sterically unfavorable. Neglecting such structures values of K_2 may be calculated which are considerably less than the observed values. For fused ring systems, the structural nature of the Ag_2Ar^{++} complex may be somewhat different from those suggested for non-fused ring molecules.

Ag_2Ar^{++} in which one silver ion is coördinated with each ring. The method used in predicting a value for K_2 is similar to that used in approximating dissociation constants for dibasic acids; *cf.* Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall Inc., New York, N. Y., 1945, p. 200.

Summary

By measurement of the solubilities of several aromatic hydrocarbons in aqueous silver nitrate solutions, evidence has been obtained for the formation of two water-soluble complexes, $AgAr^+$ and Ag_2Ar^{++}. Equilibrium constants for the reactions to form these complexes at 25° have been calculated. Structures for the complexes are suggested, and the tendencies for the various hydrocarbons to undergo argentation have been considered in terms of these structures.

A method of analysis for the aromatic hydrocarbon content of aqueous solutions is described in which the hydrocarbon is extracted from the solution with hexane, and its concentration in the hexane phase determined by spectrophotometric measurement.

DAVIS, CALIFORNIA RECEIVED MAY 3, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Absorption Spectra of ortho-Substituted Aldehydes. I. The *o*-Hydroxynaphthaldehydes[1]

BY NORTEN C. MELCHIOR[2]

The difficulties encountered in attempts to correlate the molecular structures of compounds with their absorption spectra makes careful comparisons of the spectra of closely related compounds important. During an investigation[3] of some of the metal derivatives of the *o*-hydroxynaphthaldehydes, the absorption spectra of these aldehydes and their negative ions was measured in methanol–water solutions. The striking differences in these spectra led to this extension of the measurements.

Experimental

Absorption Measurements.—All measurements were made with a Beckman model DU spectrophotometer in silica cells having a 10-mm. light path. The temperature of the cells was controlled by hollow metal plates, pierced by a small opening for the light beam, which were placed on opposite sides of the cell compartment. Water from a controlled temperature bath was circulated through these plates. A slow stream of dry air passed into the cell compartment prevented fogging of the cell windows at temperatures below the dew point of the laboratory air. Small differences in the measurements due to the volume change of the solvent were eliminated by making final dilutions at the temperature at which the spectrum was run, or by calculation from the measured temperature–volume coefficient of the solvent. Measurements at a given wave length were made with the same slit width, which was kept as small as possible.

Solvents.—Methanol was reagent grade, octane and heptane mixtures were purified by standard procedures. In all cases blanks were prepared from the same sample of solvent used for dissolving the compound studied.

Aldehydes.—The preparation of these compounds has been reported.[3,4] Each sample was sublimed several times at pressures below 0.001 mm., once immediately before use.

Results.—The more pertinent results are shown in Figs. 1 to 5. It is evident in Fig. 1 that the first band of the negative ion of 3-hydroxy-2-naphthaldehyde appears at a lower frequency but with considerably lower intensity, than do those of its isomers. It is easily seen by comparing Figs. 2, 3 and 4 that this is also the case in the neutral molecule, regardless of solvent. It is also apparent that solvent change has a greater effect on the spectrum of the 3-2-compound than upon that of either of its isomers. In addition, Fig. 5 shows the striking effect of temperature change on the absorption spectrum of the 3-2-compound in 80 mole per cent. methanol.

(1) Presented at the meeting of the American Chemical Society in San Francisco, March, 1949.

(2) Present address: Stritch School of Medicine, Loyola University, Chicago 12, Illinois.

(3) (a) Calvin and Melchior, THIS JOURNAL, **70**, 3273 (1948); (b) Thesis, N. C. Melchior, University of California, 1946.

(4) Arnold and Sprung, THIS JOURNAL, **60**, 1163–1164 (1938).

This effect is of a different order of magnitude than that shown by its isomers, or indeed by the compound itself in the other solvents studied. These latter effects would not be visible on the scale used.

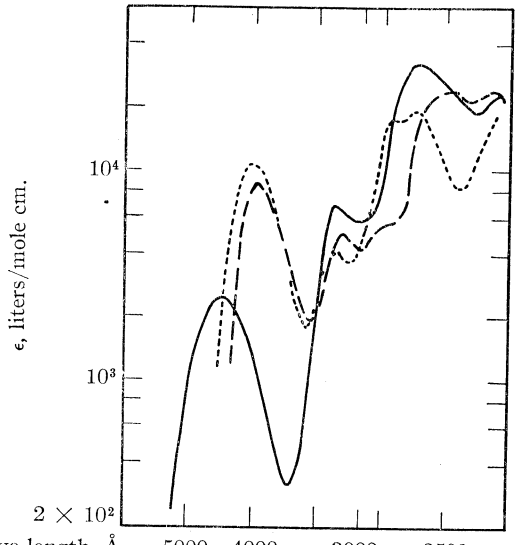


Fig. 1.—Absorption spectra of the negative ions of *o*-hydroxynaphthaldehydes at 35° in 95 mole % water, 5 mole % methanol, 0.1 *M* OH^-: solid line, 3-formyl-2-naphthoxide; dashed line, 1-formyl-2-naphthoxide; dotted line, 2-formyl-1-naphthoxide.

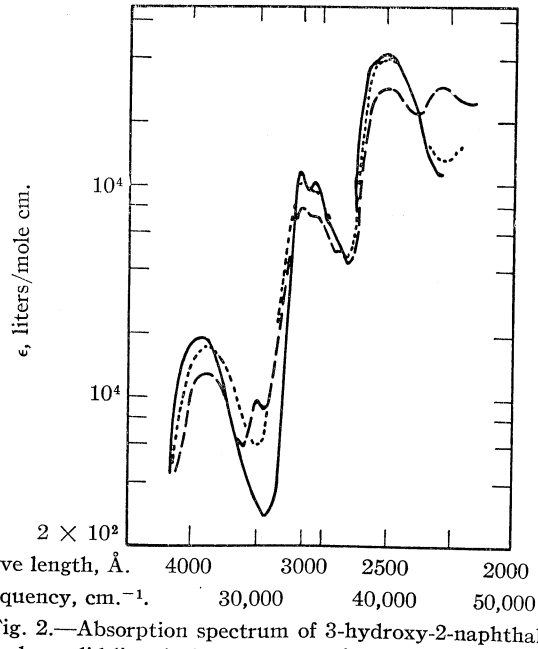


Fig. 2.—Absorption spectrum of 3-hydroxy-2-naphthaldehyde: solid line, in heptanes at 25°; dashed line, in 80 mole % methanol, 20 mole % water, 0.01 *M* hydrochloric acid at 35°; dotted line, in 5 mole % methanol, 95 mole % water, 0.01 *M* hydrochloric acid at 35°.

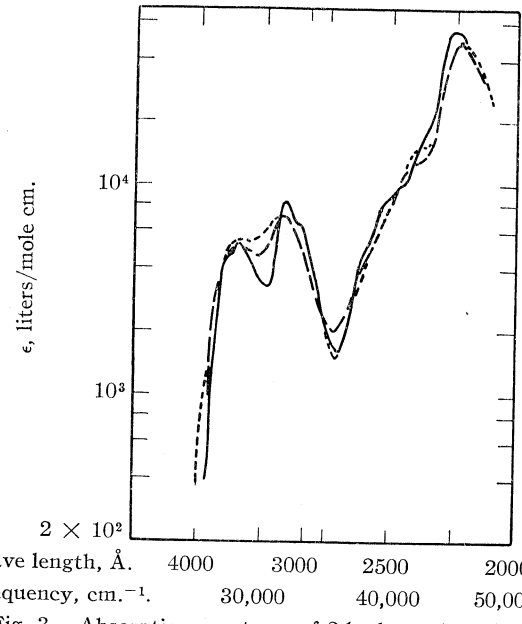


Fig. 3.—Absorption spectrum of 2-hydroxy-1-naphthaldehyde at 35°: solid line, in octane; dashed line, in 80 mole % methanol, 20 mole % water, 0.01 *M* hydrochloric acid; dotted line, in 5 mole % methanol, 95 mole % water, 0.01 *M* hydrochloric acid.

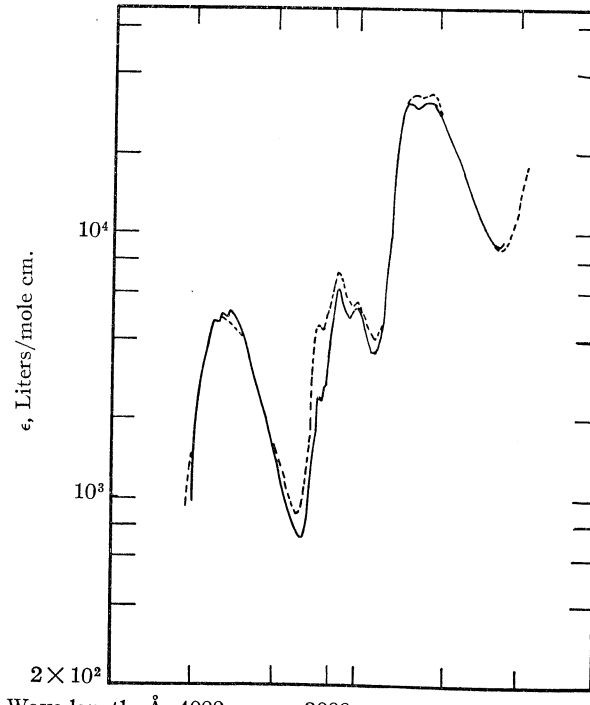


Fig. 4.—Absorption spectrum of 1-hydroxy-2-naphthaldehyde: solid line, in heptanes at 25°; dotted line, in 80 mole % methanol, 20 mole % water, 0.01 *M* hydrochloric acid at 35°.

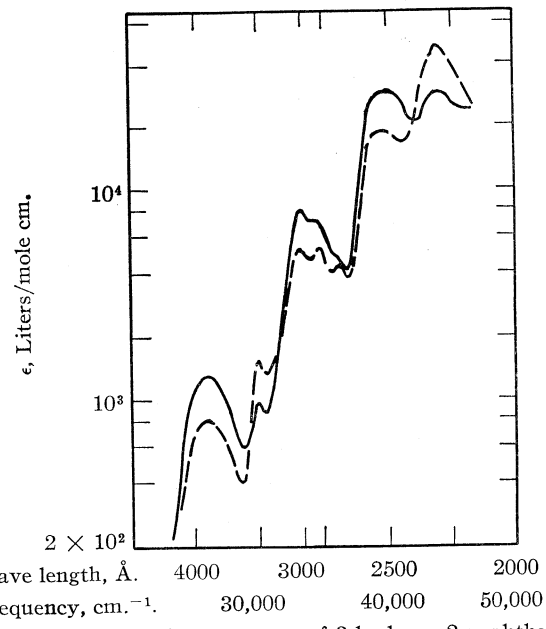
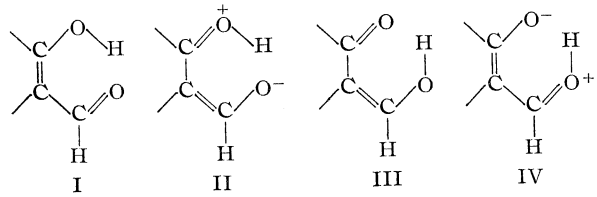


Fig. 5.—Absorption spectrum of 3-hydroxy-2-naphthaldehyde in 80 mole % methanol, 20 mole % water, 0.01 *M* hydrochloric acid; solid line, at 35°; broken line, at 2°.

Discussion

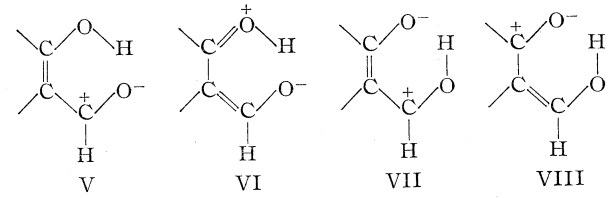
It should be possible to account for some of the observed differences in the spectra of these compounds on the basis of reasonable assumptions concerning the nature of the ground and excited states of the molecules. If we consider their common naphthalene nucleus, we find that its major resonance forms are such that the bond between carbon atoms 1 and 2 has about $^2/_3$ double bond character while that between carbon atoms 2 and 3 has only about $^1/_3$ double bond character. In the molecules considered, hydrogen bonding will be an important additional factor, so that we may expect structures such as the following to make contributions to the ground state of the molecule[5]:



I II III IV

Structures I and IV do not require a double bond between the carbon atoms holding the functional groups, but structures II and III require that a double bond be available there. Therefore, as a first approximation, we would expect the contribution of forms II and III to the resonance hybrid to be less in the case of 2-hydroxy-3-naphthaldehyde than in either of its ortho-isomers, and that therefore its ground state would be of higher energy than those of its isomers.

It is reasonable to assume that the low energy absorption band (low frequency, long wave length) is associated with absorption by the carbonyl group and that the corresponding upper state may be the hybrid with important contributions from



V VI VII VIII

It is reasonable to assume that structures VI and VIII are so much more important in the upper state than their analogs in the lower state, that, although one would still expect the upper state of the 3-2 compound to be of somewhat higher energy than that of either of its isomers, due in part to differences in the nuclear resonance forms, this energy difference will be reduced.

From this it follows that the energy difference between the upper and lower states of the 3-2 compound will be less than in its isomers; therefore its absorption maximum for this band should appear at a lower frequency, as observed. This postulated energy diagram is given in Fig. 6.

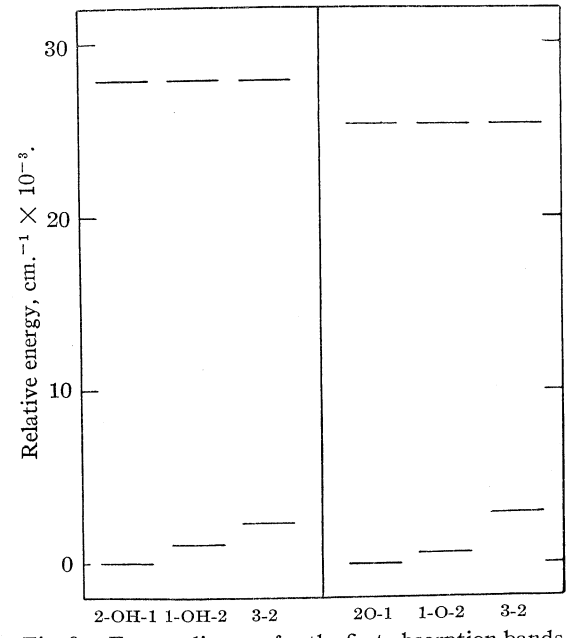


Fig. 6.—Energy diagram for the first absorption bands of hydroxynaphthaldehydes: left, in hydrocarbon solvents; right, in 0.1 *N* sodium hydroxide.

Second, from the author's assumption concerning the nature of the upper state of the low energy band of these compounds, it follows from resonance theory that the shape (*i. e.*, the bond distances and angles) of the ground state of the 1-2-

(5) Regardless of the fine structure of the hydrogen bond, its presence must decrease the energy of the molecule and this discussion does not postulate or depend on the fine structure.

and 2-1-compounds more closely approaches that of the upper state than does that of the 3-2-compound. From the Franck–Condon principle that the absorption of light occurs in a fraction of time much shorter than that required for atom vibrations, it follows that, other factors being equal, the more completely the shape of the molecule in the lower state corresponds to the shape of its upper state, the higher is the probability of light absorption. Thus one would predict that the probability of light absorption would be lower *for this band* in the 3-2 compound than for its isomers. This lowered probability would be reflected directly in the extinction coefficient if, as in this case, the bands are approximately the same shape.

This argument is applicable in its entirety to the corresponding absorption band of the negative ions of these compounds, with the resultant prediction that the first band of the negative ion of the 3-2 compound will appear at a lower frequency but with a lower extinction coefficient than those of its isomers. Both predictions are in agreement with the experimental results in Fig. 1. This relatively lower resonance interaction of the ground state of the ion of the 3-2 compound as compared with its isomers is in harmony with the results of Arnold and Sprung,[4] who found that it was a much weaker acid than its isomers, and with observations made on metal derivatives of these compounds.[3]

Extension of this reasoning to the closely related compounds, salicylaldehyde and the enol form of acetylacetone, leads to the prediction that the absorption probability for the low frequency bands of these compounds should increase in the order: 3-2, salicylaldehyde, [1-2, 2-1], acetylacetone; and that the same order should hold for the absorption probability of their negative ions. We are not, however, able to predict the energy of this transition. Table I indicates that the predictions of the order of the extinction coefficients is confirmed by experiment. The fact that the intensity of absorption in the first band of a series of diphenylpolyenes increases with the number of double bonded units in the chain[6] is in agreement with this idea. Table II shows some additional examples of variations in extinction coefficients of corresponding absorption bands in closely related compounds for which the idea of corresponding shapes may provide an explanation. In the absorption of light by a carbonyl group, the excited state is a hybrid which presumably has a single bond between the carbon and oxygen atoms. Thus any change in the molecule which would increase the C^+-O^- contribution in the ground state should, according to the idea of corresponding shapes, increase the absorption probability. The electron donating effects of the alkyl groups and their steric effects would both increase the C^+-O^- contribution in hexaethylacetone over that in acetone itself, and the expected increase in extrinction coefficient is found.

(6) Hauser, R. Kuhn and E. Kuhn, *Z. phy ik. Chem.*, **B29**, 391 (1935).

TABLE I

Compound	Hexane λ_{max}, Å.	Hexane Log ϵ	0.1 *N* NaOH λ_{max}, Å.	0.1 *N* NaOH Log ϵ	Double bond character[a]
3-Hydroxy-2-naphthaldehyde	3900	3.28	4420	3.73	1/3
Salicylaldehyde	3280	3.56	3820[b]	3.85[b]	1/2
2-Hydroxy-1-naphthaldehyde	3700	3.67	3950	3.90	2/3
1-Hydroxy-2-naphthaldehyde	3810	3.67	4050	4.02	2/3
Acetylacetone enol	2730[c]	>3.90[c]	2900[d]	4.38[d]	1

[a] Of the bond between the carbons holding the functional groups. [b] Lemon, THIS JOURNAL, **69**, 2998 (1947). [c] In absolute ethanol, Blout, Eager and Silverman, *ibid.*, **68**, 566 (1946). [d] Grossman, *Z. physik. Chem.*, **109**, 305 (1924).

TABLE II

Compound	λ_{max}.	Log ϵ
Acetone[a]	2740	1.15
Hexaethylacetone[a]	3080	1.44
1,3-Butadiene[b]	2170	4.32
Piperylene[b]	2235	4.41
2,4-Hexadiene[b]	2270	4.41
Cyclohexadiene[b]	2560	3.90
Cyclopentadiene[b]	2385	3.53

[a] Lewis and Calvin, *Chem. Revs.*, **25**, 279 (1939). [b] Booker, Evans and Gillam, *J. Chem. Soc.*, 1453 (1940).

The data in Table II for the conjugated dienes may be interpreted similarly if we assume that the upper state of the absorption considered involves an oscillation of electrons over the four-carbon conjugated system. The preferred configuration approaches a line in this case, therefore the closer the lower state is to a linear system the higher should be its absorption probability. The straight chain dienes, it is seen, have similar extinction coefficients, while in the dienes where ring formation restricts the approach to linearity, the values are considerably lower. Moreover, the values decrease with decrease in ring size as expected.

It should be emphasized that the shape factor is only one of the factors which affect absorption probability, but these data indicate that it is important and might be used with due caution in drawing conclusions about the actual shapes of molecules.

Temperature Effects.—With the exception of the 3-2 compound, the temperature effects over the small range used (25°) are too small to be shown on these figures. The expected effect is a slight broadening of each band and a shift of the band toward the red. However, when two bands are sufficiently close together, these effects add on the low frequency band and oppose on the higher frequency band with the result that the low frequency peak will increase with temperature, while the higher frequency peak decreases. These effects, however, are slight. In the case of the 3-2 compound in 80 mole per cent. methanol–water solution (Fig. 5) an effect of a far different order

of magnitude is observed. This effect is attributed to the reversible formation of the acetal and will be discussed in paper II of this series.

Summary

The absorption spectra of the three *o*-hydroxynaphthaldehydes and their negative ions has been determined in a variety of solvents. A theory, based on resonance possibilities in the ground and excited states, accounts for the striking differences in the low frequency absorption bands of these compounds.

CHICAGO 12, ILL. RECEIVED APRIL 27, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Absorption Spectra of *o*-Substituted Aldehydes. II. Aldehyde–Acetal Equilibrium in Methanol–Water Solutions[1]

BY NORTEN C. MELCHIOR[2]

The striking effect of temperature change upon the absorption spectrum of 3-hydroxy-2-naphthaldehyde in acidified 80 mole per cent. methanol–water,[3] and the fact that temperature change had no such effect on the spectra of either 1-hydroxy-2-naphthaldehyde or 2-hydroxy-1-naphthaldehyde under identical conditions led to the extension of these studies to related compounds. Under the same conditions it was found that the spectrum of salicylaldehyde was somewhat affected by temperature, while that of *o*-methoxybenzaldehyde showed a pronounced temperature effect. Further experiments showed that the temperature dependence vanished when *neutral* methanol or methanol–water was used as solvent, and that temperature dependence appeared when acidified 98 mole per cent methanol was used as solvent for either 1-hydroxy-2-naphthaldehyde or 2-hydroxy-1-naphthaldehyde. These experiments suggested that the changes observed were caused by acid catalyzed formation of acetals or hemiacetals. To distinguish between these possibilities, and to define the differences existing among these related compounds, their spectra were determined in neutral and acid methanol–water solutions over a range of temperature and methanol concentration.

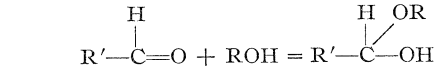
Experimental

Absorption Measurements.—A Beckman model D. U. spectrophotometer was used in all measurements. One-cm. fused silica cells with standard taper stoppers prevented solvent loss by evaporation. The temperature of the cells was controlled as previously described.[3] As a precaution, the previously purified aldehydes were distilled or sublimed immediately before use and were handled in nitrogen. Methanol was reagent grade, and blanks were prepared from the same sample of solvent in all cases.

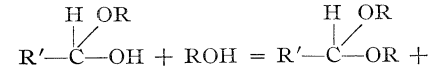
Preparation of Salicylaldehyde Methyl Acetal.—Twenty-five ml. (29 g.) of salicylaldehyde was dissolved in 100 ml. of methanol which contained 0.002 mole of hydrochloric acid. The solution was cooled in stages to Dry-Ice temperature and stored in Dry Ice for one week. It was then neutralized at that temperature with 1 *N* sodium hydroxide, and the methanol and water removed below 0.1 mm. as the mixture warmed to room temperature. The precipitated salt was filtered off with the aid of an anhydrous ether wash, and the product distilled at less than 0.01 mm. after removal of the ether below 25°. After the lapse of a week, this fraction was redistilled, and after preliminary evolution of a low-boiling liquid (possibly methanol), a 9-g. fraction (b. p. 64.5–65.0°, 0.01 mm.; d^{25}_4 1.107, $n^{25}D$ 1.5119) was obtained. The colorless residue weighed 9 g. Analysis of the distillate gave C, 64.8, 64.8; H, 7.2, 7.3. Calculated for $C_9H_{12}O_3$: C, 64.27; H, 7.19. This is apparently the same substance prepared by Pauley and v. Buttlar,[4] but these authors report only the boiling point.

Calculations and Results

The equilibria considered are



$$R'-\overset{H}{\underset{|}{C}}=O + ROH = R'-\overset{H\ OR}{\underset{|}{C}}-OH \qquad (1)$$



$$R'-\overset{H\ OR}{\underset{|}{C}}-OH + ROH = R'-\overset{H\ OR}{\underset{|}{C}}-OR + H_2O \qquad (2)$$

The equilibrium constant for the sum of reactions 1 and 2 is

$$K_{1+2} = \frac{a_{\text{acetal}}a_{\text{water}}}{a_{\text{aldehyde}}a^2_{\text{methanol}}} = \frac{\gamma_{\text{Ac}}N_{\text{Ac}}\gamma_{\text{H}_2\text{O}}N_{\text{H}_2\text{O}}}{\gamma_{\text{Al}}N_{\text{Al}}\gamma^2_{\text{MeOH}}N^2_{\text{MeOH}}} \qquad (3)$$

If we assume that hemiacetal formation is small, the ratio $N_{\text{Ac}}/N_{\text{Al}}$ can be obtained from the measured absorption spectra as

$$\frac{N_{\text{Ac}}}{N_{\text{Al}}} = \frac{\epsilon_0 - \epsilon}{\epsilon - \epsilon_1} \qquad (4)$$

where, at a given wave length,[5] ϵ_0 is the measured extinction coefficient of the aldehyde in neutral methanol, ϵ_1 is that of the acetal in neutral methanol and ϵ is the apparent extinction coefficient of the aldehyde in a given acidified methanol–water solution. If ϵ_1 is zero or small compared to ϵ_0 and ϵ, the equation reduces to (1)

$$N_{\text{Ac}}/N_{\text{Al}} = \epsilon_0 - \epsilon/\epsilon \qquad (5)$$

Measurements of the spectra of the acetals of salicylaldehyde and *o*-methoxybenzaldehyde showed that ϵ_1 was small at the wave lengths chosen in each case, and consideration of the spectra of α- and β-naphthol indicated that this

(1) Presented at the meeting of the American Chemical Society in San Francisco, March, 1949.

(2) Present address: Stritch School of Medicine, Loyola University, Chicago 12, Illinois.

(3) Paper I, THIS JOURNAL, **71**, 3647 (1949).

(4) H. Pauley and R. v. Buttlar, *Ann.*, **383**, 283 (1911).

(5) The preferred wave length is that of an absorption maximum which can be ascribed to the carbonyl group.

was also the case at the rather long wave lengths chosen for the naphthaldehyde calculations.

Preliminary calculations of K_{1+2} (equation 3) assuming that $\gamma_{Ac} = \gamma_{Al}$ and using values from the literature[6] for the activities of methanol and water gave only fair agreement between values calculated from measurements at different methanol–water ratios. Examination of the published data revealed that no measurements had been made in the range of concentration which is of interest here, although in some cases data from smoothed curves had been tabulated in this range.

It was, therefore, necessary to obtain some assurance as to the meaning of the numbers which could so easily be obtained from laboratory measurements. Rearrangement of equation (3) and combination with (5) gives

$$\frac{\epsilon_0 - \epsilon}{\epsilon} = \frac{N_{Ac}}{N_{Al}} = K_{1+2}\frac{\gamma_{Al}\gamma^2_{MeOH}N^2_{MeOH}}{\gamma_{Ac}\gamma_{H_2O}N_{H_2O}} \quad (6)$$

If the plot of $(\epsilon_0 - \epsilon)/\epsilon$ against N^2_{MeOH}/N_{H_2O} is a straight line, the quantity $(\gamma_{Al}\gamma^2_{MeOH})/(\gamma_{Ac}\gamma_{H_2O})$ is a constant over the range considered, and if that constant is unity, the slope of the line is K_{1+2}. Figure 1 shows typical measurements from which these data can be obtained, and Fig. 2 shows this test applied to the data for salicylaldehyde.[7] The linear relationship found is confirmed by the data on *o*-methoxybenzaldehyde and 3-hydroxy-2-naphthaldehyde. This test simultaneously verifies the assumption that hemiacetal formation is small, since any appreciable hemiacetal formation would cause a deviation from the straight line observed.

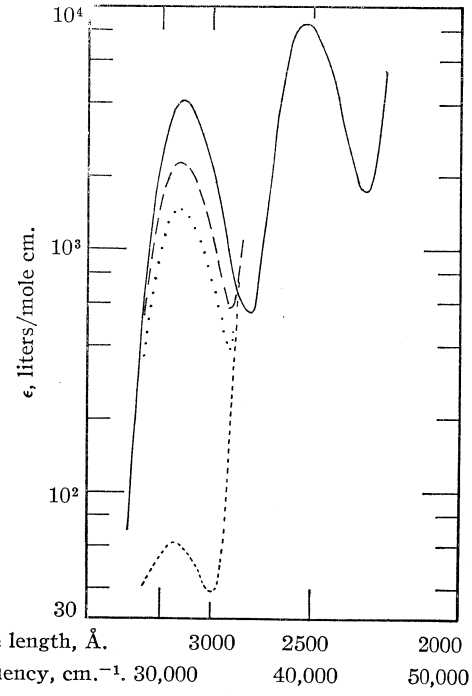


Fig. 1.—Absorption spectra of *o*-methoxybenzaldehyde in methanol–water solutions: — neutral methanol, 25°; — — eighty mole % methanol, 0.01 *M* HCl, 25°; . . . . . eighty mole % methanol, 0.01 *M* HCl, 2°; - - - - methanol, 99.8 mole %, 0.01 *M* HCl, 25°.

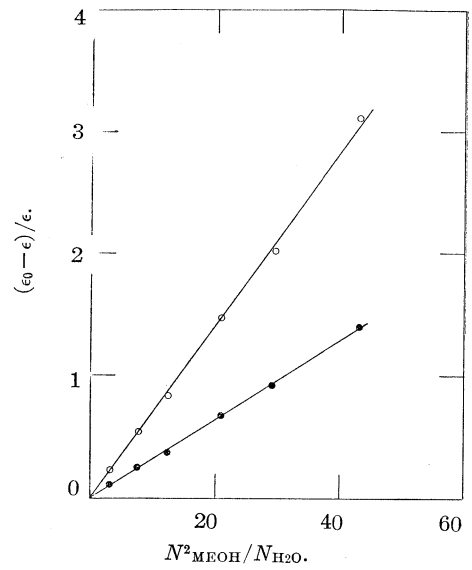


Fig. 2.—Extinction coefficients of salicyaldehyde in acidified methanol–water solutions, λ = 3250 Å.: filled circles, 25°, open circles, 2°.

One can then calculate equilibrium constants on a comparative basis. The values obtained will be subject to a constant correction when the activity coefficient of water in these solutions is available, but are useful for comparative purposes and can be used in calculation of comparative values for ΔH and ΔS without ambiguity. The data obtained are given in Table I and the calculated thermodynamic values are collected in Table II.

Discussion

The data in Table I show clearly the reason temperature has so much less effect on the spectra of 2-hydroxy-1-naphthaldehyde and 1-hydroxy-2-naphthaldehyde than on those of the other aldehydes studied. In most methanol–water solutions so little acetal is formed from either of these aldehydes that the spectrum is only slightly affected, and in 80 mole per cent. methanol even a 100% change in the amount of acetal would scarcely be measurable.

The values obtained for the equilibrium constants cannot, unfortunately, be compared with

(6) (a) Ferguson and Funnell, *J. Phys. Chem.*, **33**, 1 (1929); (b) M. Ewert, *Bull. soc. chim. Belg.*, **45**, 493 (1936); (c) Butler, Thomsen and Maclennan, *J. Chem. Soc.*, 674 (1933); (d) Dulitkaya, *J. Gen. Chem.* (*U. S. S. R.*), **15**, 9 (1945).

(7) Although the straight line relationship is found, it has not been shown that $\gamma_{Al}/\gamma_{Ac} = 1$, nor that $\gamma^2_{MeOH}/\gamma_{H_2O} = 1$. The first is probably correct, since the solutions of aldehyde were very dilute and the standard state chosen is the infinitely dilute solution. The second relation is probably not correct. In this range γ_{MeOH} is probably unity, while γ_{H_2O} is somewhat greater than unity. Over the range of interest, however, both appear to be constant.

TABLE I

ACETAL FORMATION IN METHANOL–WATER SOLUTIONS

Compound	N_{MeOH}	$\epsilon \times 10^{-3}$ 25°	$\epsilon \times 10^{-3}$ 2°	K_{1+2} 25°	K_{1+2} 2°
Salicylaldehyde, λ = 3250 Å.	1.00[a]	3.51	3.61	.....	.....
	0.978	1.46	0.88	0.0325	0.0722
	.968	1.83	1.19	.0318	.0696
	.956	2.10	1.46	.0324	.0706
	.925	2.56	1.97	.0326	.0733
	.895	2.82	2.32	.0325	.0714
	.802	3.16	2.92	.0345	.0721
				.0324[b]	.0714[b]
o-Methoxybenzaldehyde, λ = 3200 Å.	1.00[a]	4.11	4.11	.....	.....
	0.895	1.39	0.753	0.256	0.591
	.802	2.24	1.46	.257	.559
	.802	2.28	1.45	.248	.565
	.648[c]	3.12	2.34	.262	.633
				.256[b]	.582[b]
3-Hydroxy-2-naphthaldehyde, λ = 3846 Å.	1.00[a]	1.76	1.74	.....	.....
	0.956	0.447	0.217	0.141	0.337
	.895	0.847	.488	.142	.336
	.802	1.17	.511	.157	.362
				.142[b]	.336[b]
2-Hydroxy-1-naphthaldehyde, λ = 3580 Å.	1.00[a]	5.22	5.22	.....	.....
	0.978	4.04	3.44	0.0067	0.0120
1-Hydroxy-2-naphthaldehyde, λ = 3720 Å.	1.00[a]	4.90	4.90	.....	.....
	0.978	4.22	3.95	0.0037	0.0056

[a] In *neutral* methanol. [b] Value from the slope of the line as in Fig. 2. [c] Value probably outside the range of constancy of γ_{MeOH} and γ_{H_2O}.

TABLE II

THERMODYNAMIC QUANTITIES[a] FOR THE FORMATION OF ACETALS IN METHANOL–WATER SOLUTIONS

Compound	$\Delta F°_{298}$ cal.	ΔH, cal.	ΔS, e. u.
o-Methoxybenzaldehyde	+ 800	−5800	−22.2
Salicylaldehyde	+2000	−5600	−25.5
3-Hydroxy-2-naphthaldehyde	+1200	−6200	−24.6
2-Hydroxy-1-naphthaldehyde	+3000	−4100	−23.6
1-Hydroxy-2-naphthaldehyde	+3300	−2800	−20.5

[a] For comparative purposes, see note (7) and the text.

those obtained by Adkins and co-workers,[8] since, as these workers recognized, one cannot estimate the activities of any of the substances in their reaction mixtures. The only advantage the spectroscopic measurement can claim is the use of very dilute solutions of aldehyde and acetal; so that the problem is reduced to the estimation of the activities of water and the alcohol concerned. For the first time we are able to examine the separate factors which influence the formation of acetals from different aldehydes with some degree of assurance.[9]

The driving force of the reaction is found in ΔH, and is comparable to that for the formation of ethers from alcohols. The entropy of the system decreases in all cases. A portion of this decrease can be ascribed to the decrease in the number of particles, while some of the remainder may be due to differences in hydrogen bonding of water molecules as compared to alcohol molecules. These factors are constant in all the cases considered. The *differences* observed must be due to differences in the aldehydes and their corresponding acetals and their respective solvent envelopes. Comment on these differences is restricted because of the lack of a common plane of reference, but cautious analysis may yield some information.

In comparing the equilibrium formation of acetal from salicylaldehyde with that from *o*-methoxybenzaldehyde one might reason that, since a chelated hydrogen bond must be broken in the case of the salicylaldehyde but not in *o*-methoxybenzaldehyde, the formation of acetal from the latter should be favored over that from the former. This is exactly what is observed. However, the data in Table II show that this argument, based on energy considerations, has substantially nothing to do with the result, and that differences in ΔS are the basis of the observed changes. The values for ΔH, which is closely related to energy change, indicate that energy required to replace that of the chelated hydrogen bond is supplied, most probably by the formation of several new hydrogen bonds with the solvent. If, then, we accept the values for ΔH as evidence that the *increase* in the number of solvent molecules bound is greater in the formation of salicylaldehyde methyl acetal than in the formation of *o*-methoxybenzaldehyde methyl acetal, we are prepared for the experimental result that the increase in order (decrease in entropy) is greater in the former reaction. It may be noted that the values of ΔS for the sterically similar compounds salicylaldehyde and 3-hydroxy-2-naphthaldehyde are more nearly alike. This same small but, the author believes, real difference is observed in the values of ΔS in the reactions of 3-hydroxy-2-naphthaldehyde and 2-hydroxy-1-naphthaldehyde, both of which yield substituted β-naphthols with the hydroxyl group sterically available to the solvent. This is not the case with 1-hydroxy-2-naphthaldehyde, and we find definitely different values for both ΔH and ΔS, a result which is consistent with a much smaller change in solvation in the reaction than in those of the isomeric compounds considered. There are two qualitative indications that the hydroxyl group is a solvation site even when the chelate ring is presumably intact. One is the almost negligible effect of the solvent

(8) For leading references to the work of Adkins, Adams, Hartung, Street, Broderick, Minne and Dunbar, see THIS JOURNAL, **56**, 442 (1934).

(9) Parks and Huffman have calculated some standard free energies from the equilibrium data of Adkins and co-workers ("The Free Energies of Some Organic Compounds," The Chemical Catalog Co., New York, N. Y., 1932, pp. 169–170). These authors estimate the uncertainty in these free energies to be of the order of 100 calories. Since this corresponds to values of the ratio of the activity coefficients in the range 0.8 to 1.2, this author believes that their estimate of the uncertainty is too low.

change hydrocarbon to water on the spectrum[3] of 1-hydroxy-2-naphthaldehyde, while its isomers show a real, albeit small, effect which is not due to acetal formation. The second is the fact that this compound steam distils with ease, its isomers with considerable difficulty.

Further, if we assume the energies of the acetals which are substituted β-naphthols to be the same, we find that the values for ΔH indicate that the ground state of 3-hydroxy-2-naphthaldehyde is some 2,000 calories above that of 2-hydroxy-1-naphthaldehyde. This is the order deduced in the previous paper,[3] but the numerical difference is less than half that expected. It seems probable that this is due to differences in solvent interaction which were much less important in the measurements made in hydrocarbon solvents.

Summary

The differences observed in the spectra of certain aldehydes in neutral methanol as compared to solutions in acidified methanol have been shown to be due to the reversible formation of the corresponding acetal in the acid solutions. The equilibrium constants for these reactions have been determined at 25 and 2°, and from these data comparative values for ΔH and ΔS have been calculated. Comparison of these data suggests the importance of solvation in interpreting the differences observed. The spectroscopic method offers a tool for the study of this reaction which is capable of separating to some extent energy factors from orientation factors.

CHICAGO 12, ILL. RECEIVED APRIL 27, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORQUIMA, S. A.]

Ferrous Mono-α,α′-dipyridyl

BY P. KRUMHOLZ

It has been assumed until recently, that only one type of complexes between ferrous ion and α-α′-dipyridyl (D) or *o*-phenanthroline (Ph) exists in solution and that the 6-coördinated ions FeD_3^{++} and $FePh_3^{++}$ are present.[1]

The formation of lower Fe^{++}–D complexes as intermediates in the formation of FeD_3^{++} has been recently assumed and confirmed by the observation that the formation of FeD_3^{++} is less complete with an excess of Fe^{++} than with equivalent concentrations.[2]

Analogous yellow-colored complexes exist in the system Fe^{++}–Ph, and it seems that both complexes $FePh_2^{++}$ and $FePh^{++}$ may be formed under favorable conditions.[3]

We found strong evidence for the existence of the complex ion FeD^{++} studying the kinetics of formation of FeD_3^{++},[4] by the observation, that the reaction velocity, initially proportional to the Fe^{++} concentration, is retarded by a large excess of Fe^{++}. The kinetics could be correctly interpreted, assuming the very rapid formation of FeD^{++} with an equilibrium constant $K_{FeD} = 2.7 \times 10^4$ at 25° and $\mu = 0.33$.

In the present paper we confirm this indirect finding by an entirely different and direct method. We found that acid solutions of α,α′-dipyridyl, containing only a small amount of free D, form with a large excess of Fe^{++} yellow solutions which turn reddish more or less rapidly, due to the formation of FeD_3^{++}. Under suitable conditions such solutions are stable enough to determinate their extinction in dependence on the concentrations of the reactants, and thus the composition and equilibrium constant of the yellow compound. Solutions containing a very large excess of Fe^{++} are stable enough to measure the absorption spectrum of the yellow compound. As the calculation of the equilibrium constants involves the acid constant of the α,α′-dipyridylium ion (HD^+), this constant has been determined.

Experimental

Material Used.—α,α′-Dipyridyl was purified by vacuum distillation and recrystallized from diluted alcohol and hexane; m. p. 70°. Ferrous chloride solutions were prepared by dilution of a filtered 0.5 *M* solution, kept over iron powder with 0.005 *N* hydrochloric acid.

Determination of the Acid Constant of α,α′-Dipyridylium Ion.—The acid constant of HD^+ was computed from *p*H values of solutions of D and its hydrochloride, the ionic strength being adjusted with potassium chloride. The *p*H values were determined with a glass electrode, calibrated with standard biphthalate and acetate buffers at the same temperature as the sample. Temperatures were kept constant to within ±0.3°. The potential readings could be reproduced within ±0.5 m. v. Even accounting for possible errors due to diffusion potentials between the saturated potassium chloride bridge and the measured solution and for the uncertainty in the *p*H values of the buffer, the error of the absolute values of the constants should be less than 10%.

Determination of the Extinction of Fe^{++}–D Solutions.—To obtain reproducible extinction values of solutions of the yellow complex, it is necessary to establish very rapidly a high concentration of Fe^{++}, because at low Fe^{++} concentrations there appears almost immediately the red color of FeD_3^{++}. The mixing set up consisted of a 250-ml. beaker provided with two propeller stirrers rotating with the maximum speed, not yet introducing air bubbles into the liquid. About 125 ml. of the HD^+ solution, containing various amounts of hydrochloric acid and potassium

(1) C. Ferrari, *Gazz. chim. ital.*, **67**, 604 (1937); R. K. Gould and W. C. Vosburgh, THIS JOURNAL, **64**, 1631 (1942). In the solid state F. M. Jaeger and J. A. van Dijk, *Z. anorg. Chem.*, **227**, 273 (1936), prepared 1:1 compounds between α,α′-dipyridyl and ferrous sulfate.

(2) J. H. Baxendale and Ph. George, *Nature*, **162**, 177 (1948).

(3) T. S. Lee, I. M. Kolthoff and D. L. Leussing, THIS JOURNAL, **70**, 3596 (1948).

(4) P. Krumholz, *Nature*, **163**, 724 (1949). The formulation FeD^{++} does not exclude that other groups, as water or Cl^- are coördinated to Fe^{++}.

chloride, were placed in the beaker and the Fe^{++} solution introduced by means of a 25-ml. pipet with a large opening. The time of complete mixing is less than one second. A parallel light-beam was directed across the beaker, between the shafts of the stirrers, the light intensity being measured by a photronic cell and a spotlight galvanometer of 5×10^{-9} amp./mm. sensitivity, calibrated, within 0.1%. The light-beam was filtered with an interference filter in combination with a blue glass, with a transmission maximum of 438 mμ, very closely to the absorption maximum of the yellow complex. As the isolated spectral band is very narrow and the absorption curve flat, it may be taken for granted that the measured extinctions are proportional to the concentration of the yellow complex.

As ferrous chloride solutions in the concentrations used show a marked absorption, slightly dependent on the amount of free acid present, the extinction values were referred to the extinction of a blank solution containing all components except α,α'-dipyridyl.

The final galvanometer reading could be made within about two seconds after the introduction of the Fe^{++} solution. If the reading did not persist at least for a few seconds, the absorptions were read at different times and the zero time value determined by extrapolation.

The photometric accuracy was about 1% at extinctions > 0.1, decreasing to about 3% at $E = 0.03$.

Due to the large volume of the solution and the short time of measurement, the temperature could be kept constant within $\pm 0.5°$ without thermostatic device.

Determination of Absorption Spectra.—Solutions containing a very large excess of Fe^{++} were prepared in the mixing device already described, rapidly transferred in a 50-mm. Korex cell, and the extinctions determinated in intervals of 5 mμ using a Beckman spectrophotometer. The extinctions were referred as above to a α,α'-dipyridyl free blank. Readings remained constant within 2% during about two minutes.

Results

Acid Constant of α,α'-Dipyridylium Ion.—Tables I and II show pH values of 1:1 mixtures of α,α'-dipyridyl and α,α'-dipyridylium hydrochloride in 4×10^{-3} M solution at different ionic strengths and temperatures, as the corresponding values of the concentration dissociation constant K_c.

TABLE I

μ	pH	γ_{H^+}	K_c[a] $\times 10^{-5}$
4.7×10^{-3}	4.38	0.92	4.6
2.4×10^{-2}	4.41	.86	4.6
4.2×10^{-2}	4.43	.84	4.5
7.8×10^{-2}	4.45	.82	4.4
1.1×10^{-1}	4.47	.81	4.3
1.8×10^{-1}	4.50	.80	4.0
3.3×10^{-1}	4.53	.81	3.7
5.5×10^{-1}	4.59	.87	3.0

[a] $T = 25°$.

TABLE II

T, °C.[a]	pH	K_c $\times 10^{-5}$
15	4.61	3.1
20	4.57	3.4
25	4.53	3.7
30	4.49	4.1
35	4.45	4.5
40	4.40	5.0
45	4.36	5.5
50	4.32	6.1

[a] $\mu = 0.33$.

K_c was calculated by means of

$$K_c = \frac{(H^+)(D)}{(HD^+)} = \frac{(H^+)\{(D)_0 + (H^+)\}}{(HD^+)_0 - (H^+)} = K_a \frac{\gamma_{HD^+}}{\gamma_{H^+}\gamma_D} \quad (1)$$

where γ represents the activity coefficient and $(HO)_0$ the initial analytical concentrations. (H^+) was calculated from the pH values, using the values of γ_{H^+} indicated in Table I computed by the method of individual activity coefficients from the known mean activities of potassium chloride and hydrochloric acid. At low ionic strengths K_c approaches, as shown in Table I, the steady value of the thermodynamic constant K_a, which may be taken as $K_a = 4.6 \times 10^{-5}$ at 25°.[5]

From the temperature dependence of K_c, the mean heat of formation of the α,α'-dipyridylium ion may be calculated as 3.5 ± 0.5 kcal.[6]

Elucidation of the Nature of the Yellow Complex.—To establish the composition and the dissociation constant of the yellow complex, we determined the extinctions of solutions containing various amounts of Fe^{++}, HD^+ and H^+ (at 25° and $\mu = 0.33$). As the extinction coefficient of the yellow compound was unknown, we calculated first of all the concentration of the yellow complex, *supposed to be* FeD^{++}, using the previously reported "kinetic" value of the stability constant

$$K_{FeD} = \frac{(FeD^{++})}{(Fe^{++})(D)} = 2.7 \times 10^4 \quad (2)$$

To calculate (FeD^{++}) from (2), (D) has to be expressed as function of $(HD)_0$ and $(H^+)_0$, $(HD)_0$ representing the total initial concentration of α,α'-dipyridyl. In Fe^{++} free solutions this relation is given by

$$(D) = K_c \frac{(HD^+)}{(H^+)} = K_c \frac{(HD)_0 - (D)}{(H^+)_0 + (D)} \sim K_c \frac{(HD)_0}{(H^+)_0 + K_c} \quad (3)$$

Because in our experiments always $(H^+)_0 \gg (D)$, we used the last approximation throughout. Due to the formation of FeD^{++}, (HD) and (Fe^{++}) decrease by the amount of (FeD^{++}) formed, (H^+) increasing by the same amount. (FeD^{++}) may then be calculated from

$$(FeD^{++}) = K_c \times K_{FeD} \times \{(Fe^{++})_0 - (FeD^{++})\} \frac{(HD)_0 - (FeD^{++})}{(H^+)_0 + (FeD^{++}) + K_c} \quad (4)$$

The mean value of the relation of the thus calculated concentrations to the measured extinctions was used as proportionality factor (f) in the calculation of the experimental values of (FeD^{++}).

As shown in Table III, theoretical and experimental values of (FeD^{++}), calculated from E with $f = 4.95 \times 10^{-4}$, are in excellent numerical agreement. As easily may be shown, this agreement does not hold with values of K_{FeD}, differing more than 5% from the "kinetic" value, confirming thus the numerical value of this constant previously obtained by an entirely different method.

It is, of course, impossible to correlate theoretical and experimental values on the assumption that the yellow complex is FeD_2^{++}, using any value of K_{FeD_2}. Our experiments, however, do not disprove the possible existence of this complex, which hardly could be detected, if $K_{FeD_2} \leqslant K_{FeD}$ (and $\epsilon_{FeD_2} \sim \epsilon_{FeD}$).

(5) Baxendale and George, ref. 2, found $K_a = 4.2 \times 10^{-5}$ at 17° and $\mu = 0.025$ in close agreement with our corresponding value (4×10^{-5}). A. Albert, R. Goldacker and J. Philips, *J. Chem. Soc.*, 2247 (1948), indicate the rather high value of about 6×10^{-5} at 25°.

(6) Baxendale and George, ref. 2, found the lower value of about 2 kcal.

TABLE III

$(Fe^{++})_0 \times 10^3$	$(HD)_0 \times 10^5$	$(H^+)_0 \times 10^3$	$E \times 10^3$	$(FeD^{++}) \times 10^6$ Found	Calcd.
74	13.3	8.0	242	120	120
37	13.3	8.0	218	108	109
30	13.3	7.15	216	107	107
14.2	13.3	7.4	177	87.5	86.5
3.75	13.3	14.6	54	26.5	27
14.2	13.3	2.4	225	111.5	112.5
14.2	13.3	7.4	177	87.5	86.5
14.2	13.3	14.1	134	66.5	66
14.2	13.3	34	79	39	39
14.2	13.3	67.5	46	22.8	23
14.2	13.3	135	26.5	13.1	12.6
14.2	13.3	335	11	5.5	5.4
14.2	3.33	7.4	44	21.8	21.8
14.2	6.66	7.4	89	44	43.5
14.2	33.3	7.4	436	216	215
1.8	6.66	3.55	43	21.3	22
1.8	13.3	3.5	87	43	44
1.8	20.0	3.4	133	66	66
1.8	33.3	3.3	228	113	110

Table IV shows the dependence of K_{FeD}, calculated by means of (4) from $(FeD^{++})_{expt.}$, on the ionic strength.

TABLE IV

$(Fe^{++})_0 = 3.75 \times 10^{-3}$, $(HD)_0 = 1.33 \times 10^{-4}$, $(H^+)_0 = 1.46 \times 10^{-2}$, $T = 25°$

μ	$E \times 10^3$	$(FeD^{++})_{expt.} \times 10^6$	$K_{FeD} \times 10^{-4}$
0.03	56.5	28	2.3
.10	56	27.7	2.4
.20	55	27.2	2.6
.33	54	26.7	2.7

K_{FeD} decreases slowly with the decrease in μ, approaching the value of the thermodynamic constant, which may be taken to $2.3 \pm 0.3 \times 10^4$ at 25°, accounting for the possible error introduced with K_c.

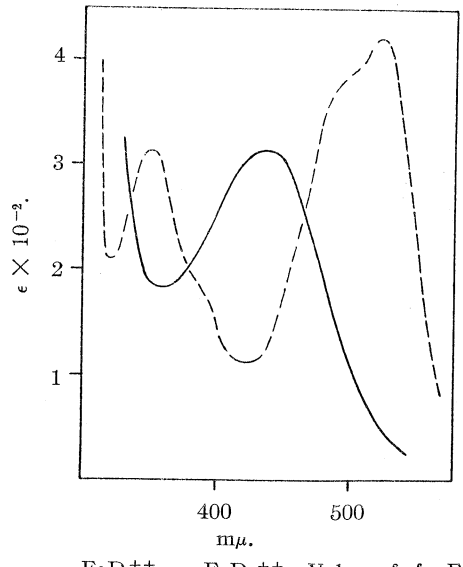


Fig. 1.———FeD^{++}, - - - FeD_3^{++}. Values of ϵ for FeD_3^{++} to be multiplied by 20.

We tried furthermore to determine the dependence of K_{FeD} on the temperature. As shown in Table V the values of K_{FeD} at 45° vary considerably with the composition of the solution, if (FeD^{++}) is calculated from E with the mean proportionality factor f, obtained at 25°.

TABLE V[a]

$(Fe^{++})_0 \times 10^3$	$(HD)_0 \times 10^4$	$(H^+)_0 \times 10^3$	$E_{25°} \times 10^3$	$E_{45°}$	$K_{25°}$	$K_{45°} \times 10^{-4}$	$\overline{K}_{45°}$
74	1.33	8.0	242	220	2.65	0.9	1.45
30	1.33	3.8	236	215	2.6	0.95	1.45
30	1.33	7.15	216.5	190.5	2.75	1.1	1.4
30	1.33	13.8	183	157	2.7	1.2	1.4
30	1.33	34	126.5	102	2.75	1.25	1.4
30	1.33	67	83	65	2.7	1.3	1.4
3.75	1.33	14.6	54.5	42.5	2.7	1.35	1.45

[a] $\mu = 0.33$.

Using however the proportionality factor $f_1 = 5.3 \times 10^{-4}$, that is assuming that the extinction coefficient decreases by about 7% from 25 to 45°, the values of $\overline{K}_{45°}$ agree perfectly.

If this assumption is valid, the heat of formation of FeD^{++} may be calculated to approximately 6 kcal.

We measured finally the absorption spectrum of FeD^{++} in the visible and near ultraviolet, shown in Fig. 1, in comparison with the spectrum of FeD_3^{++}. The extinctions were determined in a solution of the composition: $(Fe^{++})_0 = 7 \times 10^{-2}$, $(HD)_0 = 1.33 \times 10^{-4}$, $(H^+)_0 = 1.4 \times 10^{-2}$ at 25°, corresponding to a concentration of FeD^{++} of 1.1×10^{-4}. The extinction coefficient at the absorption maximum $\lambda = 435$ mμ is 3.1×10^2, and thus about 25 times less than the extinction coefficient of FeD_3^{++} at $\lambda = 523$ mμ ($\epsilon = 8.5 \times 10^3$).

Summary

The acid constant of α,α′-dipyridylium ion has been determinated at various ionic strengths and temperatures. The value of the thermodynamic constant at 25° was found to be 4.6×10^{-5}. The heat of formation was calculated to about 3.5 kcal.

The previously assumed existence of a ferrous mono α,α′-dipyridyl complex has been confirmed and its thermodynamic equilibrium constant determinated as 2.3×10^4 at 25°. An approximative value of 6 kcal. for the heat of formation of this complex has been calculated.

The absorption spectrum of the ferrous mono-α,α′-dipyridyl complex has been measured in the visible and near ultraviolet.

SÃO PAULO, BRAZIL

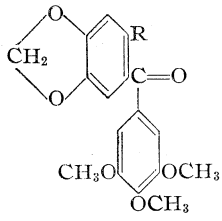
RECEIVED MAY 14, 1949

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

Synthesis of Some Compounds Related to Podophyllotoxin[1]

BY WILKINS REEVE AND JOHN D. STERLING, JR.[2]

The synthesis of a number of compounds related to podophyllotoxin has been studied. Podophyllotoxin[3] has previously been shown to have tumor-damaging activity.[4,5]

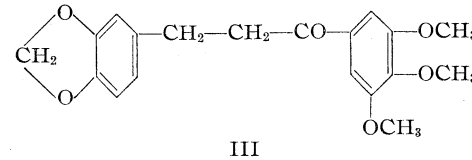


I, R = CH_3
II, R = COOH

3′,4′,5′-Trimethoxy-2-methyl-4,5-methylenedioxybenzophenone (I) was prepared by the reaction of trimethylgalloyl chloride with 3,4-methylenedioxytoluene in carbon disulfide solution using stannic chloride catalyst. Attempts to use aluminum chloride as the catalyst for this type of reaction have proven unsatisfactory presumably because of cleavage of the methoxy and methylenedioxy groups.[6] Attempts to convert I to the corresponding acid II by oxidation were not successful. The stannic chloride-catalyzed condensation of trimethylgalloyl chloride with a number of 4-substituted-methylenedioxybenzenes was tried to determine the limitations of this reaction. It was found that safrole, 3,4-methylenedioxybenzyl acetate, ethyl piperonylate, piperonal diethyl acetal, and piperonal would not react.

The 3,4-methylenedioxytoluene for the above reaction was prepared by the hydrogenation over copper–chromium–barium oxide catalyst at 160° of piperonal in dioxane solution to piperonyl alcohol, and the hydrogenolysis of this in dioxane solution over the same catalyst at 280° and 210 atmospheres starting pressure. This method has not previously been used to prepare 3,4-methylenedioxytoluene. It is of interest that the hydrogenolysis occurs under much more difficult conditions than does the hydrogenolysis of benzyl alcohol. The latter undergoes hydrogenolysis readily at 150–200° and 250 atmospheres starting pressure over this catalyst.[7]

Attempts to prepare I by condensing trimethylgallic acid with 3,4-methylenedioxytoluene in the presence of phosphorus pentoxide by Kosolapoff's procedure[8] yielded a tan colored solid, m. p. 112–120°, believed to be a mixture of compounds containing no isolatable amounts of I.



III

3,4,5 - Trimethoxy - α - piperonylacetophenone (III) was prepared by the reaction of piperonyl bromide with ethyl 3,4,5-trimethoxybenzoylacetate in alcohol solution using sodium ethoxide catalyst followed by hydrolysis and decarboxylation with barium hydroxide solution. This compound had been previously reported by Bargellini and Monti,[9] but the reported melting point was not in agreement with ours. They reported the preparation of the compound by the reduction of piperonylidene-3,4,5-trimethoxyacetophenone, but the reported melting point of this intermediate did not agree with that of other workers.[10] In view of the doubt concerning the starting compound, the uncontrolled nature of the hydrogenation reaction, and the lack of evidence that the ketone was properly characterized, it seems certain that they did not obtain ketone III.

Experimental

All melting points are "corrected."

Piperonyl Alcohol.—Ninety grams of freshly distilled piperonal in 70 ml. of dioxane (purified by refluxing over odium) was hydrogenated under 4500 lb. pressure (300 atm.) of hydrogen at 160–175° over 5 g. of copper chromite catalyst.[11] The reduction was nearly complete at 160° in fifteen minutes but was continued at 175° for another hour. Distillation gave 90 g. of piperonyl alcohol (98% yield), m. p. 51°, b. p. 125–128° at 6 mm. pressure. Reported[12]: m. p. 51°, b. p. 161° at 20 mm. pressure.

3,4-Methylenedioxytoluene.—Seventy-six grams of piperonyl alcohol in 60 ml. of purified dioxane was hydrogenated under 5500 lb. pressure (375 atm.) hydrogen at 280° over 4 g. of copper chromite catalyst.[11] The theoretical amount of hydrogen was absorbed in approximately two hours. The reaction mixture, after filtering and drying over calcium chloride, gave 58 g. of 3,4-methylenedioxytoluene (84.5% yield), b. p. 78–81° at 12–14 mm. pressure; reported[13] b. p. 81–83° at 11 mm.

Trimethylgalloyl Chloride.—This was prepared in 84% yield by stirring 191 g. of trimethylgallic acid with 175 ml. of thionyl chloride and 400 ml. of benzene at 60° for five

(1) The work reported herein was supported by a grant from the National Institute of Health.

(2) Present address: Jackson Laboratory, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

(3) The chemistry of podophyllotoxin is reviewed in the Ann. Repts. Progress Chem. (Chem. Soc. London), **30**, 191 (1933); **33**, 275 (1936).

(4) Ormsbee, Cornman and Berger, *Proc. Soc. Exp. Biol. and Med.*, **66**, 586 (1947).

(5) Hartwell, THIS JOURNAL, **69**, 2918 (1947); Hartwell and Shear, *Cancer Research*, **7**, 716 (1947).

(6) Spath, Wessely and Nadler, *Ber.*, **66**, 125 (1933); Frank and Tarbell, THIS JOURNAL, **70**, 1276 (1948).

(7) Folkers and Adkins, *ibid.*, **54**, 1145 (1932).

(8) Kosolapoff, *ibid.*, **69**, 1651 (1947).

(9) Bargellini and Monti, *Gazz. chim. ital.*, **44**, II, 28 (1914).

(10) Harding, *J. Chem. Soc.*, **105**, 2796 (1914).

(11) Prepared by a method similar to that described by Adkins in "Organic Syntheses," Coll. Vol. 2, p. 144, note 11 (1944).

(12) Mastagli, *Ann. chim.*, **10**, 281 (1938); Carothers and Adams, THIS JOURNAL, **46**, 1681 (1924).

(13) Schepss, *Ber.*, **46**, 2572 (1913).

hours,[14] b. p. 130° at 2 mm.; m. p. after crystallization from cyclohexane, 77–78°; reported[14] b. p. 168–170° at 14 mm., m. p. 77–78°.

3′,4′,5′-Trimethoxy-2-methyl-4,5-methylenedioxybenzophenone (I).—In a 250-ml. three-necked flask were placed 10 ml. (0.084 mole) of 3,4-methylenedioxytoluene, 50 ml. of anhydrous carbon disulfide and 4.5 ml. (0.037 mole) of anhydrous stannic chloride. To this was added slowly with cooling and stirring 10 g. (0.043 mole) of freshly distilled trimethylgalloyl chloride dissolved in 50 ml. of carbon disulfide. The reaction mixture was stirred at ice-bath temperature for six hours; during this time, the product separated as a red complex. The reaction mixture was decomposed with ice-cold 7% hydrochloric acid, extracted with ether, and the ether extract washed with dilute hydrochloric acid, water, dilute sodium hydroxide and with water. The ether solution was dried with calcium chloride, the ether distilled off, and the residue refluxed with a solution of potassium hydroxide in methyl alcohol for twenty minutes. The resulting mixture was diluted with water and extracted with ether. The ether solution was washed with water, dried with calcium chloride, and the ether removed by distillation. The residue was crystallized from methyl alcohol or cyclohexane giving 6.2 g. (43% yield) of product, m. p. 108–110°. The product gave a positive test for the methylenedioxy bridge when warmed with sulfuric acid and a trace of gallic acid.[15]

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45; OCH_3, 28.15. Found: C, 65.60; H, 5.61; OCH_3, 27.94.

3,4,5-Trimethoxy-α-piperonylacetophenone (III).—In a 100-ml. flask fitted with a condenser and drying tube were placed 50 ml. of absolute alcohol and 0.46 g. (0.02 mole) of sodium. The sodium ethoxide solution thus prepared was cooled in an ice-bath and 5.6 g. (0.02 mole) of ethyl 3,4,5-trimethoxybenzoylacetate[16] was added. Four and one-half grams (0.029 mole) of piperonyl bromide,[17] dissolved in 10 ml. of absolute ether was then added to the cold alcohol solution. Sodium bromide began to precipitate. After ten minutes, the ice-bath was removed, and the reaction allowed to proceed for half an hour while warming up to room temperature. The reaction mixture was then acid. It was diluted with water and extracted with ether. The ether solution was dried, the ether distilled off, and a viscous residual oil obtained. This was hydrolyzed by dissolving in 400 ml. of methanol and adding a solution of 45 g. of barium hydroxide octahydrate in 800 ml. of water at room temperature. A white solid soon formed; after twelve hours, it was removed by filtration. The organic material was separated from inorganic salts by dissolving in chloroform, the chloroform solution dried with anhydrous magnesium sulfate, and the chloroform removed by distillation. There remained 3.8 g. (55% yield for the two steps) of a white crystalline mass which after recrystallization from methanol gave 3.4 g. of product, m. p. 146–147°; reported[9] 96–98°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.83; OCH_3, 27.03. Found: C, 66.14; H, 5.95; OCH_3, 26.87.

Dinitrophenylhydrazone of III.—Accurately weighed samples of III dissolved in alcohol reacted with excess dinitrophenylhydrazine in 2 *N* hydrochloric acid to give the 2,4-dinitrophenylhydrazone according to the quantitative procedure of Iddles, *et al.*[18] Quantitative yields were obtained. After two recrystallizations from benzene, approximately half the material remained, m. p. 188.5–189°.

Anal. Calcd. for $C_{25}H_{24}O_9N_4$: C, 57.25; H, 4.61; N, 10.68. Found: C, 57.47; H, 4.62; N, 10.84.

Acknowledgment.—The authors wish to express their appreciation to the National Institute of Health for the financial assistance which made this work possible, and to Mrs. Mary H. Aldridge and Mr. Byron Baer for carrying out the microanalyses.

Summary

1. 3′,4′,5′-Trimethoxy-2-methyl-4,5-methylenedioxybenzophenone (I) has been prepared by the stannic chloride catalyzed condensation of 3,4-methylenedioxytoluene with trimethylgalloyl chloride.

2. 3,4,5-Trimethoxy-α-piperonylacetophenone (III) has been prepared by an acetoacetic ester type of synthesis.

3. 3,4-Methylenedioxytoluene has been prepared by the hydrogenolysis of piperonyl alcohol. The latter is more resistant to hydrogenolysis over a copper–chromium–barium oxide catalyst than is benzyl alcohol.

(14) Asano and Yamaguti, *J. Pharm. Soc.* (*Japan*), **60**, 34 (1940).
(15) Labat, *Bull. soc. chim. biol.*, **15**, 1344 (1933).
(16) Perkin and Weizmann, *J. Chem. Soc.*, **89**, 1655 (1906).
(17) Robinson and Robinson, *ibid.*, **105**, 1463 (1914).
(18) Iddles, Low, Rosen and Hart, *Ind. Eng. Chem., Anal. Ed.*, **11**, 102 (1939).

COLLEGE PARK, MARYLAND RECEIVED MAY 18, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Spirobarbituric Acids Containing a Six-membered Carbocyclic Ring

BY ARTHUR C. COPE, PETER KOVACIC[1] AND MARION BURG[1]

Several spirobarbituric acids have been described by Dox and Yoder[2] in which the 5-carbon atom of the barbituric acid nucleus forms part of an unsubstituted cyclobutane or cyclohexane ring, but no pharmacological data were reported for these compounds. The spirobarbituric acids present points of structural similarity and dissimilarity to the 5,5-dialkylbarbituric acids which have led us to prepare a number of such compounds for pharmacological evaluation. In both classes the two acidic hydrogen atoms in the 5-position of the barbituric acid nucleus have been replaced by establishment of carbon-to-carbon linkages, but the spiro compounds differ uniquely from the 5,5-dialkylbarbituric acids in the spatial arrangement of the two rings in perpendicular planes. Since the pharmacological characteristics of 5,5-dialkylbarbituric acids vary widely according to the size and structure of the alkyl substituents, properties of the spiro compounds could not be predicted.

The intermediate esters required for the synthesis of spirobarbituric acids were prepared by the addition of butadiene to diethyl methylene-

(1) Sharp and Dohme Research Associate.
(2) Dox and Yoder, THIS JOURNAL, **43**, 677, 1366, 2097 (1921).

TABLE I

DIETHYL 6-ALKYL-3-CYCLOHEXENE-1,1-DICARBOXYLATES (I)

Alkyl substituents in formula I	Boiling point, °C.	Mm.	Yield, %	$n^{25}D$	d^{25}_4	Formula	Molecular refraction Calcd.	Molecular refraction Found	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
None[a]	105–108	3	67	1.4540		$C_{12}H_{18}O_4$						
6-Methyl[b]	129–131	10	43	1.4570	1.0466	$C_{13}H_{20}O_4$	62.87	62.52	64.97	64.76	8.38	8.31
6-Ethyl	93–94.5	0.5	33	1.4590	1.0333	$C_{14}H_{22}O_4$	67.52	67.49	66.11	65.79	8.72	8.80
6-Isopropyl	107–108	0.95	7[c]	1.4618	1.0300	$C_{15}H_{24}O_4$	72.11	71.59	67.13	67.14	9.01	8.84
6-*n*-Propyl	114–116	1.3	39	1.4585	1.0215	$C_{15}H_{24}O_4$	72.11	71.74	67.13	67.17	9.01	9.22
6-Isobutyl	132–133	3.5	16	1.4580	1.0091	$C_{16}H_{26}O_4$	76.73	76.33	68.05	67.91	9.28	9.40
3,4,6-Trimethyl[b]	101–103	0.7	73	1.4608	1.0201	$C_{15}H_{24}O_4$	72.11	72.15	67.13	66.94	9.01	9.14
2,5-Endomethylene-6-methyl[b]	99.5–102	1.1	22	1.4659	1.0738	$C_{14}H_{20}O_4$	65.29	65.06	66.64	66.37	7.99	8.06
6-Methylmercaptomethyl	133–134.5	<1	44	1.4905	1.1069	$C_{14}H_{22}O_4S$	75.46	74.86	58.71	58.58	7.74	7.89

[a] Described in ref. 3. [b] Described in ref. 4. [c] The same yield was obtained when the reaction temperature was 190–215°.

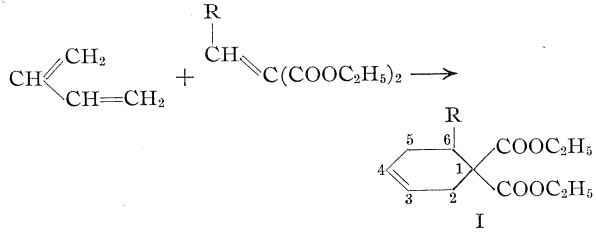
TABLE II

DIETHYL 2-ALKYLCYCLOHEXANE-1,1-DICARBOXYLATES (II)

2-Alkyl substituent in formula II	Boiling point, °C.	Mm.	Yield, %	$n^{25}D$	d^{25}_4	Formula	Molecular refraction Calcd.	Molecular refraction Found	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
None[a]	111–112	5	94	1.4438								
Methyl[b]	95–96	1	92	1.4490	1.0288	$C_{13}H_{22}O_4$	63.34	63.13	64.43	64.57	9.15	9.42
Ethyl	114.8–115.8	2.8	89	1.4516	1.0181	$C_{14}H_{24}O_4$	67.98	67.87	65.60	65.36	9.44	9.30
n-Propyl	94–97.5	0.4	83	1.4518	1.0063	$C_{15}H_{26}O_4$	72.58	72.43	66.63	66.73	9.69	9.73
Isopropyl	133–134.5	5	85	1.4556	1.0132	$C_{15}H_{26}O_4$	72.51	72.58	66.63	66.78	9.69	9.74
Isobutyl	123–125	2	88	1.4501	0.9929	$C_{16}H_{28}O_4$	77.20	76.63	67.57	67.54	9.92	10.06

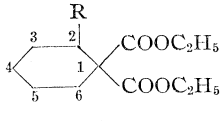
[a] The preparation by a different method is described by Dox and Yoder, THIS JOURNAL, **43**, 1366 (1921). [b] Described in ref. 4 and by Freer and Perkin, *J. Chem. Soc.*, **53**, 206 (1888).

malonate[3] or higher molecular weight diethyl alkylidenemalonates[4] to give esters of type I. Similar adducts were prepared by reaction of 2,3-dimethyl-1,3-butadiene and cyclopentadiene with diethyl ethylidenemalonate.

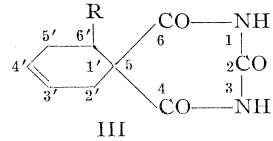


I

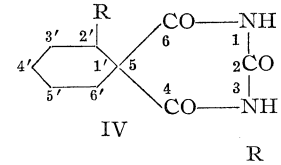
Catalytic hydrogenation of the unsaturated esters yielded corresponding saturated esters (II). Condensation of both classes of esters with urea and thiourea furnished spirobarbituric and thiobarbituric acids (III, IV, V and VI).[5]



II



III



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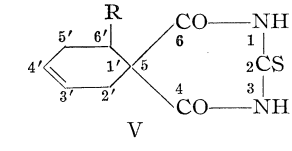
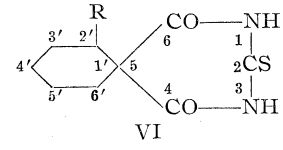


V



VI

Unsaturated esters (I) prepared by the diene synthesis are listed in Table I. The butadiene additions proceeded fairly well at 170–180° except in the case of diethyl isobutylidenemalonate, which gave a low yield of adduct. Diethyl isopropylidenemalonate and ethyl isopropylidenecyanoacetate failed to react with butadiene under the conditions investigated. Butadiene reacted with diethyl (2-methylmercaptoethylidene)-malonate to give an adduct (I, R = CH_3SCH_2–), but failed to add to diethyl (3-methylmercaptopropylidene)-malonate, which polymerized when the addition was attempted at 220°. The adduct formed from cyclopentadiene and diethyl ethylidenemalonate decomposed on distillation, except at low pressures, presumably by disproportionation into the original diene and ester. In one case (I, R = *n*-C_3H_7) the unsaturated ester was prepared by heating together the aldehyde (butyraldehyde), diethyl malonate, acetic anhydride and butadiene. The product was isolated in a yield equiva-

(3) Bachmann and Tanner, *J. Org. Chem.*, **4**, 500 (1939).

(4) Alder and Rickert, *Ber.*, **72**, 1983 (1939); U. S. Patent 2,264,-354; *C. A.*, **36**, 1615 (1942).

(5) In order to emphasize the relationship of these spiro compounds with barbituric acid the authors have chosen to describe them as derivatives of barbituric acid. By the present *Chemical Abstracts* system these spirobarbituric acids would be classified as diaza spirohydrocarbons.

TABLE III

6′-ALKYLSPIRO-[BARBITURIC ACID-5,1′-3′-CYCLOHEXENE] (III)[5]

Alkyl substitution in formula III	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Results of pharmacological tests in white mice[b] ND^{50} mg./kg.	ND^{100} mg./kg.	LD^{50} mg./kg.	Ratio LD^{50}/ND^{50}	Duration at ND^{100} Induction, min.	Duration, hr.
None	258.8–259.8	31	$C_9H_{10}N_2O_3$	55.66	55.66	5.19	5.21	14.43	14.38	>800	>800	>800	..	Mild lethargy at 0.5 hr. (800 mg./kg.)	
6′-Methyl	218.5–219	77	$C_{10}H_{12}N_2O_3$	57.68	57.93	5.80	5.78	13.45	13.41	420	550	575	1.3	15–18	3.2
6′-Ethyl	193.6–194.2	34	$C_{11}H_{14}N_2O_3$	59.44	59.33	6.35	6.31	12.61	12.40	245 ± 18	350	530 ± 23	2.16	8–10	1.47
6′-*n*-Propyl	191.5–192.5	68	$C_{12}H_{16}N_2O_3$	60.99	60.93	6.82	6.99	11.85	11.65	126	180	395	3.11	6–8	1.3
6′-Isopropyl	195–197	25	$C_{12}H_{16}N_2O_3$	60.99	61.15	6.82	7.02	11.85	11.65	125	150	408	3.26	6–11	1.0
3′,4′,6′-Trimethyl	150.5–151.5	51	$C_{12}H_{16}N_2O_3$	60.99	61.06	6.82	6.86	11.85	11.63	175	200	455	2.6	10–12	<1.0
6′-Methylmercaptomethyl[a]	168.2–168.6	21	$C_{11}H_{14}N_2O_3S$	51.95	52.04	5.55	5.60	11.02	10.90	325 ± 18	400	790 ± 44	2.43	13–15	1.12

[a] Prepared by Procedure D. [b] Tested by intraperitoneal injection in Carworth Farms strain F′ female mice weighing 16–18 g. Solutions were freshly prepared from the sodium salts for each test. Calculations are based on the equivalent weights of the free acids. Five mice were used at each dose level. The test for narcosis was performed by placing the mice on their left sides on a flat surface and striking their tails with a forefinger, then placing them on their right sides and repeating the process. A mouse which failed to right itself under these conditions was considered to be narcotized. ND^{50} is the dose at which 50% of the mice were narcotized; ND^{100} is the dose at which all were narcotized. LD^{50} signifies the dose at which 50% of the mice were killed.

TABLE IV

2′-ALKYLSPIRO-BARBITURIC ACID-5,1′-CYCLOHEXANE] (IV)[5]

2′-Alkyl substituent in formula IV	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Results of pharmacological tests in white mice ND^{50} mg./kg.	ND^{100} mg./kg.	LD^{50} mg./kg.	Ratio LD^{50}/ND^{50}	Duration at ND^{100} Induction, min.	Duration, hrs.
None[a]	279.6–280.6	33	$C_9H_{12}N_2O_3$							>800	>800	>800	..	Activity reduced (800 mg./kg.)	
Methyl	219.5–220	62	$C_{10}H_{14}N_2O_3$	57.12	57.15	6.71	6.70	13.32	13.10	185	250	445	2.4	5–6	1.4
Ethyl	194.8–195.2	34	$C_{11}H_{16}N_2O_3$	59.36	59.04	7.19	7.30	12.49	12.38	105 ± 9	150	345 ± 26	3.29	2–5	0.84
n-Propyl	185–185.5	34	$C_{12}H_{18}N_2O_3$	60.48	60.27	7.61	7.68	11.75	11.63	53	75	275	5.18	4–5	.4
Isopropyl	196.2–196.8	20	$C_{12}H_{18}N_2O_3$	60.48	60.45	7.61	7.56	11.75	11.60	67 ± 3	75	274 ± 13	4.12	10–12	.4
Isobutyl	194.2–194.6	25	$C_{13}H_{20}N_2O_3$	61.88	61.91	7.99	7.91	11.11	10.89	90 ± 4	110	217 ± 15	2.41	5–6	.4

[a] Described in ref. 2.

TABLE V

6′-ALKYL-2-THIOSPIRO-[BARBITURIC ACID-5,1′-3′-CYCLOHEXENE] (V)[5]

Alkyl substitution in formula V	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Results of pharmacological tests in white mice[a] ND^{50}, mg./kg.	ND^{100}, mg./kg.	LD^{50}, mg./kg.	Ratio, LD^{50}/ND^{50}	Duration at ND^{100} Induction, min.	Duration, hr.
None	231.4–233.2	30	$C_9H_{10}N_2O_2S$	51.41	51.45	4.79	4.91	13.33	13.34	>800	>800	>800	..	Mild lethargy at 1.0 hr. (800 mg./kg.)	
6′-Methyl	175–176	57	$C_{10}H_{12}N_2O_2S$	53.55	53.25	5.39	5.47	12.49	12.32	185	250	345	1.8	10–12	3.0
6′-Ethyl	129.2–129.4	13	$C_{11}H_{14}N_2O_2S$	55.44	55.39	5.92	6.09	11.76	11.95	155 ± 19	250	295 ± 24	1.9	4–6	2.54
3′,4′,6′-Trimethyl	171–172	52	$C_{12}H_{16}N_2O_2S$	57.11	56.96	6.39	6.40	11.10	11.03	185	250	335	1.8	3–4	>7.0
6′-*n*-Propyl	143.2–143.8	40	$C_{12}H_{16}N_2O_2S$	57.12	57.22	6.39	6.64	11.10	11.14	150 ± 13	200	310 ± 23	2.06	5–8	4.25

[a] See footnote *b*, Table III.

lent to that obtained if the condensation and diene addition reactions were carried out separately.

The catalytic hydrogenations of the unsaturated esters (I) to saturated esters II (Table II) proceeded rapidly and in good yield in the presence of Adams platinum catalyst.

The spirobarbituric acids (III and IV, Tables III and IV) were prepared by condensing the corresponding esters with urea in the presence of sodium isopropoxide in isopropyl alcohol. Isolation of the spirothiobarbituric acids (Tables V and VI) required a modification of the usual procedure because of the ease with which they were hydrolyzed to dicarboxylic acids. For example, acidification of a cold alkaline solution of 6′-methyl-2-thiospiro-[barbituric acid-5,1′-3′-cyclohexene] by

TABLE VI

2′-ALKYL-2-THIOSPIRO-[BARBITURIC ACID-5,1′-CYCLOHEXANE] (VI)[5]

2′-Alkyl substituent in formula VI	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Results of pharmacological tests in white mice: ND^{50}, mg./kg.	ND^{100}, mg./kg.	LD^{50}, mg./kg.	Ratio, LD^{50}/ND^{50}	Duration at ND^{100}: Induction, min.	Duration, hr.
None	243.2–243.8	31	$C_9H_{12}N_2O_2S$	50.92	50.98	5.70	5.69	13.20	13.18	>1200	>1200	>1200	..	Lethargy and scratch reflex (1200 mg./kg.)	
Methyl	172–172.5[a]	43	$C_{10}H_{14}N_2O_2S$	53.67	53.34	6.23	6.16	12.38	12.38	175	200	265	1.5	7–12	>3.0
Ethyl	158.4–159.2	20	$C_{11}H_{16}N_2O_2S$	54.97	55.21	6.72	6.67	11.66	11.52	170 ± 20	250	355 ± 27	2.08	3–4	1.27
n-Propyl	150.2–151.0	35	$C_{12}H_{18}N_2O_2S$	56.66	56.50	7.13	7.40	11.02	11.03	159 ± 11	200	253 ± 21	1.59	5–10	1.37

[a] Procedure C gave a crude product, m. p. 150–156.5° (dec.), which contained the corresponding dicarboxylic acid.

the addition of hydrochloric acid gave a mixture of the thiobarbituric acid derivative (V, R = CH_3) and 6-methyl-3-cyclohexene-1,1-dicarboxylic acid. This hydrolysis could be minimized by isolating the crude, dry sodium salt of the thiobarbituric acid derivative and adding it to an excess of cold hydrochloric acid (procedure D). The sodium salts of the spirothiobarbituric acids proved to be sufficiently stable in aqueous solution for pharmacological testing.

Pharmacological

Preliminary pharmacological data which were obtained for the spirobarbituric acid derivatives by Dr. Karl H. Beyer and Mr. S. E. McKinney of Sharp and Dohme, Inc., are included in Tables III–VI. Among the spirobarbituric acid (Tables III and IV) both narcotic activity and toxicity increased with increasing molecular weight, and the compounds with the highest therapeutic ratios were the 6′-isopropyl and *n*-propyl derivatives (formula III) and the 2′-isopropyl and *n*-propyl derivatives (formula IV). Both unsaturated and saturated spirothiobarbituric acids (formulas V and VI) were less active, longer acting and had poorer therapeutic ratios than the corresponding spirobarbituric acids.

Experimental[6]

Diethyl methylenemalonate was prepared from paraformaldehyde and diethyl malonate by the method of Bachmann and Tanner.[3] The crude reaction mixture was distilled through a 20-cm. Widmer column until the distillation temperature reached 116° (43 mm.). Some decomposition occurred at 105–116° (43 mm.). The pale green viscous residue was distilled through a 20 × 1.3 cm. Vigreux column with a heated jacket and the diethyl methylenemalonate fraction which collected at 124–128° (35 mm.) was treated with butadiene at once to prepare diethyl 3-cyclohexene-1,2-dicarboxylate.[3] Other diethyl alkylidenemalonates were prepared by procedures described previously.[7]

Diethyl 6-Alkyl-3-cyclohexene-1,1-dicarboxylates (I). Procedure A.—Conditions similar to those used by Alder and Rickert[4] were employed, which can be illustrated by description of the procedure followed for preparing diethyl 6-*n*-propyl-3-cyclohexene-1,1-dicarboxylate. Diethyl *n*-butylidenemalonate (112.7 g., 0.53 mole) was placed in a 500-ml. steel hydrogenation bomb which had been cooled with Dry Ice. After the ester was cooled to −15°, 115 g. (2.1 moles) of butadiene (previously collected in a Dry-Ice-cooled tube from a commercial cylinder) was added. The mixture was stirred, the bomb closed, and allowed to stand until it reached room temperature, It was then heated for twelve to fourteen hours at 170–180° without shaking. The product was distilled through a 20-cm. Widmer column. About 80 g. of vinylcyclohexene was collected at 20–60 mm., followed by 50 g. of recovered diethyl *n*-butylidenemalonate, b. p. 99–109° (3 mm.). The crude adduct (70 g., b. p. 109–125° at 2.8 mm.) was redistilled through the same column and yielded 52 g. (39%) of diethyl 6-*n*-propyl-3-cyclohexene-1,1-dicarboxylate, b. p. 114–116° (1.3 mm.). The properties of other esters prepared by this procedure are listed in Table I.

Procedure B.—Diethyl malonate (80.1 g., 0.5 mole), freshly distilled butyraldehyde (36.1 g., 0.5 mole), acetic anhydride (51.1 g., 0.5 mole) and butadiene (108 g., 2.0 moles) were mixed in a Dry-Ice-cooled 500-ml. steel hydrogenation bomb. The mixture was heated at 182–195° for twelve and one-half hours without shaking, and the product was isolated by the method described under Procedure A. The yield of diethyl 6-*n*-propyl-3-cyclohexene-1,1-dicarboxylate, b. p. 99–101.8° (0.8 mm.), (32 g., 20.3%) was equivalent to the yield obtained by carrying out the condensation and addition reactions as separate preparations.

Diethyl (2-Methylmercaptoethylidene)-malonate. (a) Methylmercaptoacetaldehyde Diethyl Acetal.—Diethyl bromoacetal[8] was treated with sodium methylmercaptide by an adaptation of the procedure of Barger and Coyne[9] suitable for a larger scale preparation. Absolute ethanol (1.3 l.) was placed in a 3-l. three-necked flask fitted with a reflux condenser and a motor-driven slip-sealed stirrer. Sodium ethoxide was prepared by the addition of 79 g. (3.44 g. atoms) of clean sodium. The solution was cooled in an ice-bath and the reflux condenser was replaced by a spiral condenser cooled with ice-water. A T-tube was attached to the top of condenser which led to a safety trap which was connected to a water aspirator. A screw clamp attached to the open end of the T-tube was used to regulate the aspiration. Methyl mercaptan (100 g., 2.08 moles) was introduced gradually through a gas inlet tube by aspiration during one hour, in an assembly of apparatus similar to that used for introducing bromine in the preparation of bromoacetal,[8] except that the methyl mercaptan was placed in a 200-ml. round-bottom flask (fitted with inlet and outlet tubes) which initially was cooled and subsequently was warmed to control the rate of addition. The inlet tube was replaced by a 500-ml. dropping funnel and 296 g. (1.5 moles) of freshly distilled diethyl bromoacetal was added during twenty-five minutes with stirring. Sodium bromide separated during the addition. The reaction mixture was allowed to stand overnight, filtered,

(6) Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy, Mrs. Louise W. Spencer and Mr. Philip H. Towle for analyses.

(7) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

(8) McElvain and Kundiger, "Organic Syntheses," Vol. 23, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 8.

(9) Barger and Coyne, *Biochem. J.*, **22**, 1417 (1929).

and the filtrate added to 2 l. of water. The oily layer was removed and the aqueous layer saturated with sodium chloride and extracted with five 100-ml. portions of benzene. The combined oil and extracts were distilled through a 20-cm. Widmer column and yielded 164 g. (67%) of methylmercaptoacetaldehyde diethyl acetal, b. p. 72.5–73.5° (11 mm.).

(b) **Methylmercaptoacetaldehyde.**—Methylmercaptoacetaldehyde diethyl acetal (86.1 g., 0.52 mole) was heated under reflux with 200 ml. of water and 2 ml. of concd. hydrochloric acid for one-half hour. The mixture became homogeneous after five minutes at the reflux temperature. The solution was cooled, extracted with 150 ml. of ether, partially saturated with sodium chloride and again extracted with 150 ml. of ether. The combined extracts were washed with two 100-ml. portions of 10% sodium bicarbonate solution, three times with 250-ml. portions of water, dried over magnesium sulfate and distilled through a 20-cm. Widmer column. The yield of methylmercaptoacetaldehyde, b. p. 93–95° (235 mm.), was 25 g. (53%).

(c) **Diethyl (2-Methylmercaptoethylidene)-malonate.**—Diethyl malonate (62.5 g., 0.39 mole), methylmercaptoacetaldehyde (70 g., 0.78 mole) and acetic anhydride (62.5 g., 0.61 mole) were heated under reflux in an oil-bath at 130° for twenty-four hours. The mixture was fractionated through a 20-cm. Widmer column at atmospheric pressure until the distillation temperature reached 113°. Continuation of the fractionation under reduced pressure yielded a crude product (42 g., b. p. 121–135° at 3 mm.) which was fractionated through a 220 × 8 mm. glass helix-packed, total condensation, variable take-off type column. The yield of diethyl (2-methylmercaptoethylidene)-malonate was 33.5 g. (37%) b. p. 123.5–125.5° (1.5 mm.), $n^{25}D$ 1.4882, d^{25}_4 1.1057; M_D calcd. 59.19, found 60.55 (exaltation 1.36).

Anal. Calcd. for $C_{10}H_{16}O_4S$: C, 51.70; H, 6.94. Found: C, 51.59; H, 6.92.

Diethyl (3-Methylmercaptopropylidene)-malonate.—Diethyl malonate (40 g., 0.25 mole), β-methylmercaptopropionaldehyde[10] (57 g., 0.55 mole) and acetic anhydride (40 g., 0.39 mole) were allowed to react under the conditions described above. Redistillation of the crude product through a 220 × 8 mm. glass helix-packed, total condensation, variable take-off type column yielded 43.8 g. (70.6%) of diethyl (3-methylmercaptopropylidene)-malonate, b. p. 143–145° (2.5 mm.), $n^{25}D$ 1.4885; d^{25}_4 1.0877; M_D calcd. 63.81, found 65.31 (exaltation 1.50).

Anal. Calcd. for $C_{11}H_{18}O_4S$: C, 53.64; H, 7.53. Found: C, 53.70; H, 7.35.

Diethyl 6-(Methylmercaptomethyl)-3-cyclohexene-1,1-dicarboxylate.—Diethyl (2-methylmercaptoethylidene)-malonate (22.5 g., 0.097 mole) was placed in a 60 × 2 cm. Pyrex bomb-tube and cooled in a chloroform–carbon tetrachloride–Dry Ice-bath. Butadiene (27 g., 0.5 mole) was added and the tube was sealed and heated in a bomb furnace at 160–170° for fourteen hours. Distillation yielded 19.4 g. of a crude product, b. p. 123–134.5° (1 mm.) which was redistilled through the helix-packed column described above. The yield of diethyl 6-(methylmercaptomethyl)-3-cyclohexene-1,1-dicarboxylate was 12.5 g. (44%), b. p. 133–133.5° (less than 1 mm.), $n^{25}D$ 1.4905, d^{25}_4 1.1069; M_D calcd. 75.46, found 74.86.

Anal. Calcd. for $C_{14}H_{22}O_4S$: C, 58.71; H, 7.74. Found: C, 58.58; H, 7.89.

Under these conditions no adduct was obtained from butadiene and diethyl (3-methylmercaptopropylidene)-malonate, and most of the ester was recovered. At 220° partial polymerization occurred and the recovery of the ester was reduced to 50%, but no adduct was isolated.

(10) Supplied by U. S. Industrial Chemicals, Inc., through the courtesy of Harry L. Fisher. Described by Hurd and Gershbein, THIS JOURNAL, **69**, 2334 (1947); Catch, Cook, Graham and Heilbron, *Nature*, **159**, 578 (1947); ref. 9.

Diethyl 2-Alkylcyclohexane-1,1-dicarboxylates (II).—Solutions of the unsaturated esters (I) (approximately 50 g.) in dry ethyl acetate (about 50 ml.) were hydrogenated in the presence of 0.5 g. of prereduced Adams platinum catalyst at room temperature and about 25 p. s. i. during one-half to two hours. The properties and yields of the saturated esters (II) which were obtained are listed in Table II.

Barbituric Acid Condensations.—The barbituric acid derivatives described in Tables III and IV were prepared by a modification of a procedure described previously,[11] which is illustrated by the synthesis of 2′-*n*-propylspiro-[barbituric acid-5,1′-cyclohexane] (IV, R = *n*-C_3H_7) (procedure C).

Diethyl 2-*n*-propylcyclohexane-1,1-dicarboxylate (14.8 g., 0.055 mole) and urea (6.6 g., 0.11 mole) were added to the sodium isopropoxide prepared from 2.3 g. (0.1 g. atom) of sodium and 95 ml. of dry isopropyl alcohol, and the mixture was heated under reflux for fifteen hours in an oil-bath at 105°. The isopropyl alcohol was removed under reduced pressure and the solid residue cooled in an ice-bath and dissolved in 100 ml. of cold water. The solution was extracted with three 30-ml. portions of ether, and the combined extracts were washed with water. The combined water washes and aqueous solution were cooled in ice and acidified by dropwise addition of a 50% excess of 20% hydrochloric acid, with stirring. The solid barbituric acid derivative was separated by filtration, washed with water and recrystallized to constant melting point from dilute alcohol. Distillation of the ether extracts resulted in recovery of 4.6 g. of diethyl 2-*n*-propylcyclohexane-1,1-dicarboxylate, b. p. 108° (0.8 mm.), $n^{25}D$ 1.4478.

Thiobarbituric Acid Derivatives.—The thiobarbituric acid derivatives described in Tables V and VI were prepared by a method (procedure D) which may be illustrated by details of the synthesis of 6′-*n*-propyl-2-thiospiro-[barbituric acid-5,1′-3′-cyclohexene] (V, R = *n*-C_3H_7).

Procedure C (above) was followed with 24.3 g. (0.088 mole) of diethyl 6-*n*-propyl-3-cyclohexene-1,1-dicarboxylate, 10.5 g. (0.14 mole) of thiourea and the sodium isopropoxide prepared from 4.0 g. (0.17 g. atom) of sodium and 200 ml. of dry isopropyl alcohol as the reactants. After the period of reflux, distillation of the isopropyl alcohol under reduced pressure left a crude solid mixture containing the sodium salt of 6′-*n*-propyl-2-thiospiro-[barbituric acid-5,1′-3′-cyclohexene]. This solid was washed with ether, collected on a filter, and added in portions with stirring to 250 ml. of 20% hydrochloric acid cooled in an ice-bath. The solid product was separated by filtration and recrystallized to constant melting point from dilute alcohol. No appreciable amount of a carboxylic acid was isolated when this procedure was followed. A similar preparation (I, R = CH_3–) according to procedure C gave a crude product which was in part soluble in aqueous sodium bicarbonate solution. Acidification of the sodium bicarbonate solution precipitated 6-methyl-3-cyclohexene-1,1-dicarboxylic acid, which after recrystallization from acetone–benzene had m. p. 175–176° (dec.).

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.56; neut. equiv., 92.09. Found: C, 58.60; H, 6.54; neut. equiv., 92.49.

Summary

The preparation, properties and pharmacological assay of a number of spirobarbituric and thiobarbituric acids derived from diethyl 6-alkyl-3-cyclohexene-1,1-dicarboxylates and diethyl 2-alkylcyclohexane-1,1-dicarboxylates and the preparation and properties of these intermediate esters are described.

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(11) Cope and Hancock, THIS JOURNAL, **61**, 96 (1939).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

Chemical Constitution and the Tanning Effect. III. Polyhydroxybenzophenones[1]

BY ALFRED RUSSELL[2] AND GEORGE B. BUTLER[3]

Previous communications from this laboratory have described the tanning properties of the gallic acid esters of certain sugars.[4,5] From an observation of the type compounds that the natural tannins are believed to be, as well as these synthetic materials, there seems to be in every case a pattern consisting of at least two benzene nuclei joined by some type of bridge, and having a sufficient number of water solubilizing groups to impart to the compound a moderate degree of water solubility. This pattern may be only a part of the molecule in some cases, but it always appears to be present. Also of the fission products of all the natural tannins, the polyhydroxybenzenes and the polyhydroxybenzoic acids are the main constituents.

The present investigation describes the preparation of a series of polyhydroxybenzophenones which conform to the above molecular pattern, and evaluation of these materials as tannins. A literature investigation of known compounds of this series revealed the fact that 3′,4′,2,4,6-pentahydroxybenzophenone,[6] commonly known as maclurin, which was isolated from the wood of *Chlorophora tinctoria*, precipitates gelatin from solution, an indication that this polyhydroxy compound might have tanning properties. Therefore, this compound was included in the series which was prepared and tested. In no case, however, did these substances exhibit tanning properties as described in detail below.

Experimental

Preparation of Materials.—The methyl ethers of vanillin, catechol, resorcinol, hydroquinone, pyrogallol and phloroglucinol were prepared by the procedure described in "Organic Syntheses," Coll. Vol. II, p. 619. Veratroyl chloride was prepared by the action of thionyl chloride on veratric acid which was obtained by the oxidation of veratraldehyde. Anisoyl chloride was obtained from anisic acid by the action of thionyl chloride.

Synthesis of the Polyhydroxybenzophenones.—Method I, a Friedel–Crafts reaction between the methoxybenzoyl chloride and the methoxybenzene followed by demethylation, gave better yields in the first step but the demethylation was unsatisfactory when the number of hydroxyl groups exceeded three. Method II, a dehydration reaction between the hydroxybenzoic acid and the hydroxybenzene in the presence of zinc chloride,[7] was used when the acid chloride was not available or when Method I did not give good results.

(1) Abstracted from a thesis presented by George B. Butler to The Graduate School of the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, June, 1942.

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(4) Russell and Tebbens, THIS JOURNAL, **64**, 2274 (1942).

(5) Russell, Tebbens and Arey, *ibid.*, **65**, 1472 (1943).

(6) Haas and Hill, "An Introduction to the Chemistry of Plant Products," Longmans, Green and Co., London, 1928.

(7) Blueler and Perkin, *J. Chem. Soc.*, **109**, 541 (1916).

A. Method I.—A solution of one-half mole of the methoxybenzoyl chloride and one-half mole of the methoxybenzene in dry carbon disulfide was added slowly to one mole of anhydrous aluminum chloride and 200 g. of dry carbon disulfide maintained at 15–20° and contained in a one-liter, three-necked flask equipped with stirrer, reflux condenser, dropping funnel and thermometer. The solution was allowed to warm up to room temperature and stirring was continued for three hours. The mixture was then let stand overnight, refluxed for three and one-half hours, cooled, poured onto ice and extracted with ether. The extract was washed with sodium carbonate solution and with water, then dried over calcium chloride. The product, isolated from the ether, was recrystallized from 50% alcohol.

The methoxybenzophenone was converted to the hydroxybenzophenone by heating with an equal weight of anhydrous aluminum chloride in anhydrous toluene for one hour at 120°. The mixture was poured into iced dilute hydrochloric acid and the toluene layer was washed with water. The hydroxybenzophenone was extracted with sodium carbonate solution and precipitated from this solution by the addition of carbon dioxide or dilute hydrochloric acid. The lower members were recrystallized from dilute ethanol, the higher members from very dilute hydrochloric acid. Over-all yields up to 65% were realized.

B. Method II.—Equal parts of the hydroxybenzoic acid and the hydroxybenzene were heated together with three parts of freshly fused and powdered zinc chloride for forty-five minutes at 125–140°. The reaction mass was taken up in dilute hydrochloric acid, filtered, the solid product washed thoroughly with sodium bicarbonate solution and finally crystallized from dilute ethanol or very dilute hydrochloric acid.

Tanning Procedure

The standard gelatin test was used as a preliminary indication of the tanning properties of these compounds. In all cases, the solutions resulting from the first crystallization of the hydroxy ketones caused gelatin precipitation, however these solutions always contained either aluminum or zinc salts, as well as other impurities. After a second crystallization, the resulting saturated solutions of the hydroxy ketones would in no case cause gelatin precipitation. Pure synthetic maclurin behaved as described above. It is probable that the sample of natural maclurin which was reported to have the property of precipitating gelatin contained some tannin material as an impurity, since the original source of maclurin is known to contain tannins also.

The standard procedure previously described[4] for conducting tannage tests could not be used since the polyhydroxybenzophenones were not soluble enough in 4% aqueous sodium chloride. The following modified procedure was therefore employed:

A standard size test piece of calfskin was dehydrated by agitation with several portions of absolute ethanol. It was then covered with three times its weight of absolute ethanol, treated with 25% of its weight of the pure material to be tested, and the whole agitated for twenty-four hours. A comparison was then made between the

TABLE I

Hydroxybenzophenone	Method of prepn.	M. p., °C.[a]	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
3,4-Di-	I	132 (134)	$C_{13}H_{10}O_3$	...	..	...	..
4,4'-Di-	I	210 (210)	$C_{13}H_{10}O_3$	...	..	...	..
3,4,4'-Tri-	I	205	$C_{13}H_{10}O_4$	67.82	4.35	67.70	4.65
2,3,4-Tri-	I	118 (140)[b]	$C_{13}H_{10}O_4$	67.82	4.35	67.66	4.55
2,4,4'-Tri-	I	198 (200)	$C_{13}H_{10}O_4$	...	..	..	..
2',2,4-Tri-	II	138 (134)	$C_{13}H_{10}O_4$	...	..	...	..
2,4',5-Tri-	I	162	$C_{13}H_{10}O_4$	67.82	4.35	67.63	4.56
2',2,5-Tri-	II	98	$C_{13}H_{10}O_4$	67.82	4.35	67.70	4.39
2,3,4,4'-Tetra-	I	219	$C_{13}H_{10}O_5$	63.41	4.06	63.20	3.94
2,4,2',4'-Tetra-	II	180 (193)[c]	$C_{13}H_{10}O_5$	63.41	4.06	63.25	4.07
2,3,4,2',4'-Penta-	II	200 (168) (187)[d]	$C_{13}H_{10}O_6$	59.54	3.82	59.85	3.94
2',4',3,4,5-Penta-	II	253 (200)[e]	$C_{13}H_{10}O_6$	59.54	3.82	59.50	3.94
3',4',2,4,6-Penta-	I	220 (220)	$C_{13}H_{10}O_6$	...	..	...	..
2,3,4,3',4',5'-Hexa-	II	276 (273)	$C_{13}H_{10}O_7$	...	..	...	..
2,3,4,2',3',4'-Hexa-	II	240 (238)	$C_{13}H_{10}O_7$	...	..	...	..

[a] Melting points recorded in literature are enclosed in parentheses. [b] Reported to crystallize with one molecule of water of crystallization.[8] The monobenzoate of pyrogallol is also reported to have a melting point of 140°. [c] Reported to crystallize with 1.5 molecules of water of crystallization.[9] [d] Controversial melting points reported.[10] [e] Heilbron[11] lists this compound as having been reported by Korczynski and Nowakowski,[12] m. p. 242°. These authors reported 3',4',2,4,5-pentahydroxybenzophenone prepared by the Hoesch reaction between protocatechunitrile and 1,2,4-trihydroxybenzene, m. p. 242°.

test piece of skin and a similar piece of skin treated with mimosa tannin under the same conditions. While the piece of skin treated with mimosa tannin was converted to leather, in no case did the samples treated with the polyhydroxybenzophenones show any change. After thorough washing with cold water, and drying in air, these samples were converted to an inflexible, horn-like material characteristic of untreated skin. On storing samples of these test pieces in aqueous media, apparently normal putrefaction occurred.

The data concerning the polyhydroxybenzophenones are presented in tabular form.

(8) Fischer and Rapaport, *Ber.*, **46**, 2393 (1913).
(9) Shoesmith and Haldane, *J. Chem. Soc.*, **125**, 113 (1924).
(10) Atkinson and Heilbron, *ibid.*, 2690 (1926).
(11) Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, 1934.
(12) Korczynski and Nowakowski, *Bull. soc. chim.*, **43**, 335 (1928).

Summary

Fifteen polyhydroxybenzophenones have been prepared and tested for tanning properties. None were found to have the property of converting hide to leather as judged by color, feel, texture, flexibility and fullness, even though one naturally occurring polyhydroxybenzophenone is reported in the literature to cause precipitation of gelatin, a preliminary test for tanning materials.

Four of these compounds have not previously been reported, while physical properties of four others reported in the literature are either controversial or fail to agree with those obtained in this investigation. Analyses are reported for these compounds.

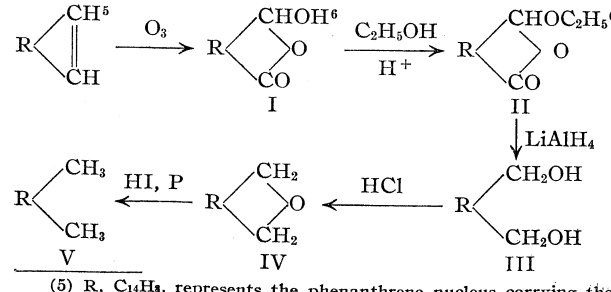
CHAPEL HILL, NORTH CAROLINA RECEIVED MAY 2, 1949

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

The Preparation of 4,5-Dimethylphenanthrene[1]

BY MELVIN S. NEWMAN AND HARRY S. WHITEHOUSE[2]

Considerable interest is associated with 4,5-dimethylphenanthrene (V) because of (1) its possible identity with the hydrocarbon,[3] $C_{16}H_{14}$, isolated from the dehydrogenation products of strophanthidin, and (2) its position as the parent hydrocarbon of compounds containing methyl groups in the so-called "impossible" positions.[4] In this paper we describe the preparation of V from pyrene by the steps outlined in the chart.



(1) The material herein presented is taken from the Ph.D. thesis of H. S. W., Ohio State University, December, 1948.
(2) Present address, Procter and Gamble Company, Chemical Division, Ivorydale, Ohio.
(3) Lewis and Elderfield, *J. Org. Chem.*, **5**, 290 (1940); Jacobs and Fleck, *J. Biol. Chem.*, **97**, 57 (1932).
(4) See discussion in Newman, THIS JOURNAL, **62**, 2295 (1940), and Newman and Hussey, *ibid.*, **69**, 3023 (1947).
(5) R, $C_{14}H_9$, represents the phenanthrene nucleus carrying the substituents indicated in positions 4 and 5.
(6) Our reasons for preferring the cyclic structure for these compounds will be set forth in a forthcoming paper.

The ozonization of pyrene was carried out essentially as described previously.[7] The aldehydo acid[6] (I) thus obtained was converted into the ethyl ester[6,8] which was subsequently reduced with lithium aluminum hydride[9] to the diol (III). This diol was converted quantitatively to the cyclic ether (IV) by a variety of acidic reagents. Reduction of IV with hydriodic acid and red phosphorus under very carefully controlled conditions afforded a hydrocarbon, m. p. 76.3–76.9°, which is assigned the structure of 4,5-dimethylphenanthrene (V) on the following counts: (1) analysis of the hydrocarbon, its picrate, and its 2,4,7-trinitrofluorenone[10] (TNF) derivative; (2) cyclodehydrogenation to pyrene; (3) the ultraviolet absorption spectrum and (4) the non-identity of V with any of the fifteen previously described 9,10-unsubstituted dimethylphenanthrenes (there are only sixteen 9,10-unsubstituted dimethylphenanthrenes).

It is interesting to note that V forms a picrate which dissociates very easily in alcohol. This picrate is also lower melting than that of any of the other above mentioned fifteen dimethylphenanthrenes. This behavior is found in other compounds having the same or a similar structural feature.[11]

The ultraviolet absorption spectrum proved similar to that of 1,4,5-trimethylphenanthrene.[11c] The intensity of the absorption, expressed in log units, at the maxima and minima are as follows[12]: 224, 3.91; 230, 3.98; 235, 3.84; 255, 4.56; 285, 3.73; 301, 3.91; 307, 3.82 and 313, 3.92.

One attempt to oxidize V to a quinone was made. As no crystalline quinone was readily isolated, an alcoholic solution of the oxidation product was treated with *o*-phenylenediamine whereupon a yellow crystalline quinoxaline derivative was obtained.

A consideration of the properties of the known dimethylphenanthrenes not containing a substituent in the 9 or 10 position indicates that 4,5-dimethylphenanthrene (V) herein reported is different from any of the others[13] and from the hydrocarbon, $C_{16}H_{14}$, obtained from strophanthidin by Lewis and Elderfield.[3]

Attempts to reduce the aldehyde group of the aldehydo acid (I) to a methyl group are of interest. On Clemmensen reduction 1,2-dihydropyrene[14] was obtained. This ready formation of a carbon–carbon bond between the carbons in the aldehydo acid (I) recalls the fact that on reaction of I with phenylhydrazine 2-phenylazo-1-pyrenol is formed.[7] Treatment of I with alkali and Raney nickel alloy[15] yielded a small amount of the lactone of 5-hydroxymethyl-9,10-dihydro-4-phenanthrenecarboxylic acid, but no acidic material was found. This is surprising in view of the ready hydrogenolysis of carbon–oxygen bonds of the benzyl type usually noted with this reductive system.[15] The lactone ring in VI could be reductively cleaved by refluxing with 47% hydriodic acid, red phosphorus, and 85% phosphoric acid but no pure acid was isolated from the reaction products. The dihydrolactone (VI) was converted into the fully aromatic lactone of 5-hydroxymethyl-4-phenanthrenecarboxylic acid (VII) by heating with sulfur. This lactone (VII) was also formed by refluxing II with toluene and aluminum isopropylate.[16] An attempt to reduce VII with hydriodic acid as with VI failed, VII being recovered quantitatively. Prior to a proposed thioacetal hydrogenolysis,[17] the aldehydo-acid (I) was treated with ethyl mercaptan. Since a compound which we believe to be the CH_3CH_2S-analog of II was obtained further work along this path was discontinued.

The extraordinary ease of cyclization of the dimethanol (III) to the seven-membered cyclic ether (IV) and the resistance of IV to cleavage are noteworthy. Any acidic reagent readily caused the cyclization of III to IV. On passing anhydrous hydrogen bromide through a refluxing solution of IV in toluene, no cleavage was observed, as was also the case on refluxing III with benzene and aluminum bromide. Reaction between hydrogen bromide and fused IV did not set in rapidly until a temperature of 150° was reached, and then a dark tar was formed.

Experimental[18]

Pseudo Ethyl 5-Formyl-4-phenanthrenecarboxylate (II).—A suspension of 8.5 g. of 5-formyl-4-phenanthrenecarboxylic acid,[19] (I) in 50 ml. of alcohol and 100 ml. of benzene containing 5 drops of concentrated sulfuric acid was refluxed on a column with a phase separating head until no further water was obtained. The ester was crystallized from benzene to yield 7.2 g. (76%) of fine silky colorless needles as a first crop, m. p. 177.2–179.2°. The analytical sample melted at 178.8–179.5°. *Anal.* Calcd. for $C_{18}H_{14}O_3$: C, 77.7; H, 5.1. Found[a]: C, 78.0, 77.7; H, 5.5, 5.1.

The same ester was prepared in quantitative yield by treatment of the acid chloride[6] with alcohol in pyridine.

(7) Vollman, *et al.*, *Ann.*, **531**, 1 (1937).

(8) The compound, m. p. 177.5–178°, described by Fieser and Novello, THIS JOURNAL, **62**, 1855 (1940), as the ethyl ester of 4-hydroxymethylphenanthrene-5-carboxylic acid is actually the cyclic ethyl ester of I. We confirmed the identity of these two compounds by a mixed melting point determination with a sample supplied by Dr. L. F. Fieser.

(9) Finholt, Bond and Schlesinger, THIS JOURNAL, **69**, 1199 (1947); Nystrom and Brown, *ibid.*, **69**, 1197 (1947).

(10) Orchin and Woolfolk, *ibid.*, **68**, 1727 (1946).

(11) (a) Cook, *J. Chem. Soc.*, 1592 (1932); (b) Newman and Hussey, THIS JOURNAL, **69**, 3023 (1947); (c) Newman and Wheatley, *ibid.*, **70**, 1913 (1948).

(12) We are indebted to Mrs. Arlene Brooks for these measurements.

(13) "Elsevier's Encyclopaedia of Organic Chemistry," Elsevier Publishing Co., Inc., New York, N. Y., 1946, Vol. 13, p. 800 ff.

(14) E. A. Coulson, *J. Chem. Soc.*, 1298 (1937).

(15) D. Papa, E. Schwenk and B. Whitman, *J. Org. Chem.*, **1**, 587 (1942).

(16) A. L. Wilds in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. II, p. 178.

(17) M. L. Wolfrom and J. Karabinos, THIS JOURNAL, **66**, 909 (1944).

(18) All melting points corrected except as otherwise noted. Analyses marked [k] by Mrs. E. H. Klotz, O. S. U., [p] by W. J. Polglase, O. S. U., [a] Arlington Laboratories, Fairfax, Va., [c] H. S. Clark, Microanalytical Laboratory, Urbana, Illinois, and [s] by G. L. Stragand, University of Pittsburgh.

(19) Prepared as described on p. 148 of ref. 7.

4,5-Phenanthrenedimethanol (III).—A warm solution of 5.0 g. of II in 250 ml. of dry sulfur-free benzene was added to a stirred solution containing 0.5 g. of lithium aluminum hydride in 100 ml. of ether. After careful hydrolysis at 0° with water and then dilute sulfuric acid, III was isolated in 90% yield as colorless crystals, m. p. 156–162°. It proved quite tedious to purify this product to its maximum melting point, 164.4–168.8°, by recrystallization from benzene as small amounts of an impurity, evidently the cyclic ether (IV) persisted. III crystallized in rosettes of stout faintly straw-colored elongated prisms. The dibenzoate, dense colorless prisms, m. p. 152.8–154.2°, was prepared in pyridine at 0° using benzoyl chloride and was recrystallized from petroleum ether, b. p. 90–97° (Skellysolve C). *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.7; H, 5.9. Found[a]: C, 80.4, 80.6; H, 6.0, 6.0. Active hydrogen: 2.0. Found (Zerewitinow): 1.8, 1.9. Calcd. for $C_{30}H_{22}O_4$: C, 80.7; H, 5.0. Found[k]: C, 81.3, 80.8; H, 5.1, 5.1.

Cyclic Ether of 4,5-Phenanthrenedimethanol (IV).—Anhydrous hydrogen chloride was passed into a suspension of 2.87 g. of III in 20 cc. of benzene at room temperature for fifteen minutes, during which the glycol disappeared, heat was evolved, and droplets of water were formed. The crude product was vacuum distilled to yield 2.41 g. (90%) of colorless IV, m. p. 72.8–76.2°, b. p. 168–169° at 1 mm. An analytical sample, recrystallized from methanol, melted at 78.5–78.8°. This ether was the main product when the glycol was treated under the following conditions: thionyl chloride in benzene–pyridine; phosphorus pentasulfide in refluxing benzene (on fusion with this reagent a violent reaction took place and no pure product was isolated); anhydrous hydrogen bromide in boiling benzene or with molten III; and *p*-toluenesulfonyl chloride in pyridine at 0°. The TNF[10] complex of IV formed orange elongated prisms, m. p. 194–195° after recrystallization from alcohol–benzene. *Anal.* Calcd. for $C_{16}H_{12}O$: C, 87.3; H, 5.5. Found[p]: C, 87.2, 87.2; H, 5.7, 5.6. Calcd. for $C_{29}H_{17}O_8N_3$: C, 65.1; H, 3.2; N, 7.9. Found[c]: C, 64.9, 65.1; H, 3.3, 3.1; N, 8.1, 8.1.

4,5-Dimethylphenanthrene (V).—In one of the better of many runs a mixture of 3.0 g. of IV, 1.5 g. of red phosphorus, and 30 ml. of 47% hydriodic acid was sealed in a tube and heated at 165° for twelve hours. Vacuum distillation at 1 mm. of the organic reaction product afforded 0.73 g. (26%) of crude V, m. p. 66–72°. There remained a large quantity of viscous non-volatile residue in the distilling flask. The crude product was converted to the TNF derivative[10] which was recrystallized once from ethanol. By chromatography over alumina the TNF derivative was decomposed and the resulting hydrocarbon was recrystallized from methanol to yield 0.47 g. (17%) of V, m. p. 76.0–76.8°. Further recrystallization from methanol yielded the analytical sample, m. p. 76.3–76.9°, as small colorless crystals. The recrystallized TNF derivative formed glistening scarlet needle-shaped crystals, m. p. 120.4–121.4° after several recrystallizations from alcohol. *Anal.* Calcd. for $C_{16}H_{14}$: C, 93.2; H, 6.8. Found[c]: C, 92.9, 92.8; H, 6.8, 6.8. Calcd. for $C_{29}H_{19}O_7N_3$: C, 66.8; H, 3.7; N, 8.1. Found[c]: C, 66.7; H, 3.6; N, 8.2.

The picrate was best formed by dissolving 0.103 g. of V and 0.115 g. of pure picric acid in alcohol. On standing at room temperature orange-red elongated prisms separated. These were collected on a small suction funnel and rinsed with small amounts of ice-cold alcohol. They melted sharply at 109.6–110.2°. *Anal.* Calcd. for $C_{22}H_{17}O_7N_3$: C, 60.7; H, 3.9; N, 9.7. Found[c]: C, 60.6, 60.7; H, 3.9, 3.9; N, 9.8, 10.0.

The separation of unreacted ether (IV) from V was effected most easily by conversion to the TNF derivatives, that of the ether (IV) being much less soluble. Considerable amounts of IV were present in hydriodic reductions which were run at lower temperatures than 165° or at this temperature for less than twelve hours. When reductions were attempted at 180–190° less V and more non-volatile residue were produced.

Conversion of V to Pyrene.—A mixture of 0.20 g. of V and 2 g. of selenium was heated for 18 hours at 300–310°. The mixture was extracted with boiling toluene. After removing the toluene the residue was sublimed and the sublimate treated with TNF to yield 20 mg. of the TNF derivative of pyrene, m. p. 228–234° (4.2%). Recrystallization from 95% alcohol yielded 12 mg. of the TNF derivative of pyrene, m. p., alone and mixed with authentic material,[10] 239–240°.

Oxidation of V.—To a warm (about 40°) solution of 0.5 g. of V in 5 cc. of acetic acid was added dropwise a solution of 1.0 g. of chromic anhydride in 5 cc. of acetic acid. After shaking as long as an exothermic reaction was noticed the reaction mixture was poured on ice. The organic oxidation product was taken into ether–benzene. Removal of the solvent yielded an oil which could not be crystallized. When dissolved in a small amount of alcohol and treated with alcoholic *o*-phenylenediamine, a yellow precipitate separated. After three recrystallizations from alcohol there was obtained 30 mg. of the quinoxaline derivative as yellow crystals, m. p. 171.8–172.8°. *Anal.* Calcd. for $C_{22}H_{16}N_2$: C, 85.7; H, 5.2; N, 9.1. Found[s]: C, 85.4, 85.6; H, 5.1, 5.3; N, 8.6, 8.7.

Reduction of I.—A mixture of 8.0 g. of I, 50 ml. of acetic acid, 50 ml. of concentrated hydrochloric acid, 25 ml. of toluene and 20 g. of amalgamated zinc was heated to reflux for seventy-two hours during which time an additional 36 ml. of hydrochloric acid was added. From the reaction products was obtained 3.8 g. (58%) of 1,2-dihydropyrene, m. p. 127–131°. On recrystallization from alcohol there was obtained pure 1,2-dihydropyrene, m. p. 131.0–132.0°, which formed a picrate melting at 145–147°. These constants agree with those previously reported.[14]

The unchanged starting material was recovered after attempts at high pressure hydrogenation of I or II over copper chromite (37 KAF[20]) in absolute alcohol at 130° and 2000 p. s. i. Similarly, I was recovered unchanged after refluxing with 47% hydriodic acid and 85% phosphoric acid for three days.

When 15.0 g. of Raney nickel–aluminum was added in small portions during one hour to a stirred solution at 90° of 5 g. of I in 200 ml. of 10% sodium hydroxide there was obtained from the neutral product (4.54 g.) 1.59 g. (34%) of the lactone of 9,10-dihydro-5-(hydroxymethyl)-4-phenanthrenecarboxylic acid (VI), m. p. 156.0–156.8°. Attempts at further reduction of VI using the Raney alloy method[15] or the hydriodic–phosphoric acid procedure above described failed to yield crystalline material. *Anal.* Calcd. for $C_{16}H_{12}O_2$: C, 81.3; H, 5.1. Found[p]: C, 81.4, 81.5; H, 4.8, 5.0.

Lactone of 5-(Hydroxymethyl)-4-phenanthrenecarboxylic Acid (VII).—Heating 0.23 g. of VI with 0.03 g. of sulfur at 230–235° for one hour afforded crude VII, m. p. 167–175°, in 66% yield. The analytical sample, purified by alkaline hydrolysis, acidification and recrystallization from alcohol, melted at 177.2–178.0°. The same lactone was obtained in 56% yield on slow distillation of a mixture of 2.78 g. of II, 2.04 g. of aluminum isopropoxide and 150 ml. of toluene until a test[16] for acetone in the distillate was negative. VII was recovered quantitatively from an attempted reduction with hydriodic–phosphoric acids as above described. *Anal.* Calcd. for $C_{16}H_{10}O_2$: C, 82.1; H, 4.3. Found[k]: C, 82.1, 82.1; H, 4.2, 4.3.

Pseudo Ethyl 5-Formyl-4-phenanthrenecarbothiolate.—To a stirred mixture at 0° of 10 ml. of ethyl mercaptan, 1.0 g. of freshly fused zinc chloride and 1 g. of anhydrous sodium sulfate was added, in portions, 0.5 g. of powdered I. After stirring for 14 hours at room temperature the mixture was diluted with ether–benzene and the organic layer washed well with 10% sodium hydroxide, water and saturated salt solution. No acidic material was recovered from the alkaline extract. After removal of the solvent and recrystallization of the residue from alcohol there was obtained a small amount (24%) of the crystalline thioester, m. p. 150.8–152.4°. The analytical sample melted at 152.2–153.0°. No further experiments were carried out on the compound. An attempt to prepare the butyl thio-

(20) R. Connor, K. A. Folkers and H. Adkins, THIS JOURNAL, **54**, 1138 (1932).

ester in a similar manner failed. *Anal.* Calcd. for $C_{18}H_{14}O_2S$: C, 73.4; H, 4.8. Found: C, 73.6, 74.0; H, 5.0, 4.9.

Summary

The preparation of 4,5-dimethylphenanthrene from pyrene is described. The steps involved are: (1) ozonization to 5-formyl-4-phenanthrenecarboxylic acid, (2) esterification, (3) reduction to 4,5-phenanthrenedimethanol, (4) cyclization to the corresponding cyclic ether and (5) reduction to 4,5-dimethylphenanthrene.

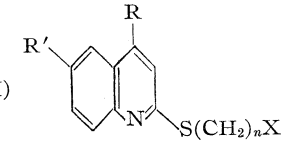
RECEIVED MAY 9, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

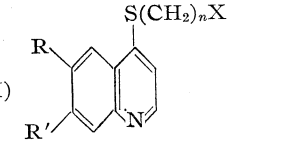
Some Dialkylaminoalkylmercaptoquinolines

BY HENRY GILMAN AND MARY ALYS PLUNKETT[1]

In connection with some studies on the pharmacological activity of certain mercapto quinolines, a series of dialkylaminoalkylmercaptoquinolines has been prepared. It seemed of interest to introduce into nuclei which have chemotherapeutic potentialities certain alkylamino groupings connected directly to the nuclei by a sulfur atom. The quinoline derivatives are of types I and II. Compounds of these types are reported by Bachman, *et al.*,[2] and by Clinton and Suter.[3]

(I) 

Where R is methyl, hydrogen or carboxy; R′ is methoxy or hydrogen; X is diethylamino, N-piperidyl or N-morpholyl; *n* is 2 or 3.

(II) 

Where R is methoxy or hydrogen; R′ is chloro or hydrogen; X is diethylamino, N-piperidyl or N-morpholyl; *n* is 2 or 3.

The compounds reported were prepared by condensation of the appropriate chloroquinoline with the sodium alkyl mercaptide or by condensation of the sodium quinolyl mercaptide with the appropriate alkyl chloride. In general, absolute ethanol was used as solvent for the condensations involving chloroquinolines. In the case of 2-chloro-4-methyl-6-methoxyquinoline it was found that the reflux temperature of methyl cellosolve was necessary for condensation. Reactions using the quinolyl mercaptides were carried out in a 1:1 mixture of ethylene glycol and methyl cellosolve.

In the preparation of 6-methoxy-2-(β-diethylaminoethylmercapto)-quinoline both the quinolyl and the alkyl mercaptides were used. Similar yields were obtained in the two cases. 6-Methoxy-4-methyl-2-(γ-diethylaminopropylmercapto)-quinoline was prepared by treating a mixture of γ-diethylaminopropylisothiouronium chloride hydrochloride and 2-chloro-4-methyl-6-methoxyquinoline in methyl cellosolve with excess sodium ethoxide. The same compound was obtained from the alkyl mercaptide and the chloroquinoline.

(1) Present address: Vassar College, Poughkeepsie, New York.

(2) Bachman, Welton, Jenkins and Christian, THIS JOURNAL, **69**, 366 (1947).

(3) Clinton and Suter, *ibid.*, **70**, 491 (1948).

In general, the mercaptoquinolines were isolated as the hydrochlorides in yields varying from 23–75%. The compounds prepared are listed in Table I. Details of the preparation of typical compounds are given in the experimental section. The sodium alkyl mercaptides were prepared in accordance with procedures described earlier from the corresponding alkyl chloride[4] or by the isothiouronium salt synthesis.[5]

Most of these compounds have been tested for their pharmacological activity toward malaria-causing plasmodia. Results of these tests will be reported elsewhere.

The authors are grateful to William Meikle for assistance and to Parke Davis and Co. for arranging for the tests.

Experimental

6-Methoxy-2-(β-diethylaminoethylmercapto)-quinoline.—A solution of 5 g. (0.04 mole) of β-diethylaminoethyl chloride and 0.02 mole of the sodium salt of 2-mercapto-6-methoxyquinoline in absolute ethanol was refluxed for four hours. After removal of the solvent the residue was dissolved in ether, dried over anhydrous sodium sulfate and treated with ethereal hydrogen chloride. Recrystallization of the dihydrochloride from absolute ethanol gave a product melting at 168–170° which was identical with that obtained from the reaction of sodium β-diethylaminoethyl mercaptide and 2-chloro-6-methoxyquinoline.[6]

4-Methyl-2-[β-(N-piperidyl)-ethylmercapto]-quinoline.—This compound was prepared by a method analogous to the above procedure from N-β-chloroethylpiperidine[7] and 2-mercapto-4-methylquinoline[8] using a 1:1 mixture of ethylene glycol and methyl cellosolve as solvent. The free base deposited from an ether solution as crystals melting at 75–76°.

The corresponding N-morpholyl compound, as well as the intermediates[9] for the reaction, were prepared in a similar manner.

2-Mercapto-6-methoxyquinoline.—This compound was prepared with some modification, according to the directions of John[10] for the preparation of 4-mercapto-6-methoxyquinoline.

(4) Gilman, Plunkett, Tolman, Fullhart and Broadbent, THIS JOURNAL, **67**, 1845 (1945); Gilman and Woods, *ibid.*, **67**, 1844 (1945).

(5) Albertson and Clinton, THIS JOURNAL, **67**, 1222 (1945); L. Fullhart, unpublished studies, Iowa State College.

(6) Magidson and Rubtsov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1896 (1937) (*C. A.*, **32**, 564 (1938)).

(7) I. G. Farbenindustrie, French Patent 802,416 (1936) (*Chem. Zentr.*, **107**, II, 4255 (1936)).

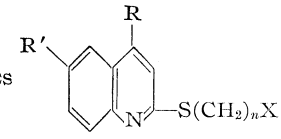
(8) Rosenhauer, *Ber.*, **62**, 2732 (1929).

(9) Mason and Block, THIS JOURNAL, **62**, 1443 (1940).

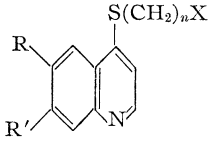
(10) John, *J. prakt. Chem.*, [2] **128**, 218 (1930).

TABLE I

DIALKYLAMINOALKYLMERCAPTOQUINOLINE HYDROCHLORIDES



Substituent groups				M. p.,	Yield,		Percentage composition					
							Nitrogen		Sulfur		Chlorine	
R	R′	n	x	°C.	%	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
H	H	2	NEt_2	192–193[d]	64	$C_{15}H_{21}N_2ClS$	9.46	9.28	10.81	10.66	11.82	11.45
H	H	3	NEt_2	141–142	50	$C_{16}H_{23}N_2ClS$	9.03	9.10	...	...	11.29	11.34
CH_3	H	2	NEt_2	216–217	43	$C_{16}H_{24}N_2Cl_2S$	8.09	8.10	9.24	9.40	20.23	20.22
CH_3	H	3	NEt_2	199–200[d]	60	$C_{17}H_{26}N_2Cl_2S$	7.77	7.80	...	...	...	...
H	CH_3O	2	NEt_2	168–170	33	$C_{16}H_{24}ON_2Cl_2S$	7.73	7.94	8.84	8.78	19.33	19.00
CH_3	H	2	NC_5H_{10}[a]	75–76[b]	40	$C_{17}H_{22}N_2S$	9.79	9.74	11.18	11.03	...	...
CH_3	H	2	NC_4H_8O[a]	85–85.5[b]	40	$C_{16}H_{20}ON_2S$	9.72	9.79	11.11	11.00	...	...
CH_3	CH_3O	3	NEt_2	200–201	50	$C_{18}H_{27}ON_2ClS$	7.91	8.09	...	...	...	...
COOH[c]	H	2	NEt_2	240–242	70	$C_{16}H_{21}O_2N_2ClS$	8.23	8.25	...	...	...	...



CH_3O	H	2	NEt_2	219–220	23	$C_{16}H_{24}ON_2Cl_2S$	7.73	7.76	8.84	8.78	19.33	19.03
H	Cl	2	NEt_2	236–238[d]	75	$C_{15}H_{21}N_2Cl_3S$	7.65	8.00	8.74	8.50	19.12	18.99

[a] NC_5H_{10} refers to the N-piperidyl radical; NC_4H_8O refers to the N-morpholyl radical. [b] M. p. of free base. [c] Starting materials for this compound were made according to references 11–12. [d] Reported by Clinton and Suter.[2]

A mixture of 14 g. (0.08 mole) of 2-chloro-6-methoxyquinoline, 11 g. of potassium hydrosulfide and 56 ml. of absolute ethanol was heated at reflux temperature for fifteen hours. The solid material which formed was washed well with water and neutralized with acetic acid. After recrystallization from absolute ethanol 5 g. (33%) of product melting at 185–187° was obtained.

Anal. Calcd. for $C_{10}H_9ONS$: N, 7.33. Found: N, 7.40.

6-Methoxy-4-methyl-2-(γ-diethylaminopropylmercapto)-quinoline.—To a solution of 7.8 g. (0.03 mole) of γ-diethylaminopropylisothiouronium chloride hydrochloride[4] in 50 ml. of methyl cellosolve was added 6.2 g. (0.03 mole) of 2-chloro-4-methyl-6-methoxyquinoline[11] dissolved in a minimum of methyl cellosolve. The mixture was heated under reflux with stirring and treated with a solution of 3.2 g. (0.14 g. atom) of sodium in absolute ethanol, added in a thin stream over a period of one hour. The reaction mixture was refluxed for seven hours, filtered and freed from solvent by distillation under reduced pressure. The residue was dissolved in ether, washed with water and dried over anhydrous sodium sulfate. Treatment with ethereal hydrogen chloride gave 46% of product which, after recrystallization from absolute ethanol, melted at 200–201°.

This compound was also prepared in 50% yield according to the usual method using sodium γ-diethylaminopropyl mercaptide and 2-chloro-4-methyl-6-methoxyquinoline.[12,13]

(11) Kindly furnished by S. P. Massie.

Summary

The preparation of a series of dialkylaminoalkylmercapto quinolines is described. The compounds were isolated and identified as the hydrochlorides.

AMES, IOWA RECEIVED JANUARY 14, 1949

(12) Ainley and King, *Proc. Roy. Soc.* (*London*), **125B**, 69 (1938).

(13) Camp, *Arch. Pharm.*, **237**, 687 (1899).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF OREGON]

The Synthesis of Derivatives of Glucose-4-phosphoric Acid[1]

BY F. J. REITHEL AND C. K. CLAYCOMB[2]

During the course of an investigation of biochemical mechanisms forming glucosidic linkages it became desirable to secure glucose-4-phosphoric acid for use as a substrate. In our hands Raymond's[3] synthesis resulted in very poor yields. The synthesis described by the present authors utilizes a novel rearrangement first described by Helferich and Klein[4] and the convenient phosphorylating agent diphenylchlorophosphonate.[5]

Experimental

1,2,3,6-Tetraacetyl-β-D-glucopyranose.—Pure β-D-glucose-1,2,3,4-tetraacetate[6] was prepared utilizing the crystallization procedure of Lardy and Fischer.[7] In accordance with the method of Helferich and Klein[4] 11.2 g. of the above compound was dissolved in 110 ml. of 95% ethanol, the specific rotation of the solution being $[\alpha]^{25}D$ +4.49°. The addition of 2.8 ml. of 0.1 *M* aqueous potassium hydroxide catalyzed a change in rotation in one minute to $[\alpha]^{25}D$ −1.03°. The alcohol solution was acidified with 0.5 *N* acetic acid, concentrated to one-half the original volume, seeded and cooled.[8] The crystal crop, filtered cold, was recrystallized from ether containing 10% pyridine and then from 95% ethanol. This procedure yielded 3.9 g. of pyridine-free 1,2,3,6-tetraacetyl-β-D-glucose, m. p. 131.5–132.5°; $[\alpha]^{22}D$ −28.6° (chloroform).[9]

1,2,3,6-Tetraacetyl-4-diphenylphosphono-β-D-glucose.—A solution of 2.0 g. of purified 1,2,3,6-tetraacetyl-β-D-glucose in 25 ml. of pure dry pyridine was warmed to 35° until clear and then cooled to 10°. To it was added 1.7 g. (1.33 ml.) of pure diphenylchlorophosphonate.[5] If turbidity developed during the first half hour after addition of the reagent the solution was warmed until it became clear, and again cooled. After a half hour reaction time the temperature of the reaction mixture was allowed to rise to 20° and was maintained at that figure for about twenty-four hours. Any solid material which had deposited was redissolved by the addition of a few drops of water and the whole was poured, with vigorous agitation, into 170 ml. of ice water. The white granular precipitate thus produced was dissolved in 10 ml. of chloroform, washed with dilute hydrochloric acid and water, and dried over anhydrous sodium sulfate. When the chloroform solution was evaporated *in vacuo* there was obtained a flaky white product soluble in acetone, alcohol and benzene, and insoluble in water or petroleum ether. Recrystallization from hot alcohol or aqueous acetone yielded 1.5 g. of silky needles, m. p. 146.5–147.5°; $[\alpha]^{25}D$ −34.4° (chloroform).

Anal. Calcd. for $C_{26}H_{29}O_{13}P$: C, 53.80; H, 5.04; P, 5.34; 4 acetyl,[10] 6.47. Found: C, 53.77, 54.00; H, 5.27, 5.23; P,[11] 5.34; acetyl, 6.35, 6.40.

1,2,3,6-Tetraacetyl-4-phosphono-β-D-glucose.—An 850-mg. sample of pure 1,2,3,6-tetraacetyl-4-diphenylphosphono-β-D-glucose was dissolved in 15–20 ml. of absolute ethyl acetate, 0.1 g. of Adams catalyst added, and hydrogenated at a pressure of 2–3 cm. After two and one-half hours reaction ceased; hydrogen used, 270 ml.; calcd., 262 ml. (8 moles). The catalyst was removed by filtration and the solution evaporated to a volume of about 5 ml. Cooling to −10° caused the deposition of 550 mg. of a crystalline compound, m. p. 168°; $[\alpha]^{20}D$ −0.42° (*c*, 1.2, H_2O).

Anal. Calcd. for $C_{14}H_{21}O_{13}P$: C, 39.2; H, 4.90; P, 7.24. Found: C, 39.04, 39.16; H, 4.81, 4.93; P, 7.26.

Di-sodium Salt of Glucose-4-phosphoric Acid.—Pure crystalline 1,2,3,6-tetraacetyl-4-phosphono-β-D-glucose was neutralized (phenolphthalein end-point) with aqueous sodium hydroxide. Water was removed *in vacuo*, the residue was dissolved in pure anhydrous methanol, and a catalytic amount of potassium methylate in methanol was added. The deacetylated di-sodium salt began to precipitate at once. After twelve hours at 0° the precipitate was centrifuged down, washed with anhydrous methanol and with ether and dried *in vacuo*. A white hygroscopic solid was obtained which decomposed at about 155° and reduced alkaline copper solutions; $[\alpha]^{20}D$ +51.5° (*c*, 2.1, H_2O).[12]

Anal. Calcd. for $C_6H_{11}O_9PNa_2$: P, 10.2. Found: P, 10.2.

1.00 ml. of an aqueous solution containing 20.7 mg. of the disodium salt was added to 1.00 ml. of 2 *N* hydrochloric acid and the mixture heated at 100° for three hours. At the beginning 0.0325 mg. of inorganic phosphorus was present. During hydrolysis an additional 0.262 mg. of inorganic phosphorus was produced. This increase corresponds to 12% hydrolysis.

Dibrucine Salt of Glucose-4-phosphoric Acid.—Pure crystalline 1,2,3,6-tetraacetyl-4-phosphono-β-D-glucose was dissolved in pure dry methanol. To this solution 0.4 *N* barium methylate in methanol was added until a drop of the solution, when added to water, turned phenolphthalein a deep pink. A voluminous white precipitate of the barium salt appeared. After standing twelve hours at 0° the mixture was again tested for excess barium methylate. If an excess was still present the barium salt was centrifuged down, washed with dry methanol and with ether and dried *in vacuo* briefly.

The barium salt of glucose-4-phosphoric acid thus obtained was dissolved in a minimum amount of water and the barium precipitated as barium sulfate by adding the proper amount of sulfuric acid. The resulting solution of glucose-4-phosphoric acid was neutralized (brom thymol blue) with a solution of brucine in methanol. After concentration *in vacuo* to about one-third of the original volume, an amount of acetone equal to the final volume was added, and the mixture cooled to −10°. Crystals slowly appeared forming clusters of rosettes. Several recrystallizations from 50% acetone–water followed by thorough drying *in vacuo* yielded a product which reduced alkaline copper solutions, m. p. 173–

(1) Presented before the Division of Sugar Chemistry at the 115th Meeting of the American Chemical Society, San Francisco, March, 1949. A portion of the work was taken from a thesis by C. K. Claycomb in partial fulfillment of requirements for the M.A. degree.

(2) Present address, University of Oregon Medical School, Portland 1, Oregon.

(3) A. L. Raymond, *J. Biol. Chem.*, **113**, 375 (1936).

(4) Helferich and Klein, *Ann.*, **450**, 219 (1926).

(5) Brigl and Müller, *Ber.*, **72**, 2123 (1939).

(6) "Organic Syntheses," **22**, 56 (1942).

(7) Lardy and Fischer, *J. Biol. Chem.*, **164**, 515 (1946).

(8) Material for seeding was obtained in the original preparation by concentrating the alcohol solution to a thick sirup and adding a small amount of pure dry pyridine. Crystallization occurred immediately.

(9) Helferich and Müller, *Ber.*, **63**, 2142 (1930).

(10) E. P. Clark, "Semimicro Quantitative Organic Analysis," Academic Press, New York, N. Y., 1934, p. 74.

(11) Fiske and SubbaRow, *J. Biol. Chem.*, **66**, 375 (1925).

(12) The concentration of salt was calculated from phosphorus analyses rather than actual weight per ml. Analyses indicated the purity of the sample to be 98.5%.

174°; $[\alpha]^{20}D$ −43.3° (*c*, 1.7, pyridine), $[\alpha]^{20}D$ −16.1° (*c*, 2.1, 20% ethanol).[13]

Anal. Calcd. for $C_{52}H_{65}O_{17}N_4P$: P, 2.96. Found: P, 2.75.

Discussion

In an effort to prove that the phosphate group was actually attached to carbon number four of the glucose, Raymond[3] compared the osazones and the rate of glucoside formation of his product with those of glucose-3- and glucose-6-phosphoric acids and found marked differences.

Steric considerations point to interaction between groups on carbons four and six as the most likely to be involved in rearrangement. The following data, when compared with values for analogous compounds to be found in the present paper, indicate that there has not been a shift of the phosphate group to carbon number six. Lardy and Fischer[7] report 1,2,3,4-tetraacetyl-6-diphenylphosphono-β-D-glucopyranose, m. p. 64–66°, $[\alpha]^{22}D$ 16.5° (*c*, 1.37, pyridine) and 1,2,3,4-tetraacetyl-β-D-glucose-6-phosphoric acid, m. p. 126–128° $[\alpha]^{25}D$ 18.7° (*c*, 1, pyridine). Robison and King[14] report the dibrucine salt of glucose-6-phosphoric acid, $[\alpha]^{20}D$ 20.6° (*c*, 0.84, water).

Both physical properties and presence of reducing power rule out a transfer of the phosphate group to carbon number one. Presumably the pyranose ring would remain intact in such a synthesis as the one presented and it would seem unlikely that carbon number five would be involved. However, until such time as glucose-5-phosphate can be studied this possibility cannot be ruled out and the nomenclature in this paper avoids specifying ring structure.

Acknowledgments.—We should like to express our sincere thanks to the Office of Naval Research for potentiating this investigation. The senior author was supported by Contract N6onr-218, Project NR-123-243.

Summary

Several derivatives of glucose-4-phosphoric acid have been obtained by an improved synthesis.

The properties of two new compounds have been reported.

(13) It should be noted that the rotation in pyridine is in good agreement with that reported by Raymond[3] but the rotation in alcohol is not. The value given here is that exhibited by several samples. For comparison, Raymond's values were −45.3 and −9.8°, respectively.

(14) R. Robison and E. J. King, *Biochem. J.*, **25**, 323 (1931).

EUGENE, ORE. RECEIVED APRIL 20, 1949

[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY[1]]

Phosvitin, the Principal Phosphoprotein of Egg Yolk

BY DALE K. MECHAM AND HAROLD S. OLCOTT

A phosphoprotein preparation containing 10% phosphorus has been isolated from egg yolk in yield sufficient to account for at least 60% of the total protein phosphorus in yolk. The proposed name "*phosvitin*" indicates both its high phosphorus content and its source in the egg yolk. Details of the isolation procedures and the results of various chemical and physical studies will be described in this paper.

A number of investigators have separated polypeptides rich in phosphorus following enzyme digestion of both vitellin and casein.[2–13] The presence of such peptides was attributed to the occurrence of groupings in these proteins resistant to digestion. In the case of vitellin at least it now appears that such polypeptides were formed from a phosphoprotein of as high phosphorus content as any of the polypeptides isolated, and that most of the phosphorus was present in the form of the phosphoprotein to be described.

Isolation

Phosphoprotein fractions containing 7% or more phosphorus[14] were first obtained by the following procedure. Fresh liquid egg yolk was extracted with chloroform to remove lipids. The residual suspension was then washed with water to remove the "livetin" fractions, and finally extracted with 10% sodium chloride in the presence of chloroform to obtain the phosphoprotein. Salt was removed by dialysis. Apparently most of the other yolk protein components were insolubilized

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Miescher, *Medizinische-Chemische Untersuchungen*, **4**, 502 (1870), cited in Jukes and Kay.[40]

(3) Bunge, *Z. physiol. Chem.*, **9**, 49 (1885).

(4) Hugounenq and Morel, *Compt. rend. acad. sci.*, **140**, 1065 (1905).

(5) Posternak, *ibid.*, **184**, 306 (1927).

(6) Posternak and Posternak, *ibid.*, **184**, 909 (1927).

(7) Rimington, *Biochem. J.*, **21**, 1179 (1927).

(8) Damodaran and Ramachandran, *ibid.*, **35**, 122 (1941).

(9) Lowndes, Macara and Plimmer, *ibid.*, **35**, 315 (1941).

(10) Rimington, *ibid.*, **35**, 321 (1941).

(11) Posternak and Pollaczek, *Helv. Chim. Acta*, **24**, 1190 (1941).

(12) Nicolet and Shinn, Abstracts, 110th Meeting, American Chemical Society, September, 1946.

(13) Mellander, *Upsala Läkareforenings Förhandlingar*, **52**, 107 (1947).

(14) Unless otherwise stated, phosphorus analyses are in terms of non-lipid phosphorus not removable by dialysis. Since Plimmer (*J. Physiol.*, **38**, 247 (1909)) cited in Needham[39]) and Schmidt and Thannhauser (*J. Biol. Chem.*, **161**, 83 (1945)) found in yolk considerably less nucleic acid phosphorus than phosphoprotein phosphorus (the latter report 11 mg. and 116 mg., respectively, per 100 g. yolk), no attempt was made to distinguish between the two in most yolk fractions. As described in the text, there is no detectable nucleic acid in phosvitin.

by shaking with chloroform[15]; then in the presence of salt, phosphoprotein was dissociated from them. Yields by this method were low.

Phosvitin then was obtained by the method outlined in a preliminary report.[16] The fraction which separated from diluted yolk (1 part yolk to 2 parts water) in a Sharples centrifuge[17] was lyophilized, extracted with ether and dispersed in a solution containing 5 g. of sodium sulfate per 100 ml. of water. Addition of sodium sulfate to a concentration of 36 g. per 100 ml. of water precipitated the bulk of the proteins. After dilution of the soluble fraction to a concentration of 22 g. of sodium sulfate per 100 ml. of water, copper acetate was added to precipitate the phosvitin as the copper salt. The precipitate was dissolved in *p*H 5, 0.5 *M* citrate buffer, dialyzed against several changes of the same buffer to remove copper, and finally against distilled water to remove citrate. The material isolated had essentially the same composition and properties as that prepared by the method described below but the latter was more satisfactory both in yield and in economy of operation.

It was noted that addition of magnesium sulfate in small amounts to solutions of phosvitin caused formation of a precipitate which slowly dissolved at higher salt concentrations. This behavior was then used to obtain a phosvitin-rich fraction directly from yolk. An outline of the process and the distribution of protein solids and phosphorus during the various steps is shown in Fig. 1, and details are given below.

Preparative.—Yolks of fresh eggs[18] were washed in tapwater and rolled on cheesecloth to free them from adhering white. Chalazae were cut off. The yolk membranes were then punctured and the contents allowed to drain out through a single layer of cheesecloth. To 2400 g. of yolk contents (from 13 dozen eggs) were added 1200 ml. of 1.2 *M* magnesium sulfate solution (containing 120 mg. of Merthiolate[19]) and the mixture was stirred vigorously, but without producing foam, for one hour. Addition of 12 l. of water (containing 600 mg. of Merthiolate) then was started and completed in one and one-half hours, the mixture being stirred as before. After eighteen hours at room temperature (surface covered with toluene) the soft sticky precipitate was collected by centrifugation (A, Fig. 1), and the soluble fraction (B, Fig. 1) was discarded. The original yolk was at *p*H 6.0; the 0.09 *M* magnesium sulfate supernatant solution was at *p*H 5.9.

The precipitate was dispersed in 1600 ml. of 0.4 *M* ammonium sulfate with forty-five minutes of stirring. The dispersion was brought to *p*H 4.0 by the careful addition of 6 *N* sulfuric acid, and 80 ml. of *p*H 4, *M* acetate buffer was added. The dispersion then was shaken vigorously with 1500 ml. of ethyl ether and allowed to stand overnight at room temperature. The addition of ether was necessary in order to collect the non-phosvitin residue into a separable layer; filtration in the absence of ether did not remove all of the non-phosvitin protein. The slightly opalescent aqueous layer was drawn off and the remaining

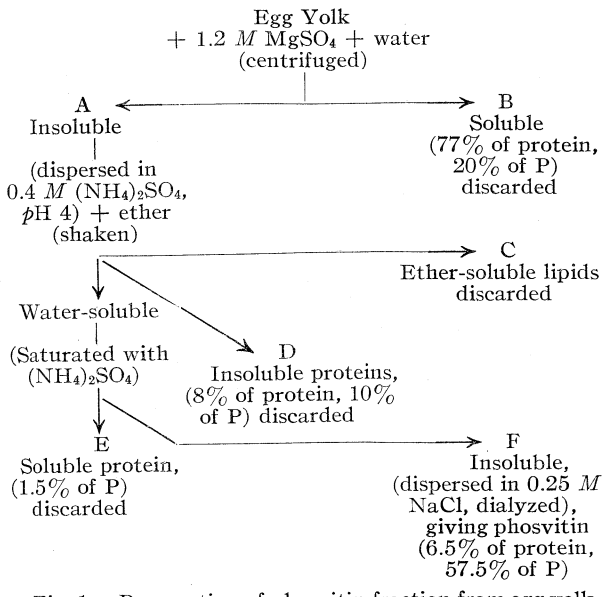


Fig. 1.—Preparation of phosvitin fraction from egg yolk. Analyses refer to dry, lipid-free protein and phosphorus of original yolk. Total recovery of protein was 92%, of phosphorus, 90%. Phosphorus contents of protein solids: original yolk, 1.09%; fraction B, 0.29%; fraction D, 1.36%; fraction F, 9.7%.

mixture was centrifuged to obtain some additional aqueous extract. The free ether layer (C, Fig. 1) was discarded. Three additional extractions of the residue (a gelatinous emulsion) were made with 0.4 *M* ammonium sulfate plus *p*H 4, *M* acetate in the ratio previously used, the successive volumes employed being 1,000, 800, and 800 ml.; 300 ml. of ether was added with the first of these, and no ether was then removed until after the final salt extraction. Only the last of these extracts was separated by centrifuging, the others being allowed to stand overnight before drawing off the aqueous layer. The gelatinous insoluble residue (D, Fig. 1) was discarded.

The *p*H 4, 0.4 *M* ammonium sulfate extracts were shaken in successive portions as obtained with one portion (approximately 200 ml.) of ethyl ether. After thirty to forty-five minutes, standing, the aqueous layers were drawn off and filtered through coarse paper. The filtrates were again shaken with 200 ml. of ethyl ether and the aqueous layers filtered through medium porosity sintered glass covered with one-half inch of Hy-flo filter aid (analytical grade).[19] The filtrate (4420 ml.; *p*H, 4.1) was perfectly clear and slightly yellow in color. It was next dialyzed overnight against two liters of saturated ammonium sulfate plus excess solid ammonium sulfate. A slow stirrer kept the solution agitated. The sacks then were transferred to two liters of saturated ammonium sulfate solution adjusted to *p*H 4 with glacial acetic acid, again with solid ammonium sulfate present.

After overnight dialysis, a white gelatinous solid had separated, most of which could be collected by centrifugation. The rest was collected by filtration through sintered glass. The saturated ammonium sulfate supernatant (E, Fig. 1) was discarded after it was found to contain only 2.5% of the phosphorus present in the 0.4 *M* ammonium sulfate extracts.

The precipitate was mixed with 50 ml. of 5 *M* sodium chloride, then diluted to 1000 ml. total volume. The viscous dispersion was dialyzed against several changes of 2 *M* sodium chloride, the first portion being made 0.01 *M* in sodium acetate to hasten solution of the precipitate, and then against water.

No systematic investigation of the effects of small variations in the separation procedures was made. In

(15) Sevag, Lackman and Smolens, *J. Biol. Chem.*, **124**, 425 (1938).

(16) Mecham and Olcott, *Fed. Proc.*, **7**, 173 (1948).

(17) Alderton and Fevold, *Arch. Biochem.*, **8**, 415 (1945).

(18) No difference in yield of phosvitin by the procedure given was found between eggs less than twenty-four hours old or grade A eggs purchased at retail markets.

(19) Mention of this material does not constitute endorsement.

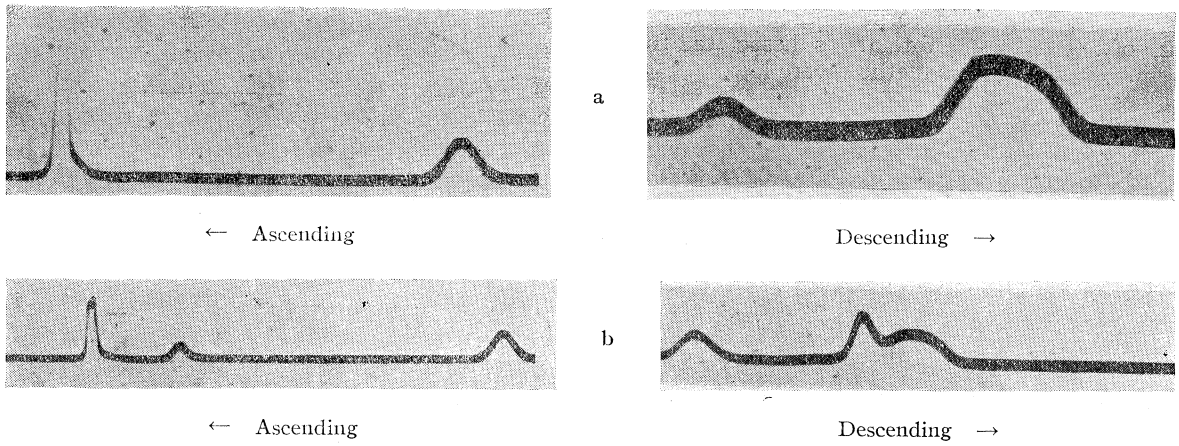


Fig. 2.—Svensson–Philpot electrophoresis records: phosvitin (citrate-dialyzed, magnesium sulfate method of preparation), 1.7% solution; "*a*" in sodium acetate buffer, *p*H 4.6, μ 0.1; mobility of rising boundary, $-12(\times 10^{-5})$ cm.^{2} volt^{-1} second^{-1} referred to 0°; delta boundary at right. Larger falling boundary represents unresolved components ranging in mobility from −8 to −10 units; epsilon boundary at left. "*b*" in sodium citrate buffer: *p*H 4.6, μ 0.1. The small slower moving rising boundary, about 25% of the whole, has a mobility of about −12 units. The faster 75%, which appears further resolvable, has a mobility of about −15 units; delta boundary at right. The slower moving falling component, comprising about 40% of the whole, has a mobility of −9 units; the faster 60%, about −12 units; epsilon boundary at left.

general, however, it was observed that in the magnesium sulfate precipitation step, dilution to 0.05 *M* concentration (instead of 0.09 *M*) caused precipitation of more non-phosvitin protein, while above about 0.3 *M* concentration, there was little precipitation of phosvitin. Also, after removal of the 0.09 *M* magnesium sulfate precipitate at a *p*H near 6, additional precipitate could be obtained by raising the *p*H to 8 or 9, but almost no phosvitin could be separated from this second precipitate. In the ammonium sulfate–ether extraction step, separation of the non-phosvitin fraction into the ether–gel layer became less complete as the *p*H was increased above 4 or the ammonium sulfate concentration was increased above 0.4 *M*. At lower salt concentrations (*ca.* 0.1 *M*) dissociation of phosvitin from the magnesium sulfate precipitate was quite incomplete.

When it was found that phosvitin preparations were apparently unaffected by heat (solutions at levels of *p*H from 4 to 8 when heated for several hours at 100° did not precipitate nor show any other evidence of change), attempts were made to devise methods of preparation in which the non-phosvitin proteins of yolk were heat-denatured. Small amounts of phosvitin could be recovered but the procedures were definitely less satisfactory than those described above.

Analyses.—The dialyzed preparation (F, Fig. 1) was at *p*H 6.05, and contained 24.4 g. of solids. The solids contained 9.7% phosphorus and 11.9% nitrogen (molar ratio N/P, 2.72). Total lipids were 0.7%; total lipid phosphorus, less than 0.03% of the lipid; total inorganic phosphorus, about 0.01% of the total solids. Neither purine nitrogen (method of Hitchings[20]) nor pentoses (orcinol–ferric chloride method[21]) were detectable. Ninety-six per cent. of the phosvitin phosphorus was removed from a sample of the preparation by 0.25 *N* sodium hydroxide at 35° in twenty-four hours. This is the method used by Plimmer[22] to characterize phosphoproteins. Thus, practically all of the phosphorus of phosvitin is present as phosphoprotein phosphorus.

Attempts to obtain products containing still lower nitrogen-to-phosphorus ratios by further fractionation procedures applied to fraction F were unsuccessful. In each case the molar ratios were within the range of 2.5–2.9.

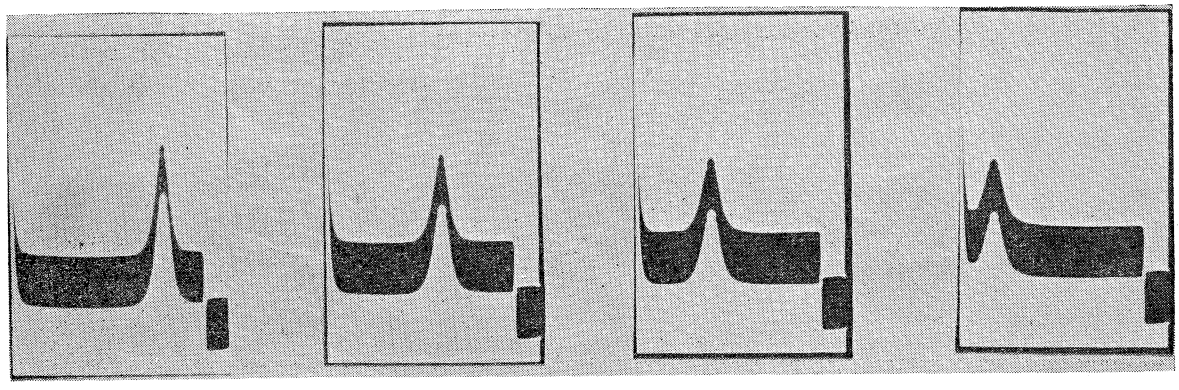
In preparations carried out on a smaller scale with more nearly complete recovery of the starting material, the amount of yolk protein phosphorus recovered as phosvitin phosphorus was consistently between 60 and 70%. In these preparations the 0.4 *M* ammonium sulfate extracts were separated by centrifuging; more complete extraction of phosvitin was indicated by a lower phosphorus content (about 1.1%) of the insoluble protein (D, Fig. 1). The phosphorus not precipitated by 0.09 *M* magnesium sulfate (B, Fig. 1) was consistently about 20% of the total.

Characterization

Physical Properties.—Typical electrophoretic patterns obtained by W. H. Ward with phosvitin are shown in Fig. 2. In sodium citrate buffer, two main components or groups of components were present. About 40% had a falling mobility of −9, and about 60%, −12 ($\times 10^{-5}$ cm.^{2} volt^{-1} second^{-1}) at *p*H 4.6, ionic strength, 0.1. In sodium acetate buffer the boundaries were not resolved and the mobilities were less by 2 or 3 units ($\times 10^{-5}$). Such data indicate that phosvitin preparations consist of at least two groups of substances, not easily resolved electrophoretically, with high mobilities centering about the values given above. Because of the high charge on this material, the use of higher ionic strength buffers would have been desirable.

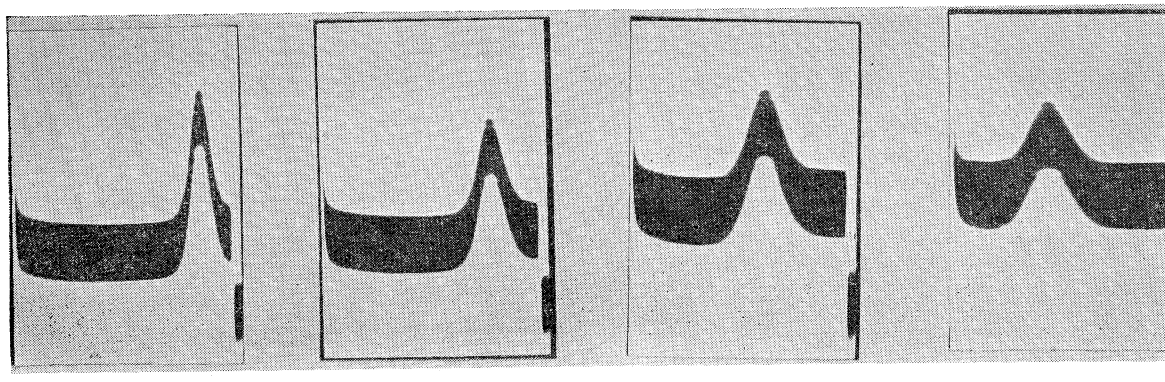
The osmotic pressure method of Bull[23] was used to estimate the molecular weight of phosvitin. Values ranging from 18,000 to 25,000 were obtained with samples prepared by the salt fractionation, copper precipitation method. The runs varied in sample concentration from 0.3 to 1.4%, in *p*H from 5.7 to 6.5, and sodium chloride concentration from 0.5 to 2.5 *M*. Observed molecular weights in the presence of 6.7 *M* urea and 0.5 *M* sodium chloride were also in the range given above.

(20) Hitchings, *J. Biol. Chem.*, **139**, 843 (1941).
(21) Brown, *Arch. Biochem.*, **11**, 269 (1946).
(22) Plimmer and Scott, *J. Chem. Soc.*, **93**, 1699 (1908).
(23) Bull and Currie, THIS JOURNAL, **68**, 742 (1946).



← 80 min. ← 144 min. ← 208 min. ← 272 min.

Phosvitin in 0.1 *N* sodium chloride, *p*H 5.



← 24 min. ← 40 min. ← 72 min. ← 104 min.

Phosvitin in 0.1 *N* sodium chloride–0.05 *M* magnesium chloride, *p*H 5.

Fig. 3.—Ultracentrifuge (Spinco) analysis of 0.8% solution of phosvitin (upper series of pictures) in 0.1 *M* sodium chloride at *p*H 5. Computed sedimentation constant, 1.84 *S* (10^{-13} second) referred to distilled water at 20°. This confirms an earlier measurement made for us by W. B. Dandliker, University of California. The lower series of records represents an analysis made in 0.1 *M* sodium chloride with 0.05 *M* magnesium chloride at *p*H 5. Computed sedimentation constant, 3.79 *S*, referred to distilled water at 20°. The discontinuity at the right of each record shows the position of the liquid surface.

The behavior of phosvitin in the ultracentrifuge (Spinco) was determined and interpreted by W. H. Ward. When magnesium ions were present, an apparent aggregation of phosvitin was observed both in the ultracentrifuge and with osmotic pressure measurements. A preparation obtained by the magnesium sulfate method and citrate-dialyzed was centrifuged at 0.8% concentration in 0.1 *M* sodium chloride, *p*H 5.0, solutions in the absence and presence of 0.05 *M* magnesium chloride. Patterns are shown in Fig. 3. Corrected sedimentation constants (S_{20}) of 1.84 and 3.79 were obtained. These correspond to minimum molecular weights of approximately 12,000 and 39,000, in the absence and presence, respectively, of magnesium. By osmotic pressure measurements the corresponding values were 21,000 and 38,000. The data suggest that, under these conditions, the protein acts as a dimer in the presence of magnesium ions. Possibly magnesium forms a bridge between phosphate groups on adjacent molecules.

The optical rotation of a 2% phosvitin solution in water was measured at *p*H 7.5 and 4.5; values for $[\alpha]^{20}D$ of −71 and −51° were found. In 2 *M* sodium chloride, corresponding values were −68 and −46°. Hewitt[24] found that the optical rotation of a serum albumin preparation (−67°) was the same at *p*H 4.9 and 7.2; Almquist and Greenberg[25] reported that the optical rotation of egg albumin (−31°), livetin (−39°) and serum albumin (−49°) did not vary in the *p*H range 4.5 to 10. The positive effect of *p*H on the rotation of phosvitin probably reflects the change of ionization state of the phosphate group.

Amino Acid Composition.—Results of amino acid determinations on a phosvitin preparation

(24) Hewitt, *Biochem. J.*, **21**, 216 (1927).

(25) Almquist and Greenberg, *J. Biol. Chem.*, **105**, 519 (1934).

are given in Table I. The large amount of serine and the absence of sulfur amino acids are noteworthy.

TABLE I

AMINO ACID COMPOSITION OF PHOSVITIN PREPARATIONS[a]

Component	Untreated %	Untreated Residues per 10^4 g.	Dephosphorylated[b] %	Dephosphorylated[b] Residues per 10^4 g.
Total nitrogen	11.9	85	..	..
Amino nitrogen	0.7	5	..	..
Total phosphorus	9.7	31	..	..
Total sulfur	<0.1	...	..	..
β-Hydroxy-α-amino acids[c,d]		29	..	36
Ammonia nitrogen[c,d]		13	..	6
Serine[c,d]	....	...	32.3	31
Threonine	....	...	Trace	..
Arginine	4.8	2.8	...	..
Arginine[e]	5.8[e]	...	...	..
Histidine	4.8	3.1	...	..
Lysine	5.9	4.0	...	..
Aspartic acid	4.4	3.2	...	..
Glutamic acid	3.4	2.3	...	..
Glycine	1.6	2.1	...	..
Leucine	1.0	0.8	...	..
Methionine	0.4	.3	...	..
Methionine[e]	0.3[e]	.2	...	..
Phenylalanine	0.7	.4	...	..
Proline	1.0	.9	...	..
Tyrosine	0.1	< .1	...	..
Tryptophan[c]	0.6	.3	...	..
Cystine plus cysteine	0.0	.0	...	..

[a] With exceptions noted, all analyses are on a single preparation of the partial sodium salt (*p*H 6), moisture-free basis. Samples were hydrolyzed by refluxing sixteen hours with 6 *N* hydrochloric acid (except for tryptophan). Amino acid analyses are by microbiological methods except as noted. [b] Eighty per cent. dephosphorylated with grapefruit phosphatase. Values are expressed in terms of the original untreated phosvitin. The dephosphorylated product was not isolated; aliquots of the dephosphorylation digest were frozen and dried in vacuum in the vessels subsequently used for hydrolysis. [c] Determined by chemical methods (see methods section). [d] Observed values corrected for estimated 10% destruction of hydroxy amino acids during hydrolysis, and a corresponding increase in ammonia nitrogen. [e] Values obtained on different phosvitin preparation.

It was of particular interest to determine whether a sufficient number of serine residues were present to permit all of the phosphorus to be present as the serine phosphate ester, since the isolation by Levene and co-workers,[26,27] of phosphoserine from yolk indicated that at least part of the phosphoric acid was present in this form.

It is usually assumed that about 10% of the total serine in proteins is destroyed during acid hydrolysis.[28] Lowndes, *et al.*,[9] showed that destruction of serine in hydrochloric acid was somewhat accelerated in the presence of added phosphoric acid. However, the comparative stability in acid of peptide-linked serine and phosphoserine residues is not well established; Lipmann and Levene[26] considered residues of both kinds approximately equal in lability, while the results of Posternak and Posternak,[6] Damodaran and Ramachandran[8] and Nicolet and Shinn[29] suggest that the phosphorylated residues are more labile. Results of the determination of the total hydroxyamino acid and ammonia contents of hydrolysates of phosvitin and dephosphorylated phosvitin (see Table I) were in agreement with the latter authors in showing that phosphorylated hydroxyamino acid residues of phosvitin are somewhat less stable to acid than non-phosphorylated. Therefore, serine was determined only in enzyme dephosphorylated samples. Correction of the serine values for 10% destruction during hydrolysis brings the serine and phosphorus contents (of phosvitin) to equivalence. Microbiological determinations of serine and threonine gave values of 28–35 equivalents per 10^4 g., and traces, respectively (not corrected for destruction during hydrolysis). Although the microbiological methods were not considered completely satisfactory in the case of these two amino acids,[30] the results are in agreement with the chemical methods, in indicating both a preponderance of serine, and a serine content approximately equivalent to the phosphorus present.

The inhomogeneity of phosvitin indicated by electrophoresis (but not by the ultracentrifuge) is also suggested by the amino acid analyses. Of the amino acids determined, methionine, tyrosine and tryptophan were definitely present but in amounts too small to permit the presence of one residue in a molecule of molecular weight 21,000. Small amounts (less than 1%) of isoleucine and valine were present but were not determined accurately. Alanine was not determined, but might be expected (by elimination of other common amino acids) to be present in considerable amounts.

Subtraction of amide nitrogen (corrected for destruction of hydroxyamino acids) and of the non-α-amino nitrogen of arginine, histidine and lysine from the total nitrogen gives a value for α-amino nitrogen which on a molar basis is about double that of the phosphorus present. Consequently, there is about one phosphate group for each two amino acid residues.

Rietz, *et al.*,[31] found that when proteins are treated with cold concentrated sulfuric acid the aliphatic hydroxyl groups of serine and threonine residues form acid sulfate esters. A sample of phosvitin was treated by this technique; 86% of the original nitrogen was recovered after dialysis. In the recovered material, only one sulfur atom per thirty phosphorus atoms was present. This

(26) Lipmann and Levene, *J. Biol. Chem.*, **98**, 109 (1932).
(27) Levene and Schormüller, *ibid.*, **103**, 537 (1933).
(28) Rees, *Biochem. J.*, **40**, 632 (1946).
(29) Nicolet and Shinn, Abstracts, 104th Meeting, American Chemical Society, Sept., 1942.
(30) Meinke and Holland (*J. Biol. Chem.*, **173**, 535 (1948)) have shown that excess serine interferes with the microbiological determination of threonine.
(31) Rietz, Ferrel, Fraenkel-Conrat and Olcott, THIS JOURNAL, **68**, 1024 (1946).

result indicates that practically all of the hydroxy-amino acid residues in phosvitin are phosphorylated, and that the sulfuric acid treatment does not replace phosphate with sulfate groups.

Ultraviolet Absorption.—Nicolet and Shinn[32] have presented evidence that serine in peptide linkage forms dehydroalanyl residues upon treatment with dilute alkali; phosphorylated serine residues might be expected to form dehydroalanyl residues even more readily.[29] Since Carter and Greenstein[33] reported that dehydropeptides absorb light very strongly in the ultraviolet range, the ultraviolet absorption spectra of phosvitin, enzyme-dephosphorylated phosvitin, and alkali-treated phosvitin were determined. Results are presented in Fig. 4. There was nearly a tenfold increase in density at 250 mμ with 36% dephosphorylation in four hours of treatment with 0.25 *M* potassium hydroxide at 35°. An additional twenty hours of treatment, with 95% dephosphorylation, gave a relatively small additional increase in density, possibly because of degradation beyond the dehydroalanyl stage.

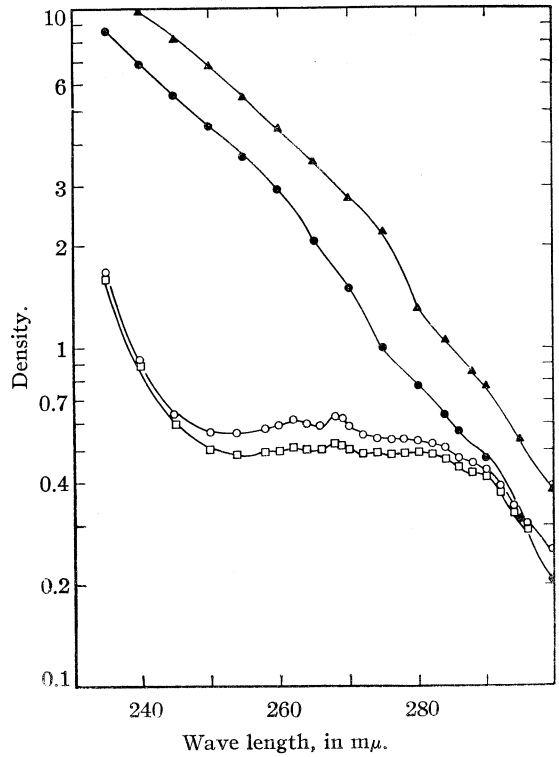


Fig. 4.—Ultraviolet absorption of phosvitin samples (density calculated to sample concentration equivalent to 165 micrograms of phosphorus per ml.; solvent, 0.1 *M* potassium chloride; samples at *p*H 6.5–6.7): □, untreated (citrate-dialyzed) phosvitin; ○, enzyme dephosphorylated (80% dephosphorylated); ●, four hours, 0.25 *M* potassium hydroxide, 35° (36% dephosphorylated); ▲, twenty-four hours, 0.25 *M* potassium hydroxide, 35° (95% dephosphorylated). Enzyme and potassium hydroxide digestions made with citrate-dialyzed phosvitin at a concentration of 825 micrograms of phosphorus per ml.

Titration.—Phosvitin samples were titrated in an attempt to determine whether all of the phosphorus was present as mono-esterified orthophosphate. Phosvitin prepared by the magnesium sulfate method was citrate-dialyzed, then electrodialyzed. Electrodialysis was very slow; ten days were required before the current through the cell failed to increase markedly from the time water was added until it was replaced (eighteen hours).

Titration curves for aliquots of the resulting solution containing 6.24 mg. of phosphorus are shown in Fig. 5. Although the inflection points (points of maximum slope) occurred at different *p*H values in the different solutions, the equivalents of alkali required to reach these points were in reasonable agreement.

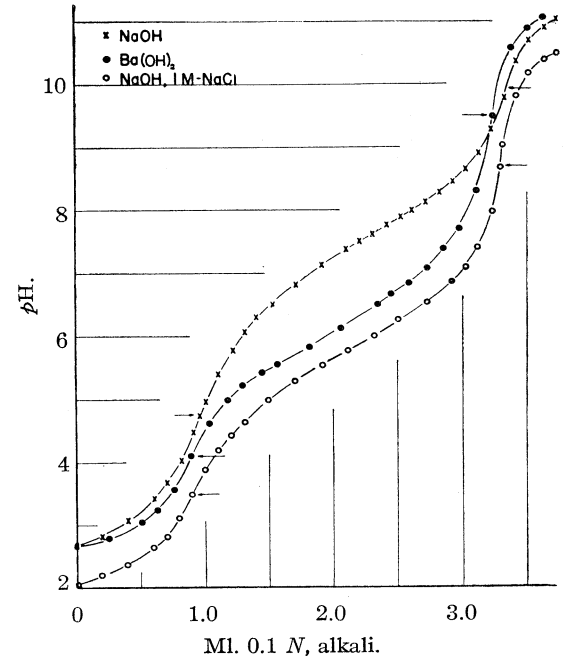


Fig. 5.—Electrodialyzed phosvitin titrations: 10-ml. solution (6.24 mg. phosphorus) titrated with 0.101 *N* sodium hydroxide (X); 0.101 *N* sodium hydroxide in the presence of 1 *M*, final concentration, sodium chloride (O); and 0.131 *N* barium hydroxide (●). Calculated to 0.100 *N* base before plotting. Arrows indicate inflection points.

The milliequivalents of the basic amino acids present with 6.24 mg. (0.201 millimole) of phosphorus, calculated from their ratio obtained from Table I were arginine 0.018, lysine 0.026 and histidine 0.020. It was assumed that all the basic amino acid residues neutralized their equivalent of acidity at *p*H values below the first inflection point, but only the arginine and about one-half the lysine ε-amino groups (of *pK* values around 12.5 and 10, respectively) did so at the *p*H of the second inflection point. The titration results expected, with all the phosphorus present as mono-esterified orthophosphate, then can be given as follows (in milliequivalents): to the first inflection point, acidity from phosphorus, 0.201, neutralized by basic residues, 0.064, net expected 0.137; total to the second inflection point from phosphorus, 0.402, neutralized by basic groups, 0.031; net expected, 0.371. Actually, only 0.092 and 0.328 milliequivalent of alkali were required. Because

(32) Nicolet and Shinn, *J. Biol. Chem.*, **142**, 609 (1942).
(33) Carter and Greenstein, *ibid.*, **165**, 725 (1946).

the discrepancy between the acidity expected and found occurred in titration to the first inflection, rather than between the first and second inflections, the results indicated failure to remove all metal ions from the sample rather than the existence of diesterified orthophosphate.[34,35]

Accordingly a 500-mg. lyophilized portion of phosvitin prepared by the magnesium sulfate method, not citrate-dialyzed, was suspended in 10 ml. of 1 *N* hydrochloric acid in absolute ethanol, let stand thirty min., centrifuged, and the extraction with acidic ethanol repeated four times more. (The first and second extracts were definitely yellow, presumably because of extraction of iron and copper (see below)). Residual solvent was removed from the solid in vacuum over potassium hydroxide at room temperature; 490 mg. of solid was recovered. Portions were weighed out, titrated (results given in Fig. 6), and phosphorus and nitrogen contents of the titrated solutions determined. Nitrogen–phosphorus ratios were not significantly changed by the acid–alcohol extractions (2.72 in the original preparations; 2.69, 2.64 in the washed solids).

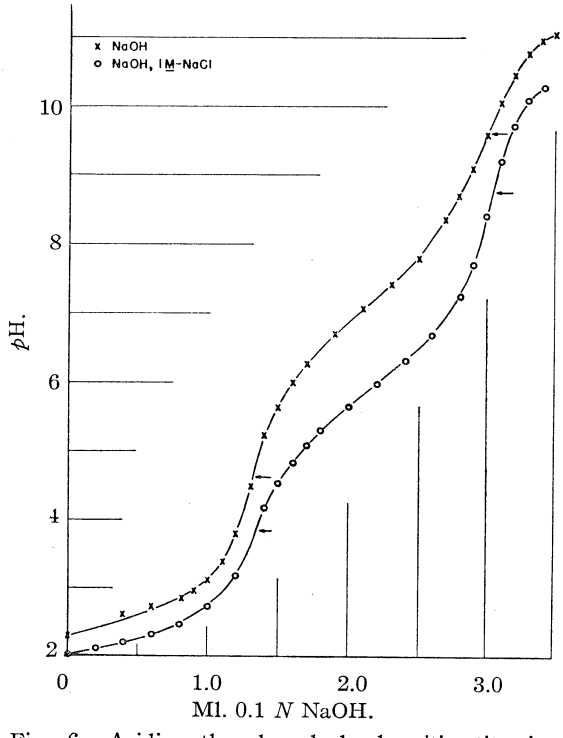


Fig. 6.—Acidic ethanol-washed phosvitin titrations: ×, 0.100 *N* sodium hydroxide, 4.2 mg. of phosphorus in sample; O, 0.100 *N* sodium hydroxide in presence of 1 *M*, final concentration, sodium chloride, 4.4 mg. of phosphorus in sample. The solid samples, suspended in 10 ml. of water at the start of the titration, did not dissolve completely until about 1.0 ml. of alkali had been added. Arrows indicate inflection points.

In the case of these samples, it was assumed that all of the basic amino acid residues would be present as hydrochlorides at the start of the titration, but that the histidine imidazole and approximately one-half the lysine ε-amino groups would, at higher *p*H values, release hydrochloric acid and cause an increase in alkali requirement over that expected; the increased requirement would occur between the first and second inflection points. Calculated to the same quantity of phosphorus as the preceding titrations, the average results then were as follows: To the first inflection, expected acidity from phosphorus, 0.201 milliequivalent; found, 0.194; total titration expected from phosphorus, 0.402, acid released from basic amino acid hydrochlorides during titration, 0.033; found, 0.436. Thus, in the case of the acid–ethanol washed samples the results are interpretable as indicating that all of the phosphorus is present as mono-esterified orthophosphate.

Heavy Metals.—Miescher,[2] Bunge[3] and Hugounenq and Morel[4] found about one-twentieth as much iron as phosphorus in the products of high phosphorus content which they separated from pepsin digests of vitellin. Phosvitin prepared by the magnesium sulfate procedure was found to contain 0.4% iron. By spectrographic examination of the ash of phosvitin, copper and calcium were found to be present in amounts approximately equal to that of iron. No other metallic elements except sodium were present in more than trace amounts. No magnesium was found, despite its use in the preparation. Samples of phosvitin then were dialyzed against *p*H 5 citrate buffer followed by water, the procedure used previously[16] for removal of copper from the copper–phosvitin precipitate. Only traces of iron, copper and calcium remained in the phosvitin. The nitrogen–phosphorus ratio was not changed by the citrate dialysis. The affinity of phosphate esters for heavy metals is well-recognized. Hence it is possible that phosvitin preparations picked up these ions not only from the yolk but also from impurities in the large amounts of salts used in the fractionation sequence.

Susceptibility to Enzyme Action.—Phosphatases in general have not been found capable of dephosphorylating intact phosphoproteins. However, Axelrod[36] showed that a purified orange phosphatase would dephosphorylate phosvitin. An unfractionated preparation of grapefruit flavedo press-juice solids subsequently was found to be a satisfactory phosphatase source for this purpose. It is of interest that casein also was dephosphorylated by the grapefruit preparation. The grapefruit and orange phosphatases therefore fall into the class of phosphoprotein phosphatases. Harris[37] demonstrated phosphoprotein phosphatase activity in frogs' eggs.

Typical results obtained using the grapefruit preparation and a bone phosphatase preparation are given in Table II. Below phosvitin concentrations of 1%, dephosphorylation occurred rapidly with citrus phosphatase preparations. A sweet potato extract fraction capable of hydrolyzing *p*-nitrophenyl phosphate rapidly was nearly inactive on phosvitin.

In some cases, amino nitrogen determinations were obtained before and after dephosphorylation of phosvitin samples with the grapefruit preparations. A slight increase occurred during dephosphorylation; typical values were 5.3% amino nitrogen of the total nitrogen originally, 7.3% after 89% dephosphorylation. Comparable values for casein digests were 5.8% of the total nitrogen originally, 10.1% after 82% dephosphorylation. Thus the grapefruit preparation appears to have caused some proteolysis, but so little that, at least with phosvitin, the dephosphorylation of a protein rather than of a peptone is indicated.

The dephosphorylated phosvitin was insoluble, separating slowly during the later stages of the re-

(34) Reid, Mazzeno and Buras, in preparation for press.
(35) Kumler and Eiler, THIS JOURNAL, **65**, 2355 (1943).
(36) Axelrod, *J. Biol. Chem.*, **167**, 57 (1947).
(37) Harris, *ibid.*, **165**, 541 (1946).

TABLE II

PHOSPHOPROTEIN DEPHOSPHORYLATION BY PHOSPHATASE PREPARATIONS[a]

Phosphatase Source	Concentration mg. per ml.	Substrate	Protein phosphorus, mg. per ml.	Digestion conditions Hr.	°C.	pH	Dephosphorylation, %
Bone	6.0	Phosvitin	1.86	72	25	9.1	2
Grapefruit	0.6	Phosvitin	1.84	72	25	6.7	36
	.6	Casein	0.17	48	25	6.6	71
	.26	Phosvitin	0.87	64	35	6.6	90

[a] Bone phosphatase preparation according to Martland and Robison, *Biochem. J.*, **23**, 237 (1929), from veal shank bone. Grapefruit preparation, flavedo press-juice solids. Relative activity of preparations against *p*-nitrophenyl phosphate : bone (*p*H 9.1), 12 (not changed by addition of 0.003 *M* magnesium sulfate); grapefruit (*p*H 5), 70. The bone phosphatase preparation was not completely soluble in the digestion mixtures; such digests therefore were shaken gently throughout the digestion period. Phosvitin dephosphorylation was not changed by the presence of 0.003 *M* magnesium sulfate in either grapefruit or bone preparation digests.

action as a gel. In this property it is similar to sericin, the hot-water soluble protein of silk, which it also resembles in amino acid content (high serine, absence of sulfur amino acids).

The numerous reports of isolation of phosphopeptones[2-13] from enzyme digests of both egg yolk and milk proteins indicate that peptides containing phosphorylated amino acid residues are resistant to protease activity, consequently it was thought that phosvitin might not be as rapidly digested by trypsin and pepsin as are proteins containing little or no phosphorus. A single experiment was performed (Table III) along this line.

TABLE III

DIGESTION OF PHOSVITIN BY TRYPSIN AND PEPSIN[a]

Substrate	Concn., mg. N per ml.	Original *p*H	Enzyme	Concn., mg. per ml.	Amino N as % of total N 0 hr.	4 hr.	24 hr.
Phosvitin	1.0	8.4	Trypsin	0.06	6.3	8.8	9.6
Heated phosvitin	1.0	8.4	Trypsin	.06	...	..	9.4
Dephosphorylated phosvitin	0.8	8.4	Trypsin	.06	8.4	13.6	14.8
Casein	1.1	8.5	Trypsin	.06	6.5	11.8	13.0
Phosvitin	1.0	1.9	Pepsin	.11	6.3	7.1	7.6
Dephosphorylated phosvitin	0.8	1.8	Pepsin	.11	8.6	10.1	11.0
Casein	1.1	1.9	Pepsin	.11	6.5	11.4	14.0

[a] To 8 ml. of substrate solution at the *p*H indicated, 1 ml. of enzyme solution (trypsin in 0.001 *N* hydrochloric acid, pepsin in water) was added. After the indicated period of digestion at 35°, trypsin samples were acidified with glacial acetic acid, pepsin samples were neutralized with sodium hydroxide, made to 10 ml., and analyzed. The trypsin and pepsin were crystallized preparations.

With trypsin, phosvitin was less rapidly attacked than was either casein or dephosphorylated phosvitin. Heated phosvitin was digested only to the same extent as the unheated sample, hence it appears that phosvitin resists the action of trypsin rather than inhibits it in the manner of ovomucoid, the trypsin-inhibitor of egg white.[38] The results with pepsin do not permit strict comparison between phosvitin and casein, because the former gelled shortly after being adjusted to *p*H 1.9 and after twenty-four hours had formed a fairly dense gel occupying approximately one-half the volume of the digest.

Discussion

Extensive reviews of the literature on yolk proteins are available.[39,40] It was generally considered that there were two fractions, vitellin, the water-insoluble part, accounting for about 80% of the total, and livetin, the water-soluble fraction, accounting for the remaining 20%. Vitellin was a lipoprotein and contained 0.8–1.2% protein phosphorus,[41,42,43,44] livetin contained no lipid and no phosphorus.[45] Evidence that lipovitellin is not homogeneous was furnished recently by Alderton and Fevold[17] and Fevold and Lausten,[46] who separated the lipoprotein fraction of yolk into two fractions, one containing 2% and the other, 0.4%, protein phosphorus.[47]

It has now been shown that 60 to 70% of the protein phosphorus of yolk can be obtained by mild fractionating procedures in the form of phosvitin.[48] Hence all past vitellin preparations probably contained 5–10% phosvitin, an amount sufficient to influence markedly many of the reported properties. Phosvitin shows a high affinity for other proteins,[49] presumably through electrostatic bonds. Consequently a reasonable explanation for the differing phosphorus contents reported for vitellin is that more or less phosvitin was carried down in the lipovitellin precipitation as salt was removed to differing extents and at differing rates. In fact, Alderton and Fevold[17] reduced the pro-

(38) Lineweaver and Murray, *J. Biol. Chem.*, **171**, 565 (1947).

(39) Needham, "Chem. Embryology," Cambridge Press, 1931, Vol. I, pp. 287–294.

(40) Jukes and Kay, *J. Nutrition*, **5**, 81 (1932).

(41) McFarlane, *Biochem. J.*, **26**, 1061 (1932).

(42) Blackwood and Wishart, *ibid.*, **28**, 550 (1934).

(43) Chargaff, *J. Biol. Chem.*, **142**, 491 (1942).

(44) Calvery and White, *ibid.*, **94**, 635 (1931).

(45) Kay and Marshall, *Biochem. J.*, **22**, 1264 (1928).

(46) Fevold and Lausten, *Arch. Biochem.*, **11**, 1 (1946).

(47) Shepard and Hottle (*J. Biol. Chem.*, **179**, 349 (1949)) have recently shown electrophoretically that livetin contains three main components, an observation in agreement with unpublished work of this Laboratory.

(48) The results with yolk proteins suggested that the phosphorus of casein also might occur as a separable high phosphorus phosphoprotein. However, attempts to prepare a phosphorus-enriched fraction from a casein solution or from skim milk by the magnesium sulfate precipitation procedure were unsuccessful.

(49) Equal weights (100 mg.) of phosvitin and protamine sulfate in solution formed a precipitate containing 95% of the phosphorus when mixed (*p*H 6.7; total volume, 140 ml.). The precipitate could be dissolved in 2 *M* sodium chloride. When dialyzed against 2 *M* sodium chloride the protamine nitrogen was eventually all removed with no loss of phosphorus. Since sodium chloride solutions of less than 2 *M* concentration would not dissolve the precipitate completely, the electrostatic bonds must be relatively strong. Phosvitin (2 mg. per ml.) and bovine serum albumin (18 mg. per ml.) in the absence of salt formed a precipitate at *p*H 6 but not at *p*H 4. In the presence of sodium sulfate (0.25 *M*), no precipitate formed at either *p*H.

tein phosphorus content of their lipoprotein precipitate from 2 to 1% by repeated solution in 5% sodium chloride and precipitation by dialysis, a procedure which probably left some phosvitin in solution with each repetition.

Similarly, Francis and Wormall[50] reported that only 25% of the total phosphorus of a precipitate of lipovitellin–antilipovitellin was protein phosphorus, although protein phosphorus accounted for 53% of the total in the original antigen preparation. It appears likely that this difference may represent a separation of the originally antigenic lipoprotein from phosvitin.

The separation of phosphopolypeptides from yolk proteins and casein during enzyme hydrolysis has been mentioned.[2-13] Presumably the vitellinic acid preparations of Levene and Alsberg[51] were somewhat less degraded fractions, very similar in composition to phosvitin. Vitellinic acid was prepared by exposure of vitellin to 12% ammonia for two hours. The yields were low; Jukes and Kay,[40] quoting unpublished results of Kay and Marshall, state that the maximum yield was 35% of the phosphorus of vitellin (of 1% original content). The low yields, together with the fact that no evidence was ever presented indicating that the material might be of higher molecular weight than the phosphopeptones separated from enzymic digests, probably were responsible for the failure to appreciate the possible significance of such material in the yolk proteins.

Whether phosvitin functions in the egg as a storehouse for phosphate, or for metals, or whether it plays an active role during metabolism remains to be determined.[52] Chargaff[53] found that radioactive phosphorus injected into a hen as disodium phosphate was more rapidly incorporated into the vitellin fraction than into the phospholipids of yolk. He therefore suggested that phosphorylated serine residues might be involved in phospholipid synthesis.

Analytical Methods.—Total and inorganic phosphorus was determined usually by the method of Allen[54]; isobutanol extraction was used if samples became turbid in the inorganic phosphorus determination. The methods of Fontaine, Pons and Irving[55] and of Lowry and Lopez[56] also were used occasionally for the determination of inorganic phosphorus. Total nitrogen was determined by the micro-Kjeldahl method recently shown not to require lengthy digestion times,[57] or by macro-Kjeldahl. Amino nitrogen was determined by the manometric Van Slyke method[58] with a fifteen minute reaction time. In order to determine moisture content, samples were dried to constant weight at 78° *in vacuo* over phosphorus pentoxide (Abderhalden pistol heated with 95% ethanol). Total lipid was determined as follows: The material was extracted with absolute ethanol (Soxhlet) for eighteen hours followed by ethyl ether for two hours. After careful evaporation of these solvents, the residue was taken up in chloroform, filtered from insoluble material, dried and weighed. Total sulfur was determined by a sodium peroxide fusion method.[59] Iron was determined by a thiocyanate method.[60]

Dialyses were performed with Visking tubing. Protein preparations were dried by lyophilization. The glass electrode was used for *p*H determinations.

Amino acids were determined chemically as follows: serine, threonine and ammonia by periodate procedures,[61,62,63] tryptophan by the method of Horn and Jones,[64] methionine by the method of Horn, Jones and Blum,[65] cystine and cysteine by the method of Mecham,[66] arginine by the method of Brand and Kassel.[67] The microbiological determinations were carried out by methods to be described elsewhere by J. C. Lewis and N. Snell.

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Summary

Sixty to seventy % of the phosphoprotein phosphorus of egg yolk can be isolated in a protein fraction (the phosvitin fraction) representing 6.5 to 7.0% of the yolk protein and containing about 10% phosphorus. The separation is made by dispersing whole fresh yolk in 0.4 *M* magnesium sulfate solution and diluting to approximately

(50) Francis and Wormall, *Biochem. J.*, **42**, 469 (1948).

(51) Levene and Alsberg, *Z. physiol. Chem.*, **31**, 543 (1900).

(52) A series of sulfated proteins[30] was found by Kazal, Spicer and Brahinsky (Abstracts, 114th Meeting, American Chemical Society Sept., 1948) to possess blood anti-clotting activity, a possibility suggested by the fact that heparin contains acid sulfate groups. It was thought that phosvitin might also possess such activity, particularly since Doyon and Sarvonat (*Compt. rend. soc. biol.*, **65**, 368 (1913)) reported that an extract of "haemotogen" (a phosphopeptone obtained from a pepsin digest of vitellin), prepared according to Hugounenq and Morel,[4] prevented coagulation of blood *in vitro*. However, a phosvitin preparation was not active in a preliminary trial. Injection of 10 mg. of phosvitin caused no apparent ill effects in mice.

(53) Chargaff, *J. Biol. Chem.*, **142**, 505 (1942).

(54) Allen, *Biochem. J.*, **34**, 858 (1940).

(55) Fontaine, Pons and Irving, *J. Biol. Chem.*, **164**, 487 (1946).

(56) Lowry and Lopez, *ibid.*, **162**, 421 (1946).

(57) White, Secor and Long, *J. Assoc. Official Agr. Chem.*, **31**, 657 (1948).

(58) Van Slyke, *J. Biol. Chem.*, **83**, 425 (1929).

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0.09 *M* magnesium sulfate concentration. The 23% of the total yolk protein that precipitates contains 80% of the phosphoprotein phosphorus. Phosvitin is then extracted from the precipitate with 0.4 *M* ammonium sulfate at *p*H 4; ethyl ether is added to coagulate non-phosvitin components. A typical preparation contained 11.9% nitrogen, 9.7% phosphorus (molar ratio N/P = 2.72). The phosphorus is present as mono-esterified orthophosphate.

Amino acid analyses indicated (in equivalents per 10^4 g.): total β-hydroxy-α-amino acids, 33, and serine, 28 (not corrected for destruction during hydrolysis), compared to 31 moles of phosphorus. There is approximately one phosphoserine residue for each two amino acid residues. Basic amino acids account for nearly one-third of the remaining amino acids.

Osmotic pressure measurements indicated a molecular weight of about 21,000. The best preparations were homogeneous in the ultracentrifuge but showed appreciable boundary spreading on electrophoresis. Inhomogeneity was also indicated by the presence of small amounts (less than 1 g. equivalent per 21,000 g.) of tyrosine, methionine and tryptophan.

A pronounced aggregating effect of magnesium ions was shown by both osmotic pressure and ultracentrifuge measurements; in 0.05 *M* magnesium chloride, the molecular weight found was 38,000 and 39,000, respectively, by the two methods.

Phosvitin was dephosphorylated by citrus phosphatases but not by a bone phosphatase preparation. Alkaline dephosphorylation caused an increase in ultraviolet absorption indicative of the formation of dehydroalanyl residues. Trypsin and pepsin acted more slowly on phosvitin than on casein.

ALBANY 6, CALIFORNIA RECEIVED APRIL 20, 1949

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY AND CHEMOTHERAPY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

1,5-Anhydrolactitol and 1,5-Anhydromaltitol

BY HEWITT G. FLETCHER, JR., LEONORE H. KOEHLER[1] AND C. S. HUDSON

A previous publication[2] from this Laboratory described the synthesis of 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol (synonym, 1,5-anhydrocellobiitol) and 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol (synonym, 1,5-anhydrogentiobiitol) through the reductive desulfurization of the appropriate aryl 1-thioglycosides with Raney nickel. The present communication describes the extension of this synthetic method to the lactose and maltose series which was undertaken in order to obtain data for certain generalizations regarding the relationships between rotatory power and configuration among the various 1,5-anhydroglycitols and certain related compounds.[3]

Several well-characterized 1-thioglycosides suitable for the present purpose have been reported in the literature for the lactose and maltose series. Purves described phenyl 1-thio-β-lactopyranoside and its heptaacetate[4] as well as phenyl 1-thio-β-maltopyranoside heptaacetate (III).[5] Haskins, Hann and Hudson[6] prepared by the procedure of Purves, among other 1-thioglycosides, 2′-naphthyl 1-thio-β-lactopyranoside (I) and its heptaacetate as well as 2′-naphthyl 1-thio-β-maltopyranoside heptaacetate.

The reductive desulfurization by Raney nickel of 2′-naphthyl 1-thio-β-lactopyranoside (I) has now been carried out to give crystalline 1,5-anhydro-4-(β-D-galactopyranosyl)-D-glucitol (II), which may be assigned the alternative name of 1,5-anhydrolactitol. The specific rotation of this substance in water, $[\alpha]^{20}D$, proved to be +49.4°. Comparison of the molecular rotations of β-cellobiopyranose, β-lactopyranose and 1,5-anhydrocellobiitol listed in Table I shows that 1,5-anhydrolactitol would be expected to be dextrorotatory. Calculation based upon the isorotation hypothesis affords a numerical value of (7040 + 9550) ÷ 326 = +50.9°.

TABLE I

COMPARISON OF SOME MOLECULAR ROTATIONS IN THE CELLOBIOSE, LACTOSE AND MALTOSE SERIES

	Mol. wt.	$[\alpha]_D$ (H_2O)	$[M]_D$	Difference
β-Lactopyranose	342	+34.9°	+11,900	
β-Cellobiopyranose	342	+14.2°	+ 4,860	+ 7,040
1,5-Anhydrolactitol	326	+49.4°	+16,100	
1,5-Anhydrocellobiitol	326	+29.3°	+ 9,550	+ 6,550
		($CHCl_3$)		
Methyl β-maltopyranoside heptaacetate	651	+53.5°	+34,800	
Methyl β-cellobiopyranoside heptaacetate	651	−25.7°	−16,700	+51,500
1,5-Anhydromaltitol heptaacetate	621	+82.0°	+50,900	
1,5-Anhydrocellobiitol heptaacetate	621	+ 4.0°	+ 2,500	+48,400

(1) Present address: Cedar Crest College, Allentown, Pa.

(2) H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **70**, 310 (1948).

(3) H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **71**, 3682 (1949).

(4) C. B. Purves, *ibid.*, **51**, 3619 (1929).

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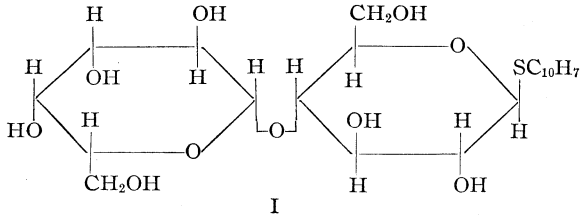
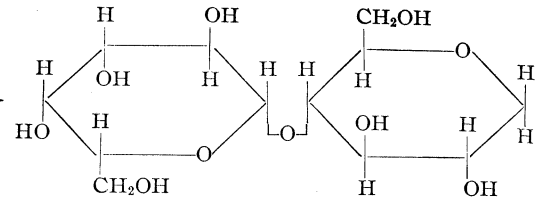
(6) W. T. Haskins, R. M. Hann and C. S. Hudson, *ibid.*, **69**, 1668 (1947).



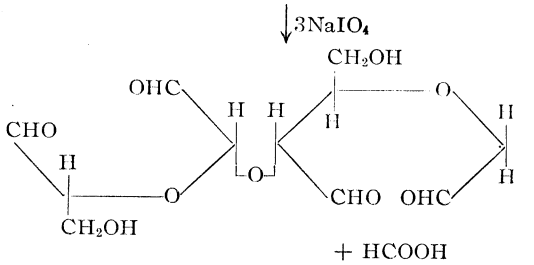
I

2′-Naphthyl 1-thio-β-lactopyranoside

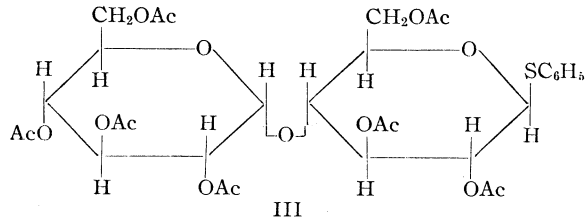


II

1,5-Anhydro-4-(β-D-galactopyranosyl)-D-glucitol

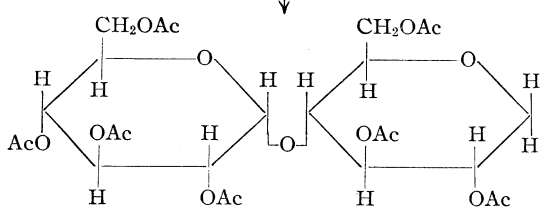


+ HCOOH



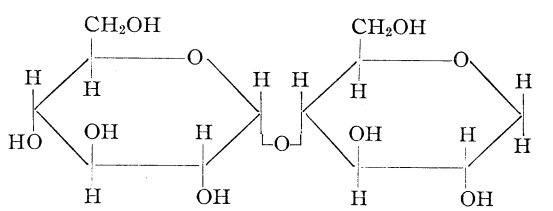
III

Phenyl 1-thio-β-maltopyranoside heptaacetate



IV

1,5-Anhydro-4-(α-D-glucopyranosyl)-D-glucitol heptaacetate



V

1,5-Anhydro-4-(α-D-glucopyranosyl)-D-glucitol

Repeated attempts to prepare the heptaacetate of 1,5-anhydrolactitol in crystalline condition through the reductive desulfurization of both phenyl 1-thio-β-lactopyranoside heptaacetate and 2′-naphthyl 1-thio-β-lactopyranoside heptaacetate as well as through the direct acetylation of the anhydride itself gave only amorphous products.

The structure of the 1,5-anhydro-4-(β-D-galactopyranosyl)-D-glucitol (II) was confirmed by oxidation with periodate. As was to be expected, the substance consumed on a molar basis three moles of periodate with the concomitant formation of one mole of formic acid. As a further confirmation of its structure, the anhydride was hydrolyzed with aqueous acid and the products identified as 1,5-anhydro-D-glucitol (polygalitol) and D-galactose, the latter isolated as its α-methyl-α-phenylhydrazone.

Phenyl 1-thio-β-maltopyranoside heptaacetate (III) was reductively desulfurized with Raney nickel to yield crystalline 1,5-anhydro-4-(α-D-glucopyranosyl)-D-glucitol heptaacetate (IV) (1,5-anhydromaltitol heptaacetate) rotating +82° in chloroform. A calculation similar to that shown above for 1,5-anhydrolactitol but based upon the molecular rotations of methyl β-cellobiopyranoside heptaacetate, methyl β-maltopyranoside heptaacetate and 1,5-anhydrocellobiitol heptaacetate (Table I) leads to the prediction of a value of +87° for 1,5-anhydromaltitol heptaacetate through the isorotation hypothesis.

Catalytic deacetylation of 1,5-anhydromaltitol heptaacetate afforded the free 1,5-anhydromaltitol (V), (synonym, 1,5-anhydro-4-[α-D-glucopyranosyl]-D-glucitol), which could not be induced to crystallize. Confirmation of its structure as a derivative of polygalitol was obtained through acid hydrolysis to 1,5-anhydro-D-glucitol (*i. e.*, polygalitol) and D-glucose, identification of the latter being made through the phenylosazone and the particularly convenient D-glucose phenylosotriazole.

Acknowledgment.—We are indebted to Mrs. Margaret M. Ledyard for microanalyses and to Dr. W. T. Haskins for samples of 2′-naphthyl 1-thioglycosides. One of us (L. H. K.) held a Fellowship from the Corn Industries Research Foundation while engaged in this research.

Experimental[7]

1,5-Anhydro-4-(β-D-galactopyranosyl)-D-glucitol (II).—Two grams of pure 2′-naphthyl 1-thio-β-lactopyranoside, prepared according to the method of Haskins, Hann and Hudson,[6] was dissolved in 200 ml. of 70% aqueous alcohol, treated with approximately 25 g. of freshly prepared Raney nickel and boiled gently under reflux for one hour. The supernatant solution was then removed, the nickel washed successively with three 100-ml. portions of boiling water and the combined solution and washings concentrated *in vacuo* at 55° (bath) to a volume of approximately 2 ml.

(7) Melting points were measured with a calibrated Anschütz type thermometer completely immersed in the bath liquid. Rotations are specific rotations for sodium light at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

On scratching with a glass rod at room temperature, hard, clear prismatic crystals formed; these, combined with two additional crops obtained from the mother liquor by the addition of alcohol, amounted to 850 mg. (63%). Two recrystallizations from water brought the product to a rotation of +49.4° in water (*c*, 2.512) which was unchanged by further recrystallization. 1,5-Anhydro-4-(β-D-galactopyranosyl)-D-glucitol melts with decomposition, the melting point range varying with the rate of heating. When a sample in a capillary tube was plunged into a bath whose temperature of 226° was rising uniformly at the rate of 3° per minute, a melting point of 233–237° was obtained.

1,5-Anhydrolactitol is insoluble in methanol, dioxane, methyl cellosolve and methyl ethyl ketone, difficultly soluble in boiling glacial acetic acid and readily soluble in hot water.

Anal. Calcd. for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.80. Found: C, 44.20; H, 6.82.

One gram of the anhydride was hydrolyzed by boiling for two hours in 2.5 ml. of 0.39 *N* sulfuric acid. After quantitative removal of the acid and reconcentration to a volume of 3 ml. the hydrolyzate was treated with 0.4 g. of α-methyl-α-phenylhydrazine. After three hours at room temperature 100 mg. of crystalline material was removed by filtration. Recrystallization from 30% ethanol gave colorless leaflets melting at 191–192° either alone or in admixture with an authentic sample of the α-methyl-α-phenylhydrazone of D-galactose. The remainder of the hydrolyzate was heated for several hours on the steam-bath, filtered through decolorizing carbon, and concentrated to a colorless sirup which in methanol solution gave a deposit of 200 mg. (40%) of 1,5-anhydro-D-glucitol melting at 142°. Mixed with authentic polygalitol the material melted at 142–143°. Thus the synthetic 1,5-anhydro-4-(β-D-galactopyranosyl)-D-glucitol was shown to be a derivative of polygalitol.

Sodium Metaperiodate Oxidation of 1,5-Anhydro-4-(β-D-galactopyranosyl)-D-glucitol.—The anhydride (98.1 mg.) was oxidized in aqueous solution with sodium metaperiodate, using the technique of Jackson and Hudson.[8] After twenty-six hours at room temperature, analysis showed the consumption on a molar basis of 2.98 moles of oxidant and the formation of 1.02 moles of formic acid.

1,5-Anhydro-4-(α-D-glucopyranosyl)-D-glucitol Heptaacetate, IV.—Ten grams of phenyl 1-thio-β-maltoside heptaacetate, prepared according to the method of Purves,[5] melting at 87–92° and showing a rotation of +48.7° in chloroform was suspended in 100 ml. of absolute alcohol and treated with approximately 40 g. of freshly prepared Raney nickel. The suspension was boiled for one hour and the supernatant liquor then decanted while still hot, the nickel being washed repeatedly, first with hot absolute alcohol and then with boiling acetone. Concentration of the combined decantate and washings *in vacuo* at 60–70° (bath) led to the spontaneous formation of fine, needle-like crystals amounting to 6.66 g. (78%) and melting at 127–128°. Recrystallized once from a mixture of 1.8 parts acetone and 2.3 parts of ether and then thrice from ten parts of alcohol, the substance melted at 133–134° and rotated +82.0° in chloroform (*c*, 3.4). 1,5-Anhydro-4-(α-D-glucopyranosyl)-D-glucitol heptaacetate is insoluble in water and pentane, sparingly soluble in ether and cold alcohol and readily soluble in acetone and in hot alcohol.

Anal. Calcd. for $C_{26}H_{36}O_{17}$: C, 50.32; H, 5.85. Found: C, 50.35; H, 6.03.

(8) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937).

1,5-Anhydro-4-(α-D-glucopyranosyl)-D-glucitol, V.—The catalytic deacetylation of 1,5-anhydro-4-(α-D-glucopyranosyl)-D-glucitol heptaacetate with barium methylate in the conventional manner gave a sirup which could not be induced to crystallize. On reacetylation, a sample of the amorphous material gave the original heptaacetate identified by melting point and mixed melting point, demonstrating that the catalytic deacetylation had produced no unforeseen change in the anhydride.

A portion (1.2112 g.) of the amorphous 1,5-anhydro-4-(α-D-glucopyranosyl)-D-glucitol which had been dried *in vacuo* at 45° was hydrolyzed by boiling in 3.0 ml. of 0.39 *N* sulfuric acid for two hours. One-half of the resulting solution was treated with phenylhydrazine in the usual manner to yield 60 mg. of D-glucose phenylosazone, identified by its melting point and by its inability to depress the melting point of authentic D-glucose phenylosazone. By way of confirmation the D-glucose phenylosazone was converted to D-glucose phenylosotriazole by the procedure of Hann and Hudson.[9] The 4.6 mg. of D-glucose phenylosotriazole thus obtained melted at 196–197° either alone or in admixture with authentic D-glucose phenylosotriazole. The second half of the hydrolysis solution was freed of sulfuric acid and then subjected for two days to the action of baker's yeast to remove the D-glucose. After filtration through decolorizing carbon and removal of solvent there was obtained a colorless sirup which, when diluted with methanol, gave 100 mg. (33%) of clear prismatic crystals melting at 142–143°. Mixed with authentic polygalitol these showed the same melting point.

The specific rotation of 1,5-anhydro-4-(α-D-glucopyranosyl)-D-glucitol in water was obtained by quantitative deacetylation of its pure heptaacetate in the following manner. The heptaacetate (0.6919 g.) was dissolved in a mixture of 2 ml. of chloroform and 10 ml. of methanol and treated with 0.3 ml. of approximately 1.3 *N* sodium methylate solution. After two days at room temperature the solvent was removed with a gentle stream of filtered air and the residual colorless sirup diluted with water to 25.00 ml. From the rotation of this solution a specific rotation of +132° (*c*, 1.455) for 1,5-anhydromaltitol was obtained.

(9) R. M. Hann and C. S. Hudson, *ibid.*, **66**, 735 (1944).

Summary

1,5-Anhydro-4-(β-D-galactopyranosyl)-D-glucitol has been obtained through the reductive desulfurization with Raney nickel of 2′-naphthyl 1-thio-β-lactopyranoside. Its structure has been confirmed by periodate oxidation and by hydrolysis to 1,5-anhydro-D-glucitol (*i. e.*, polygalitol) and D-galactose.

Phenyl 1-thio-β-maltopyranoside heptaacetate has been reductively desulfurized with Raney nickel to give crystalline 1,5-anhydro-4-(α-D-glucopyranosyl)-D-glucitol heptaacetate. Catalytic deacetylation of this heptaacetate gave amorphous 1,5-anhydro-4-(α-D-glucopyranosyl)-D-glucitol the structure of which was confirmed by hydrolysis to 1,5-anhydro-D-glucitol and D-glucose.

BETHESDA, MARYLAND RECEIVED MAY 5, 1949

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY AND CHEMOTHERAPY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Relations between Rotatory Power and Structure in the Sugar Group. XXXVI.[1] The 1,5-Anhydrides of the Glycitols and Related Sugar Derivatives

BY HEWITT G. FLETCHER, JR., AND C. S. HUDSON

Twelve years ago, when Werner Freudenberg and E. F. Rogers[2] published their article on "the chemistry of naturally occurring monoanhydrohexitols" it had already been determined that polygalitol and styracitol are 1,5-anhydrides of D-mannitol and D-glucitol but it was not known which of these epimeric structures applies to each anhydride. Styracitol, to be sure, had been synthesized through the catalytic hydrogenation of tetraacetyl-2-hydroxy-D-glucal by Zervas[3] but this synthesis did not distinguish between the epimeric anhydrides since carbon atom two of tetraacetyl-2-hydroxy-D-glucal is symmetric. Freudenberg and Rogers obtained two indications that styracitol is of the D-mannitol series and polygalitol of the D-glucitol series. As the first of these indications, the rate of oxidation of styracitol by lead tetraacetate was found to be much faster than that of polygalitol, from which they inferred for styracitol the *cis*-relationship of hydroxyl groups on carbon atoms two and three that occurs in the 1,5-anhydro-D-mannitol configuration in contrast to the absence of such a pair of adjacent hydroxyl groups in the 1,5-anhydro-D-glucitol pattern; their inference was based upon the previous generalization by Criegee[4] that the *cis* arrangement is attacked more rapidly than is the *trans* by this type of selective oxidation. The second indication came from their comparison of optical rotatory values by the isorotation method. The pyranose (*i. e.*, 1,5-ring) substances of the D-glucose series are much more dextrorotatory than their epimers of the D-mannose series; thus the molecular rotation of methyl α-D-glucopyranoside is +30,860 and that of methyl α-D-mannopyranoside is +15,380, and the epimeric difference is thus 30,860 − 15,380 = +15,480, a large value. For polygalitol the molecular rotation is +6,950, for styracitol it is −8340 and the epimeric difference is +15,290. The closeness of the numerical agreement may possibly be fortuitous, since a comparison of the molecular rotations of methyl β-D-glucopyranoside (−6,640) and methyl β-D-mannopyranoside (−13,550) gives +6,910 for the epimeric difference. In either case, however, the comparison of rotations indicated in a qualitative way that polygalitol belongs in the D-glucose series and styracitol in the D-mannose series, on the assumption that the isorotation hypothesis applies to the substances with sufficient approximation to exclude an actual reversal of the sign of a large epimeric difference. These two agreeing indications that were noted by Freudenberg and Rogers have been shown by the later conclusive structural and configurational chemical proofs[5] to have led them to the correct assignment of configurations to polygalitol and styracitol. Since this example shows that the isorotation comparisons gave valuable early indications of configurations, we seek in the present article to extend such comparisons to a rather large group of sugar derivatives that are related through the common possession of a tetrahydropyrane structure, with particular emphasis on the 1,5-anhydroglycitols and their 2-desoxy derivatives, the hydroglycals.

Examination of Table I will demonstrate that the isorotation hypothesis holds well for the 1,5-anhydropentitols and for the four known 1,5-anhydrohexitols as well as for the fully acetylated derivatives of all these substances. The large epimeric differences of molecular rotation are of the correct sign throughout and they range in value between 5,500 and 7,650 for the 1,5-anhydrides and between 8,480 and 13,400 for the acetates of these anhydrides. In the hexitol series the 1,5-anhydrides of allitol, altritol, gulitol and iditol are still unknown; they constitute two epimeric pairs and its seems reasonable to predict that the epimeric difference for each pair will have the sign that is shown by the known pairs of Table I. If a member of one of these epimeric pairs should be discovered through a synthetic method that does not distinguish between epimers, as for example through the catalytic reduction of an acylated 2-hydroxyglycal, is it possible to assign the full configuration through the use of isorotation hypotheses? The answer to this question may be obtained through the following considerations.

The hydroglycal that is common to the D-glucose and D-mannose series (III) is closely related to polygalitol (I) and styracitol (II); it is a 2-desoxypolygalitol, which is synonymous with 2-desoxystyracitol. If the molecular rotation of polygalitol is expressed as B + A and that of styracitol as B − A, where A represents the contribution from carbon atom two and B that from the remainder of the structure, the molecular rotation of hydroglucal, in the structure of which carbon atom two is symmetric, may be written [(B + A) + (B − A)]/2 = B, if it be assumed that iso-

(1) Number XXXV, by W. T. Haskins, R. M. Hann and C. S. Hudson, was published in THIS JOURNAL, **69**, 1668 (1947).

(2) W. Freudenberg and E. F. Rogers, *ibid.*, **59**, 1602 (1937).

(3) L. Zervas, *Ber.*, **63**, 1689 (1930).

(4) R. Criegee, *Ann.*, **495**, 211 (1932); **507**, 159 (1933).

(5) (a) L. Zervas and I. Papadimitriou, *Ber.*, **73**, 174 (1940); (b) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **65**, 64 (1943); (c) N. K. Richtmyer, C. J. Carr and C. S. Hudson, *ibid.*, **65**, 1477 (1943); (d) R. C. Hockett and Maryalice Conley, *ibid.*, **66**, 464 (1944).

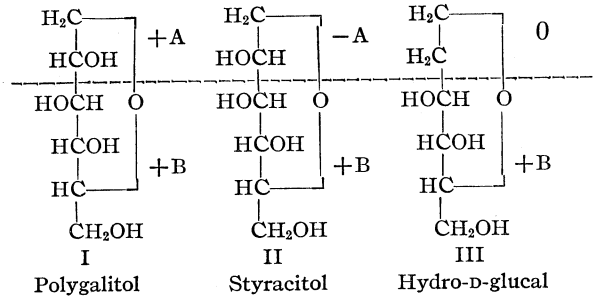
TABLE I

PROPERTIES OF 1,5-ANHYDROGLYCITOLS DERIVED FROM MONOSACCHARIDES

	Formula	C_2–OH (or OAc) group	M. p., °C.	Mol. wt.	$[\alpha]^{20}D$	Solvent	$[M]^{20}D$	B	B_{Ac}
4-Desoxypentitol Series									
1,5-Anhydro-D-*threo*-4-desoxypentitol[a]	XV	–	67–68[b]	118	−44.9[b]	H_2O	− 5,300	5500	
1,5-Anhydro-D-*erythro*-4-desoxypentitol[a]	XI	+	Amorph.[c]	118	+48.2[c]	H_2O	+ 5,690		
Diacetate of XV		–	Amorph.[b]	202	−38.8[b]	C_2H_5OH	− 7,840		8,480
Diacetate of XI		+	Amorph.[d]	202	+45.1[d]	$CHCl_3$	+ 9,110		
Pentitol Series									
1,5-Anhydro-D-arabitol	XVII	–	96–97[e]	134	−98.6[e]	H_2O	−13,200	6600	
1,5-Anhydroribitol	XIX	+	128–129[f]	134	0 (*meso*)		0		
Triacetate of XVII		–	58[e]	260	−74.2[e]	$CHCl_3$	−19,300		9,660
Triacetate of XIX		+	133–134[f]	260	0 (*meso*)		0		
1,5-Anhydro-D-lyxitol[a]	XVII	–	96–97[e]	134	−98.6[e]	H_2O	−13,200	6600	
1,5-Anhydroxylitol	XVI	+	116–117[g]	134	0 (*meso*)		0		
Triacetate of XVII		–	58[e]	260	−74.2[e]	$CHCl_3$	−19,300		9,660
Triacetate of XVI		+	122[g]	260	0 (*meso*)		0		
Hexitol Series									
1,5-Anhydro-D-mannitol	II	–	155[h]	164	−50.9[h]	H_2O	− 8,340	7650	
1,5-Anhydro-D-glucitol	I	+	141–142[i]	164	+42.4[i]	H_2O	+ 6,950		
Tetraacetate of II		–	66–67, 58[j]	332	−42.0[k]	$CHCl_3$	−13,900		13,400
Tetraacetate of I		+	73–74[l]	332	+38.9[l]	$CHCl_3$	+12,900		
1,5-Anhydro-D-talitol	VI	–	Amorph.[m]	164	−11.4[m]	H_2O	− 1,870	7240	
1,5-Anhydro-D-galactitol	VII	+	114[n]	164	+76.6[n]	H_2O	+12,600		
Tetraacetate of VI		–	106–107[m]	332	−16.2[m]	$CHCl_3$	− 5,380		10,800
Tetraacetate of VII		+	75–76[n]	332	+49.1[n]	$CHCl_3$	+16,300		

[a] The names of XV, XI and XVII are systematic alternative designations of the known hydro-D-xylal, hydro-L-arabinal and 1,5-anhydro-D-arabitol. [b] M. Gehrke and F. Obst, *Ber.*, **64**, 1724 (1931). [c] G. E. Felton and W. Freudenberg, THIS JOURNAL, **57**, 1637 (1935). [d] See text of present paper and also M. Gehrke and F. X. Aichner, *Ber.*, **60**, 918 (1927). [e] H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **69**, 1672 (1947). [f] R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **70**, 4052 (1948). [g] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **69**, 921 (1947). [h] R. C. Hockett and Maryalice Conley, *ibid.*, **66**, 464 (1944). [i] N. K. Richtmyer and C. S. Hudson, *ibid.*, **65**, 64 (1943). [j] Y. Asahina, *Ber.*, **45**, 2363 (1912). [k] This hitherto unpublished value was obtained in this Laboratory using a concentration of 2.634 g. per 100 ml. of solution. Asahina (*loc. cit.*) reported a rotation of −20.9° in alcohol. [l] N. K. Richtmyer, C. J. Carr, Jr., and C. S. Hudson, THIS JOURNAL, **65**, 1477 (1943). [m] D. A. Rosenfeld, N. K. Richtmyer and C. S. Hudson, *ibid.*, **70**, 2201 (1948). [n] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **70**, 310 (1948).

rotation holds for the three substances. Even though it cannot be expected that it will hold with



mathematical precision, it may be that the approximation will be such that the molecular rotation of hydroglucal will lie well between those of polygalitol and styracitol. Such is indeed the case, as is shown by the data in Tables I and III; polygalitol (+6,950), hydro-D-glucal (+2,440) and styracitol (−8,340). Likewise the molecular rotation of hydro-D-arabinal (−5,690) lies between those for 1,5-anhydro-D-arabitol (−13,200) and 1,5-anhydroribitol (0), the molecular rotation of hydro-D-xylal (−5,300) lies between those for 1,5-anhydro-D-lyxitol (synonym, 1,5-anhydro-D-arabitol) (−13,200) and 1,5-anhydroxylitol (0) while the molecular rotation of hydro-D-galactal (+7,120) is between those for 1,5-anhydro-D-talitol (−1,870) and 1,5-anhydro-D-galactitol (+12,600). As is to be expected, the molecular rotations of those acetates of these compounds that are known are similarly related. Thus triacetylhydro-D-glucal has a molecular rotation (+9,750) which is between the values for tetraacetylstyracitol (−13,900) and tetraacetylpolygalitol (+12,900); in the five-carbon series the molecular rotation of diacetylhydro-D-xylal (−7,840) is seen to lie between those for triacetyl-1,5-anhydro-D-lyxitol (synonym, triacetyl-1,5-anhydro-D-arabitol) (−19,300) and triacetyl-1,5-anhydroxylitol (0).

The literature reveals that an amorphous diacetylhydroarabinal having a dextrorotation in

TABLE II

PROPERTIES OF THE SUBSTITUTED 1,5-ANHYDROGLYCITOLS DERIVED FROM THE DISACCHARIDES

	Formula	C_2–OH (or OAc) group	M. p.	Mol. wt.	$[\alpha]^{20}D$	Solvent	$[M]_D$
1,5-Anhydro-4-(β-D-glucopyranosyl)-D-glucitol (= 1,5-anhydrocellobiitol)	VIII	+	172[a]	326	+ 29.3[a]	H_2O	+ 9,550
Heptaacetate of VIII		+	75–76[a]	621	+ 4.0[a]	$CHCl_3$	+ 2,500
1,5-Anhydro-6-(β-D-glucopyranosyl)-D-glucitol (= 1,5-anhydrogentiobiitol)	XXI	+	239–240[a]	326	+ 3.6[a]	H_2O	+ 1,200
Heptaacetate of XXI		+	153[a]	621	+ 13.0[a]	$CHCl_3$	+ 8,070
1,5-Anhydro-4-(β-D-galactopyranosyl)-D-glucitol (= 1,5-anhydrolactitol)	XII	+	233–237 (dec.)[b]	326	+ 49.4[b]	H_2O	+16,100
1,5-Anhydro-4-(α-D-glucopyranosyl)-D-glucitol (= 1,5-anhydromaltitol)	XIII	+	Amorph.[b]	326	+132[b]	H_2O	+43,000
Heptaacetate of XIII		+	133–134[b]	621	+ 82.0[b]	$CHCl_3$	+50,900

[a] H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **70**, 310 (1948). [b] H. G. Fletcher, Jr., L. H. Koehler and C. S. Hudson, *ibid.*, **71**, 3679 (1949).

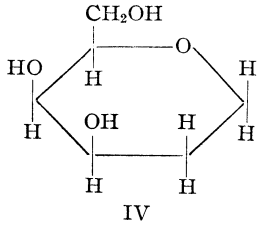
TABLE III

PROPERTIES OF THE HYDROGLYCALS (1,5-ANHYDRO-2-DESOXYGLYCITOLS)

	Formula	M. p., °C.	Mol. wt.	$[\alpha]_D$	Solvent	$[M]_D$
Hydro-D-arabinal[a]	XVIII	Amorph.[a]	118	−48.2[a]	H_2O	−5690
Diacetate of XVIII[b]		Amorph.[b]	202	−45.1[b]	$CHCl_3$	−9110
Hydro-D-xylal	XV	67–68[c]	118	−44.9[c]	H_2O	−5300
Diacetate of XV		Amorph.[c]	202	−38.8[c]	C_2H_5OH	−7840
Hydro-D-glucal	III	86–87[d]	148	+16.5[d]	H_2O	+2440
Triacetate of III		Amorph.[e]	274	+35.6[e]	C_2H_5OH	+9750
Hydro-D-galactal	IV	128[d]	148	+48.1[c]	H_2O	+7120
4-(β-D-Glucopyranosyl)-hydro-D-glucal (hydrocellobial)	IX	222[f]	310	+ 4.5[f]	H_2O	+1400
Hexaacetate of IX		133–134[f]	563	+11.2[f]	$C_2H_4Cl_2$	+6310
6-(β-D-Glucopyranosyl)-hydro-D-glucal (hydrogentiobial)	XX	.....	310	−10.2[g]	H_2O	−3160
Hexaacetate of XX		132–133[g]	563	+11.8[g]	C_5H_5N	+6640
4-(β-D-Galactopyranosyl)-hydro-D-glucal (hydrolactal)	XIV	204–205[h]	310	+28.6[h]	H_2O	+8800

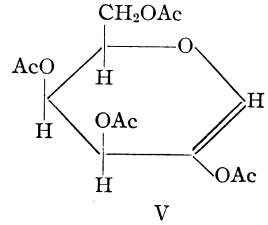
[a] Hydro-D-arabinal has not been reported; its enantiomorph was made by G. E. Felton and W. Freudenberg, THIS JOURNAL, **57**, 1637 (1935), and, with changed sign, we use here the rotational value reported by these authors. [b] See text of present paper and also M. Gehrke and F. X. Aichner, *Ber.*, **60**, 918 (1927). [c] M. Gehrke and F. Obst, *ibid.*, **64**, 1724 (1931). [d] H. Lohaus and O. Widmaier, *Ann.*, **520**, 301 (1935). [e] E. Fischer, *Ber.*, **47**, 196 (1914). [f] E. Fischer and K. von Fodor, *ibid.*, **47**, 2057 (1914). [g] M. Bergmann and W. Freudenberg, *ibid.*, **62**, 2783 (1929). [h] E. Fischer and G. O. Curme, Jr., *ibid.*, **47**, 2047 (1914).

chloroform of +43.1° was reported by Gehrke and Aichner.[6] These authors, however, failed to state to which series (D or L) their substance belonged and internal evidence was lacking since both D- and L-arabinose derivatives are reported elsewhere in the same paper; the present authors have therefore repeated this preparation. Diacetyl-D-



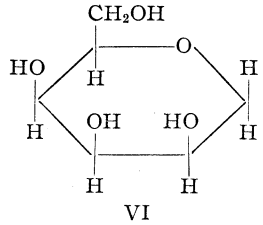
IV

Hydro-D-galactal
$[M]_D$ +7,120



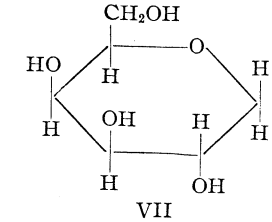
V

Tetraacetyl-2-hydroxy-D-galactal



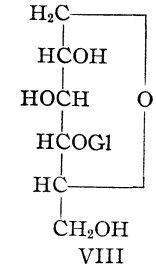
VI

1,5-Anhydro-D-talitol
$[M]_D$ −1,870



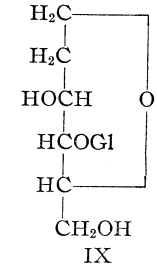
VII

1,5-Anhydro-D-galactitol
$[M]_D$ +12,600



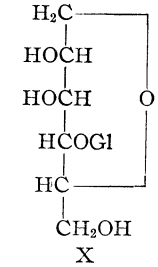
VIII

1,5-Anhydro-4-(β-D-glucopyranosyl)-D-glucitol
$[M]_D$ = +9550
(Gl = β-D-glucopyranosyl)



IX

Hydrocellobial
$[M]_D$ = +1400



X

1,5-Anhydro-4-(β-D-glucopyranosyl)-D-mannitol
(unknown)

(6) M. Gehrke and F. X. Aichner, *Ber.*, **60**, 918 (1927).

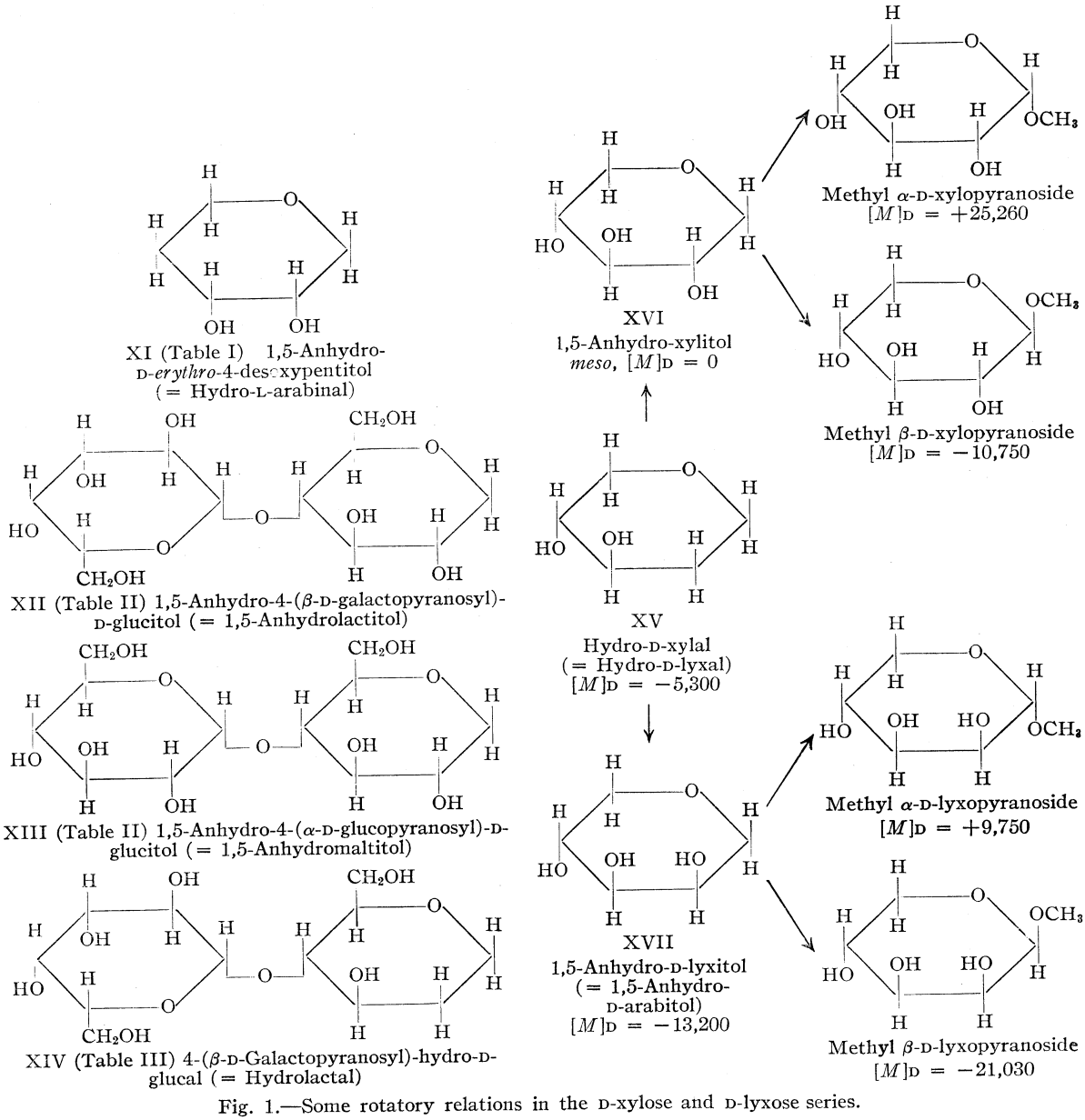


Fig. 1.—Some rotatory relations in the D-xylose and D-lyxose series.

arabinal, prepared from 2,3,4-triacetyl-D-arabinosyl bromide in 66% yield according to the method of Karrer and co-workers[7] was hydrogenated, following the directions of Gehrke and Aichner,[6] to give in 86% yield diacetylhydro-D-arabinal as a colorless, viscid liquid boiling at 0.2 mm. pressure at 90° and having $n^{20}D$ 1.4523. The specific rotation of this substance, $[\alpha]^{20}D$, in chloroform was found to be −45.1° (*c*, 3.02) and it is therefore evident that the product having a rotation of +43.1° reported by Gehrke and Aichner was diacetylhydro-L-arabinal. In agreement with the examples cited above the molecular rotation of diacetylhydro-D-arabinal (−9,110) lies well between those of the two corresponding 1,5-anhydropentitol acetates, triacetyl-1,5-anhydro-D-arabitol (−19,300) and triacetyl-1,5-anhydroribitol (0).

This relationship between the molecular rotations of a hydroglycal and its two corresponding 1,5-anhydroglycitols thus appears to be a general one in a qualitative way and it may be said that *although the molecular rotation of a hydroglycal is not the exact mathematical average of those of the corresponding epimeric 1,5-anhydroglycitols, it lies well between their greatly differing values.*

If this generalization had been known at an earlier date, which was not possible because the pertinent data upon which it is founded were not then known, one could have inferred that the 1,5-anhydrohexitol which Freudenberg and Rogers[2]

(7) P. Karrer, B. Becker, F. Benz, P. Frei, H. Salomon and K. Schöpp, *Helv. Chim. Acta*, **18**, 1435 (1935).

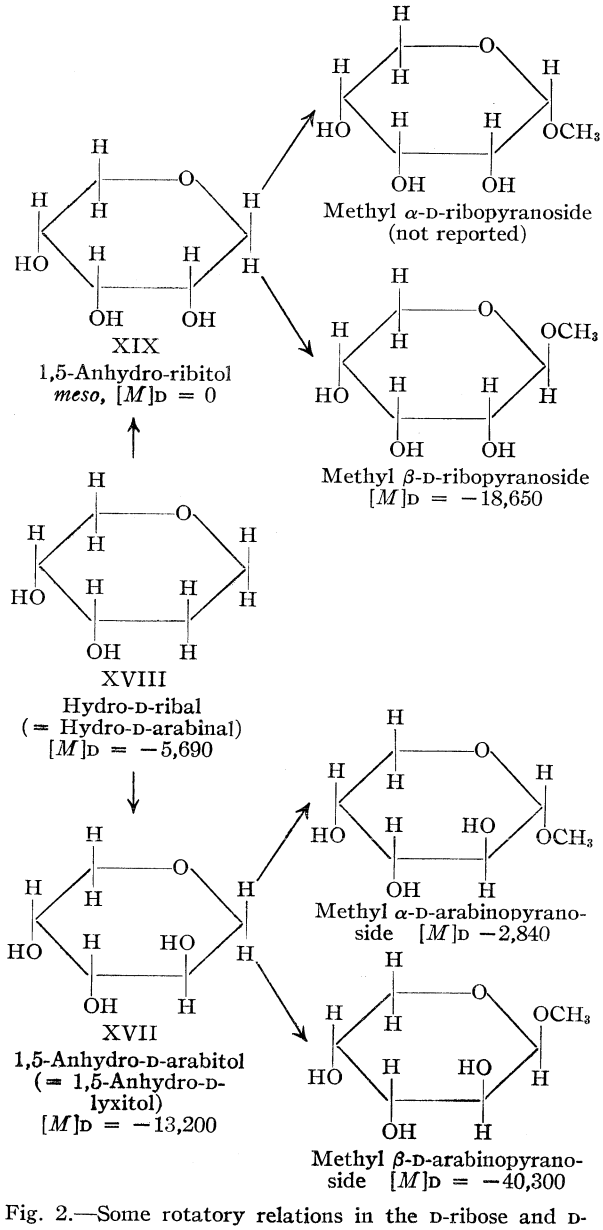


Fig. 2.—Some rotatory relations in the D-ribose and D-arabinose series.

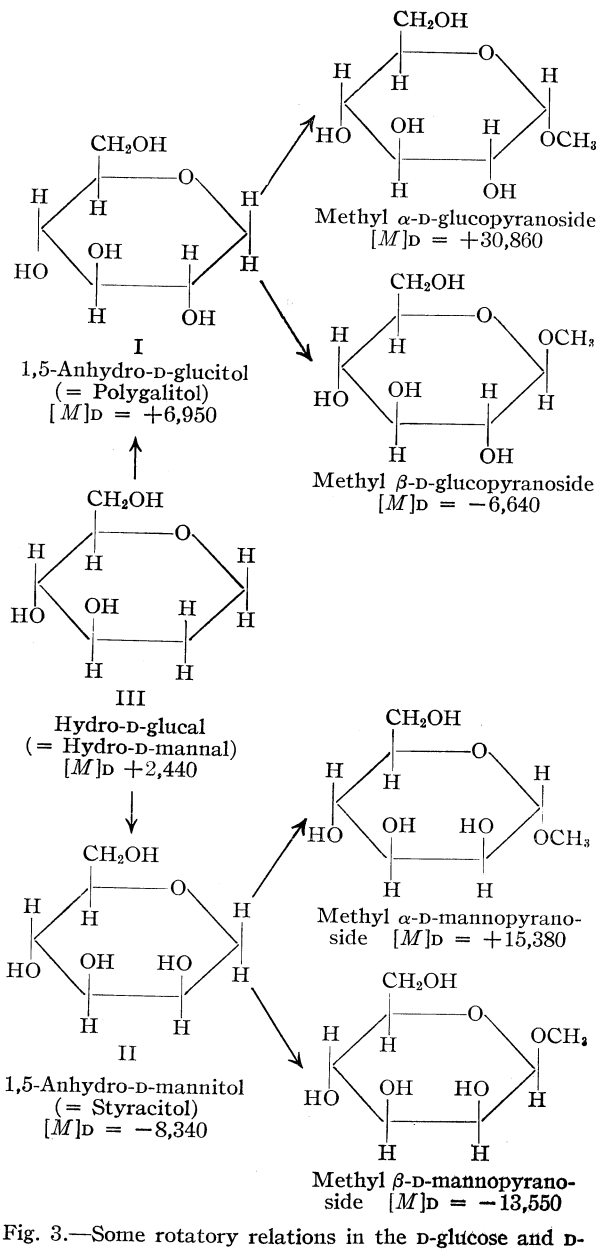


Fig. 3.—Some rotatory relations in the D-glucose and D-mannose series.

synthesized through the catalytic reduction of tetraacetyl-2-hydroxy-D-galactal (IV) was of the D-talitol rather than D-galactitol series since the 1,5-anhydroglycitol which these authors obtained had a molecular rotation of −1,870 and was thus more levorotatory than hydro-D-galactal (IV) (+7,120). Actual proof of the configuration of the substance in question as 1,5-anhydro-D-talitol finally came through unequivocal independent syntheses of 1,5-anhydro-D-talitol[8] and 1,5-anhydro-D-galactitol.[9]

From the above it is apparent that should the catalytic reduction of an acetylated 2-hydroxyglycal ever give rise to both of the expected 1,5-anhydroglycitols[10] each of the two substances may at once be assigned its proper configuration, solely on the basis of its rotation and without recourse to comparison with the rotation of the corresponding hydroglycal.

The foregoing discussion has been limited to derivatives of the monosaccharides; those of some

(8) D. A. Rosenfeld, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **70**, 2201 (1948).

(9) H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **70**, 310 (1948).

(10) The palladium-catalyzed reduction of tetraacetyl-2-hydroxy-D-glucal has, for instance, been shown (ref. 5c) to produce a small quantity of 1,5-anhydro-D-glucitol although 1,5-anhydro-D-mannitol is the predominating product. Hockett and Conley (ref. 5d) have indicated that the nature of the catalyst employed may influence the proportions of products formed.

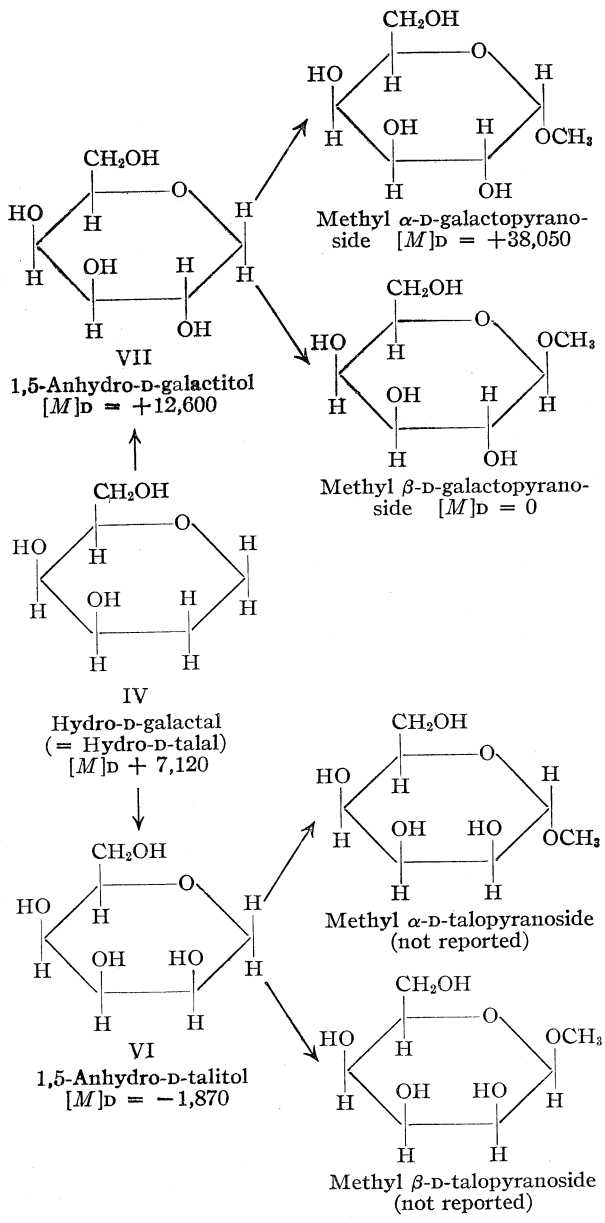


Fig. 4.—Some rotatory relations in the D-galactose and D-talose series.

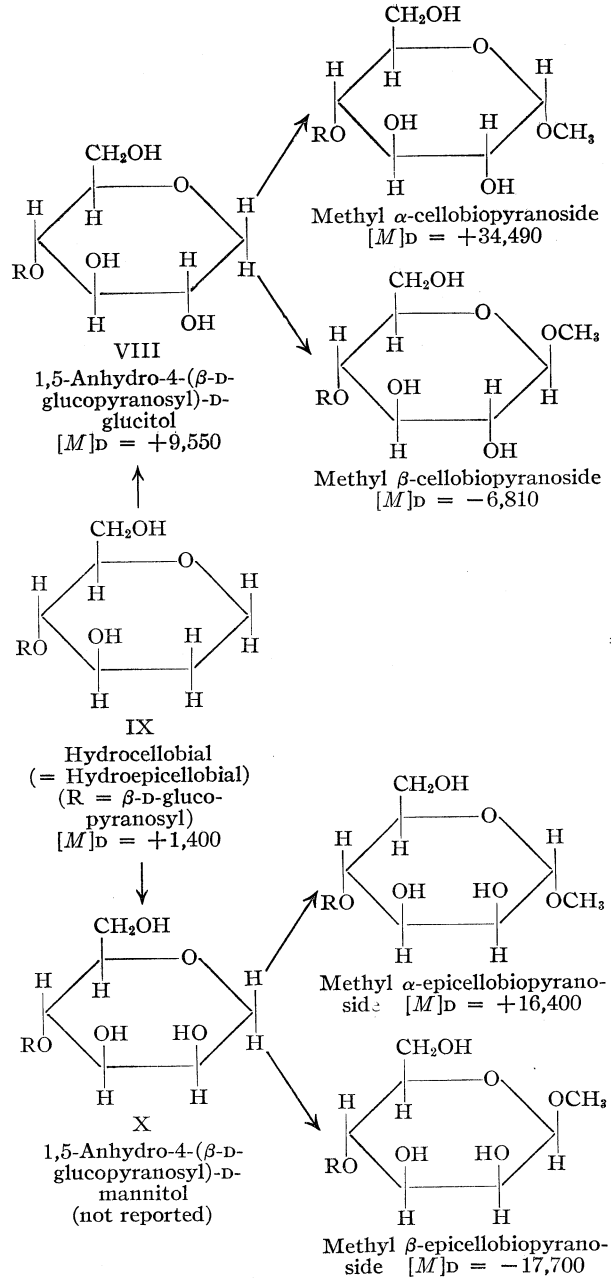


Fig. 5.—Some rotatory relations in the cellobiose and epicellobiose series.

disaccharides will now be considered. In no case are data now known for an epimeric pair of the pertinent 1,5-anhydro derivatives. The hydroglycals from cellobiose, gentiobiose and lactose were synthesized many years ago; the data concerning them are shown in Table II. Maurer and Plötner[11] synthesized 1,5-anhydro derivatives in the cellobiose and gentiobiose series through the palladium-catalyzed reduction of the respective heptaacetyl-2-hydroxyglycals, and though they designated these anhydrides as substituted styracitols (*i. e.*, as derivatives of D-mannitol by present knowledge) it is apparent that there was no just basis for excluding the possibility that they were substituted polygalitols. Indeed, a consideration of the pertinent rotatory relations as developed previously in this article leads clearly to the inference that these two 1,5-anhydro derivatives, one from cellobiose and one from gentiobiose, are substituted polygalitols. In each case the substituted 1,5-anhydride is more dextrorotatory than the corresponding hydroglycal (see Tables II and III), just as polygalitol is more dextrorotatory than hydro-D-glucal. All doubt concerning the allocations has been removed lately through the syn-

(11) K. Maurer and K. Plötner, *Ber.*, **64**, 281 (1931).

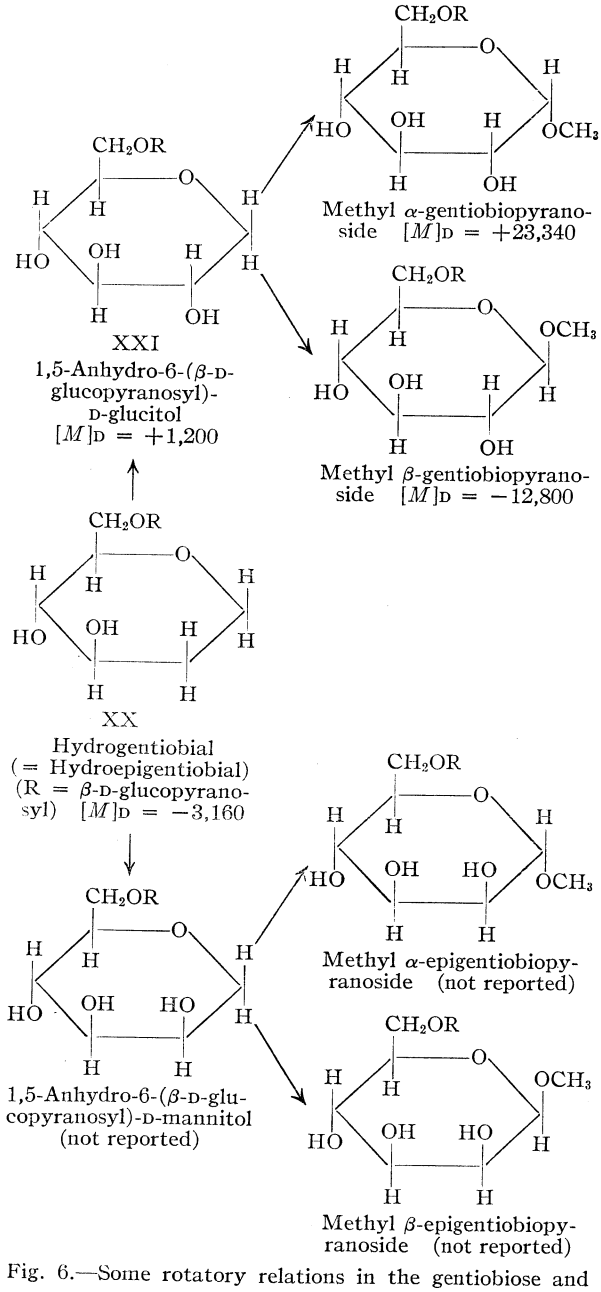


Fig. 6.—Some rotatory relations in the gentiobiose and epigentiobiose series.

thesis of authentic 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol by the reductive desulfurization of phenyl 1-thio-β-cellobioside heptaacetate and of 1,5-anhydro-6-(β-D-glucopyranosyl)-D-glucitol from phenyl 1-thio-β-gentiobioside heptaacetate in like manner.[9] The substances proved to be identical with those discovered by Maurer and Plötner; they are substituted polygalitols rather than substituted styracitols.

The recent preparation of an anhydride in the lactose series, 1,5-anhydro-4-(β-D-galactopyranosyl)-D-glucitol[12] affords an analogous example; as will be seen from Tables II and III the anhydride (+16,100), a substituted polygalitol, is more dextrorotatory than the long known hydrolactal (+8,800).

With the data which are available in Tables I, II and III, and assuming isorotation, it is possible to predict the sign and order of magnitude of the rotations of some 1,5-anhydrides which have not as yet been reported. Thus, using the molecular rotation of the known 1,5-anhydro-4-(β-D-glucopyranosyl)-D-glucitol (+9,550) and the molecular rotation of hydrocellobial (+1,400), it is simple to calculate the molecular rotation of the unknown epimeric anhydride, 1,5-anhydro-4-(β-D-glucopyranosyl)-D-mannitol, as 2 × 1,400–9,550 = −6,750, corresponding to a specific rotation of −21°. Alternatively, the difference between the epimers polygalitol and styracitol (+6,950 − (−8,340) = +15,290) may be used to calculate a value of 9,550 − 15,290 = −5,740, corresponding to a specific rotation of −17° for the same anhydride.

Attention is next directed to the Figs. 1–6.[13] In the left hand column of each of these figures one will observe that the arrangements portray the relationship that has been shown between the molecular rotation of a hydroglycal and those of the members of the related epimeric pair of 1,5-anhydroglycitols. An inspection of the two combined columns of these figures leads to a new generalization which may be stated as follows: *the molecular rotation of a 1,5-anhydroglycitol lies well between the molecular rotations of the anomeric methyl glycopyranosides of the corresponding aldose.* Each methyl α-D-glycopyranoside is much more dextrorotatory, and each methyl β-D-glycopyranoside is much more levorotatory, than the corresponding 1,5-anhydro-D-glycitol. This generalization is not a purely empirical one; it has the same type of basis upon the isorotation hypothesis as does the relationship between the rotation of a hydroglycal and the corresponding 1,5-anhydroglycitol. From Figs. 1–6 it will be seen that the molecular rotation of a 1,5-anhydroglycitol is not the exact mathematical mean of the molecular rotations of the corresponding methyl glycopyranosides but that it does lie so well between them that the generalization can be applied without uncertainty.

Summary

Some relationships between molecular rotation and configuration among the hydroglycals, the 1,5-anhydroglycitols and the methyl glycopyranosides have been pointed out.

BETHESDA, MARYLAND RECEIVED MAY 5, 1949

(12) H. G. Fletcher, Jr., L. H. Koehler and C. S. Hudson, THIS JOURNAL, **71**, 3679 (1949).

(13) The molecular rotations of the methyl glycopyranosides in Figs. 1 to 6 have been taken from the book by F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," U. S. Govt. Printing Office, Washington, D. C., 1942.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF "SYNTEX," S. A.]

Steroids. I. 3-Thio-enol Ethers of Δ^4-3-Keto Steroids

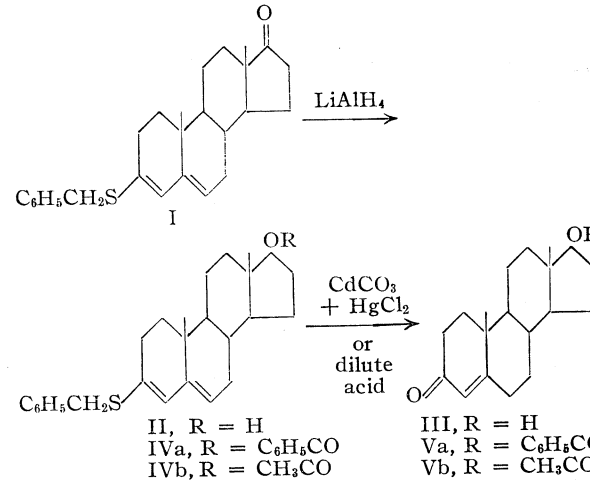
BY G. ROSENKRANZ, ST. KAUFMANN AND J. ROMO

The reaction of 3-keto steroids with alcohols in the presence of condensing agents is well known.[1a,b,c,d] In the case of Δ^4-3-keto steroids, the reaction with monohydric alcohols leads preferably to 3-enol ethers while with glycols cyclic ketals are formed.[2]

It is to be expected that analogous reactions will occur with mercaptans and thioglycols. Bernstein and Dorfman[3] and Hauptmann[4] reported some thioenol ethers and mercaptols of cholestenone, dehydrocholic acid and cholestanone.[5]

We decided to study the exact reaction conditions for the condensation of Δ^4-androstene-3,17-dione with benzyl mercaptan. In order to avoid the reaction of the 17-keto group, as it occurs in the case of dehydroisoandrosterone acetate and several mercaptans,[6,7] we carried out the condensation either at room temperature with anhydrous zinc chloride and sodium sulfate in dioxane solution or by azeotropic distillation of the benzene solution of equimolar quantities of the ketone and mercaptan in the presence of *p*-toluenesulfonic acid. In both cases the resulting product was the well-characterized 3-benzylthioenol ether of Δ^4-androstene-3,17-dione (I). This product can be reconverted easily into the parent ketone by known methods, *e. g.*, with cadmium carbonate and mercuric chloride or by acid hydrolysis.

A very important reaction of the 3-enol ethers (and also of the 3-ketals) of Δ^4-androstene-3,17-dione is their reduction to the corresponding derivatives of testosterone.[1d] The best known method for this reduction is with sodium and alcohol. Applying this method to our 3-thioenol ethers, we encountered difficulties to accomplish the reduction of the 17-keto group without altering the thioenol ether group, while the reaction of these compounds with alkyl-magnesium halides (Miescher[5]) takes place very neatly, involving only the 17-keto group and leaving the 3-grouping unaffected. We found, however, that the 17-keto group of the 3-benzylthioenol ether of Δ^4-androstene-3,17-dione (I) can be transformed into the hydroxyl group with lithium aluminum hydride[8] whereby the 3-benzylthioenol ether of testosterone (II) is obtained in good yield. This latter compound can be hydrolyzed by means of dilute mineral acids or cadmium carbonate and mercuric chloride to testosterone (III). By careful acylation of the 3-benzylthioenol ether of testosterone (II) the corresponding esters (IV) are obtained. The mild hydrolysis of these 3-thioenol-ether 17-esters with cadmium carbonate and mercuric chloride leads to the corresponding esters of testosterone (V). It is obvious that the preceding reactions represent a new synthesis for the preparation of testosterone and its esters.



II, R = H
IVa, R = C_6H_5CO
IVb, R = CH_3CO

III, R = H
Va, R = C_6H_5CO
Vb, R = CH_3CO

The thioenol ethers described in this paper are well-crystallized substances which are fairly alkali resistant. They are stable in acid-free solvents but in presence of traces of acids they decompose rapidly with development of vile-smelling vapors. They also decompose under the influence of light and must be stored in dark containers.

As an interesting alternative we also studied the reaction between Δ^4-androstene-3,17-dione and monothioglycol since the latter compound contains simultaneously a hydroxyl and a sulfhydryl group. In analogy to the reaction of the Δ^4-3-keto-compounds with ethylene glycol[2] and dithioglycol[4,5] we expected the formation of a cyclic hemithioketal (VI).

Theoretically two other compounds might also be formed: the 3-(β-hydroxyethyl)-thioenol ether (VII) and the 3-(β-mercaptoethyl) enol ether (VIII) of androstenedione.

The formation of other theoretically possible reaction products, where the double bond of the

(1) (a) Schwenk, Fleischer and Whitman, THIS JOURNAL, **60**, 1702 (1938); (b) Schwenk and Whitman, U. S. Patent 2,246,540; (c) Westphal, Serini and Köster, U. S. Patent 2,294,433; (d) Köster U. S. Patent 2,363,338.

(2) Fernholz, U. S. Patent 2,356,154.

(3) Bernstein and Dorfman, THIS JOURNAL, **68**, 1152 (1946).

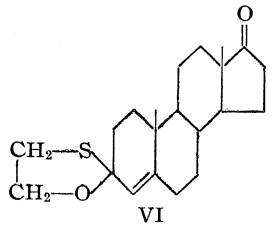
(4) Hauptmann, *ibid.*, **69**, 562 (1947).

(5) In one of his patents which recently became available to us (U. S. Patent 2,435,013), Miescher describes the reactions of androstene-3,17-dione with ethyl mercaptan and dithio-glycol, respectively. No characteristics of the corresponding reaction product are given. After the conclusion of our work a U. S. Patent (2,451-434) of Dorfman and Bernstein became available. This patent refers to the preparation of the ethylthioenol ether of testosterone propionate by the reaction of testosterone propionate with ethyl mercaptan. The product is described as a yellow viscous oil.

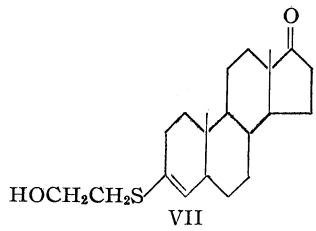
(6) Norymberska, Norymberski and Olalde, THIS JOURNAL, **70**, 1256 (1948).

(7) Levin and Thompson, *ibid.*, **70**, 3140 (1948).

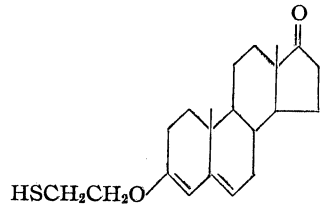
(8) Nystrom, Weldon and Brown, *ibid.*, **69**, 1197 (1947).



VI



VII

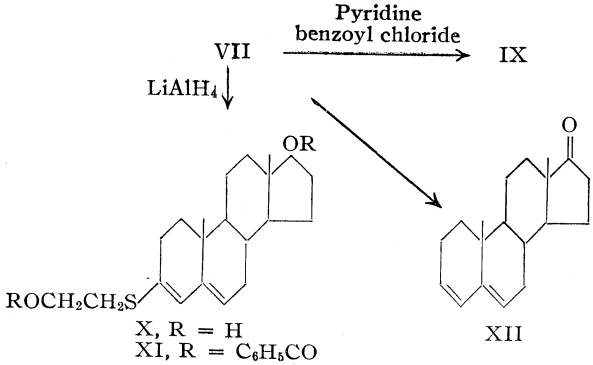


VIII

α,β-unsaturated ketone would react with the mercaptan seems remote since Hauptmann[4] was unable to obtain any sulfur-containing steroid compounds in the reaction of Δ^4-cholestene-3-one and benzyl mercaptan using as a catalyst, piperidine which is supposed to favor particularly the reaction between mercaptans and the α,β-double bond.

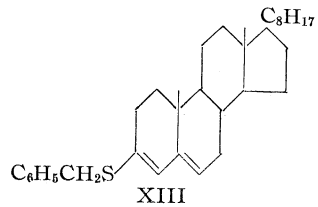
Working under different conditions we were able to isolate two compounds: using pyridine hydrochloride as condensing agent we isolated the thioenol ether (VII) and using zinc chloride and sodium sulfate or *p*-toluenesulfonic acid we obtained another compound which is probably the cyclic hemithioketal of the formula (VI).[9]

The thioenol ether (VII) behaves exactly as the 3-benzylthioenol ether of Δ^4-androstene-3,17-dione (I) and can be converted into the corresponding derivatives of testosterone by the same process as mentioned above. With benzoyl chloride and pyridine a monobenzoate (IX) can be prepared. The same reaction applied to the corresponding 17-hydroxy compound (X) which was obtained by the action of lithium aluminum hydride on (VII) gives a crystalline dibenzoate (XI).



X, R = H
XI, R = C_6H_5CO

XII



XIII

In order to decide between formulas (VII) and (VIII) and for a definite proof of structure we submitted the compound to hydrogenolysis with Raney nickel. We obtained the known $\Delta^{3,5}$-androstadiene-17-one (XII), which proved beyond doubt structure (VII) for the compound obtained in the reaction of monothioglycol and androstenedione in presence of pyridine hydrochloride. Formula (VIII) can be excluded because on desulfuration one could expect a 3-ethyl ether of the androstane series. In order to establish the behavior of the double bonds of the thioenol ethers on desulfuration, it was necessary to submit several thioenol ethers of the androstane and cholestane series to hydrogenolysis under different conditions. As this reaction has not been described before we selected the following compounds for our study: 3-benzylthioenol ether of Δ^4-androstene-3,17-dione (I); 3-benzylthioenol ether of testosterone (II); 3-(β-hydroxyethyl)-thioenol ether of Δ^4-androstene-3,17-dione (VII); 3-(β-hydroxyethyl)-thioenol ether of testosterone (X) and 3-benzylthioenol ether of Δ^4-cholestenone (XIII).

This latter compound had not been prepared before. We obtained it by the reaction of equimolar quantities of benzyl mercaptan and Δ^4-cholestenone using as condensing agents either *p*-toluenesulfonic acid or zinc chloride and sodium sulfate. It seemed to us that if an excess of the mercaptan is used, the formation of the mercaptol predominates, whereas, using equimolar quantities, thioenol ethers are formed. However, Bernstein and Dorfman[3] reported the preparation of the 3-ethylthioenol ether of Δ^4-cholestenone using ethyl mercaptan in excess. We are inclined to regard this as an exception, due perhaps to the volatility of the mercaptan used. Hauptmann[4] using excess benzyl mercaptan obtained the corresponding mercaptol of Δ^4-cholestenone.

For the hydrogenolytic desulfuration, we used the method described by Wolfrom and Karabinos.[10] The hydrogenolysis was carried out in two different series: in the first series the Raney nickel was partially deactivated according to the method of Spero, McIntosh and Levin.[11] These authors refluxed the acetone suspension of the catalyst during two hours and subsequently added the compound which was to be desulfurated, completing the reaction by further refluxing. In the second series of experiments fully active Raney nickel, prepared according to the method of Mozingo,[12a,b] was used in ethanol or dioxane as reaction medium.

With the deactivated catalyst we obtained $\Delta^{3,5}$-

(9) Investigation of this compound is now on the way in our laboratories. The results will be published at some future date.

(10) Wolfrom and Karabinos, THIS JOURNAL, **66**, 909 (1944).

(11) Spero, McIntosh and Levin, *ibid.*, **70**, 1907 (1948).

(12) (a) Mozingo, *Org. Syntheses*, **21**, 15 (1941); (b) in the classification of Adkins and Pavlic (THIS JOURNAL, **69**, 3039 (1947)) this Raney nickel is referred to as "catalyst W-2."

compounds throughout the whole series. With fully active catalyst the thioenol ethers of testosterone and cholestenone were desulfurated to the saturated compounds of the androstane and cholestane series, respectively.

When desulfurizing the thioenol ether of Δ^4-androstene-3,17-dione, a mixture of $\Delta^{3,5}$-androstadiene-17-one and androstan-17(β)-ol[13] was obtained. It is very probable that the first action of the Raney nickel on the thioenol ether molecule consists in the elimination of the sulfur atom. If the nickel catalyst is partially deactivated, its action ceases when desulfuration is complete, but with an active catalyst, and in a medium which does not exercise a deactivating action, the Raney nickel reduces the 17-keto group and then saturates the conjugated double bonds.

The simultaneous formation of the $\Delta^{3,5}$-androstadiene-17-one and androstan-17(β)-ol indicates that the carbonyl group of the thioether molecule acts as a partial deactivator of the nickel, hindering the saturation of the double bonds, but when it is reduced to the alcohol group its influence disappears and the double bonds are saturated.

The isolation of $\Delta^{3,5}$-androstadien-17-one from the desulfuration products of the thioenol ether of Δ^4-androstene-3,17-dione is the first direct evidence for this position of the double bonds in this compound, because under the extremely mild conditions of the desulfuration the shifting of the double bond is not likely to occur. That same position of the double bonds was suggested by some authors[1] for the enol ethers of the Δ^4-3-keto steroids but so far no direct proof for this assumption has been presented.

As additional evidence for the heteroannular location of the double bonds in our thioenol ethers, we may mention the fact that we failed to obtain an addition product with maleic anhydride, working in benzene solution under the usual conditions, while such an addition product would most likely have been formed in the case of a homoannular diene.

The ultraviolet absorption spectra of the thioenol ethers have an absorption maximum at 268 mμ; the corresponding enol ethers show a maximum at 240 mμ.[14] Gillam, *et al.*,[15] found a difference of 22 mμ between the absorption maxima of certain semicarbazones and thiosemicarbazones, and Bowden, *et al.*,[16] report a similar bathochromic effect of the –SR group attached to the ethylenic linkage. In the light of these findings and of the evidence presented above by ourselves, we feel justified in ascribing the Δ_λ of 28 mμ between the λ_{max} of the enol ethers and of the thioenol ethers (240–268 mμ) to the introduction of a sulfur-containing substituent, and not to any rearrangement in the steroid molecule itself.[17]

(13) We ascribe to this compound the β-configuration at C_{17} in accordance with the convention advanced in Fieser and Fieser "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corp., New York, N. Y., 1949, pp. 325–327.

(14) See ref. 1b; confirmed by measurements in this Laboratory.

(15) Gillam, *et al.*, *J. Chem. Soc.*, 486 (1942), (*C. A.*, **37**, 625[1] (1943)).

(16) Bowden, *et al.*, *J. Chem. Soc.*, 948 (1946).

Experimental[18,19,20,21]

3-Benzylthioenol Ether of Δ^4-Androstene-3,17-dione (I).—(a) Pure Δ^4-androstene-3,17-dione (4.9 g., 0.017 mole) was dissolved in 25 cc. of anhydrous dioxane; 4 g. (0.034 mole) of benzyl mercaptan, 8 g. of freshly fused and pulverized zinc chloride and 8 g. of anhydrous sodium sulfate were added under external cooling. After seventeen hours at room temperature the orange-colored mixture was diluted with benzene, washed with water to remove the inorganic salts, dried over sodium sulfate and evaporated to dryness. The residue was crystallized from acetone–methanol whereby 3 g. (45%) of small pale-yellowish needles of I, m. p. 177–179°, $[\alpha]^{20}D$ −84°, λ_{max} 268 mμ, log E_m 4.15 was obtained.

Anal. Calcd. for $C_{26}H_{32}OS$: C, 79.54; H, 8.21; S, 8.16. Found: C, 79.59; H, 8.10; S, 7.88.

(b) A solution of 10 g. (0.035 mole) of Δ^4-androstene-3,17-dione in 100 cc. of benzene to which 5.3 g. (0.043 mole) of benzyl mercaptan and 0.5 g. of *p*-toluenesulfonic acid were added was refluxed for six hours. Every two hours 15 cc. of the azeotropic mixture was distilled off. After the end of the reaction the mixture was diluted with 100 cc. of benzene, washed neutral with 5% sodium carbonate solution and water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was crystallized from acetone–methanol, whereby 7.5 g. (55%) of I, m. p. 177–179°, was obtained.

To a solution of 2 g. of I in 200 cc. of ethanol, 3 cc. of concentrated hydrochloric acid and 3 cc. of water were added. After refluxing for two hours the mixture was poured into water, extracted with ether, washed neutral with water, sodium bicarbonate solution and water, dried over sodium sulfate and evaporated to dryness.[22] The residue on crystallization from acetone–hexane gave 1.2 g. of crystals, m. p. 166–170°, $[\alpha]^{20}D$ + 190° (in ethanol). A qualitative test of sulfur was negative; mixed with an authentic sample of Δ^4-androstene-3,17-dione it gave no depression.

To a solution of 2 g. of I in 250 cc. of acetone, 3 g. of freshly prepared cadmium carbonate and 3 g. of finely pulverized mercuric chloride were added. The mixture was refluxed for eight hours, the inorganic salts were filtered off and washed with acetone. The filtrate was concentrated to a volume of 50 cc., poured into water and ex-

(17) Moreover, we calculated the differences between the molecular rotations of our thioenol ethers and of the corresponding Δ^4-3-keto steroids and found in five out of seven cases a Δ_M of −873 ± 3 (in two cases the values differed by 10% from the above mean value; see note 20). This strongly levorotatory shift supports a $\Delta^{3,5}$ rather than a $\Delta^{2,4}$ location of the double bonds (see Fieser, ref. 13, p. 210) and comes near the corresponding values for the oxygen analogs (Δ_M about −760),[1a] thus suggesting once more that the oxygen-containing and the sulfur-containing enol ethers possess the same structure.

(18) The microanalyses were carried out by Dr. Carl Tiedcke, New York, N. Y., and in our microanalytical laboratory under the direction of Miss Amparo Barba.

(19) All the melting points were determined on the Kofler micro-melting point apparatus.

(20) The rotations of the sulfur-containing substances were determined in anhydrous dioxane; these compounds decompose rapidly in chloroform. The decomposition in dioxane, though somewhat slower, probably accounts for the 10% discrepancy in the molecular rotations of compounds II and VII (see note 17). Attempts to stabilize the dioxane solutions by the addition of a few drops of pyridine were not satisfactory. All determinations were carried out in appr. 2% solutions, using a 10-cm. tube of 2-cc. capacity.

(21) The ultraviolet absorption spectra were determined in alcoholic solution, using a Beckman Model DU Quartz Spectrophotometer with 1-cm. quartz cells.

(22) In the following, this procedure is briefly referred to as "usual workup."

tracted with ether. After the usual workup the residue was recrystallized from acetone–hexane. Androstenedione (1.1 g.) m. p. 167–172° was obtained, characterized by a mixed melting point with an authentic sample.

3-(β-Hydroxyethyl)-thioenol Ether of Δ^4-Androstene-3,17-dione (VII).—A solution of 10 g. (0.035 mole) of Δ^4-androstene-3,17-dione in 100 cc. of benzene, 3 g. (0.038 mole) of monothioglycol and 0.8 g. of pyridine hydrochloride in 10 cc. of absolute alcohol was refluxed for six hours. Every two hours 10 cc. of the azeotropic mixture was distilled off. At the end of the reaction the mixture was diluted with 100 cc. of benzene and worked up as described above. The residue was crystallized from methanol, whereby 4 g. (33%) of white prisms of VII, m. p. 166–177°, $[\alpha]^{20}D$ −113°, λ_{max} 268 mμ, log E_m 4.41 was obtained. From the mother liquors additional 2 g. (16.5%) could be collected on further standing.

Anal. Calcd. for $C_{21}H_{30}O_2S$: C, 72.78; H, 8.72; S, 9.25. Found: C, 72.74; H, 8.69; S, 9.15.

The hydrolysis of this thioenol ether was accomplished under the same conditions as described above for I. In both cases Δ^4-androstene-3,17-dione was obtained, identified by melting points, mixed melting point and rotation.

The benzoate (IX) was prepared by dissolving 4 g. (0.011 mole) of VII in 10 cc. of anhydrous pyridine to which 5 g. (0.036 mole) of benzoyl chloride was added. The mixture was left standing at room temperature for eighteen hours, then diluted with pure chloroform and washed with 2% sulfuric acid, water, sodium carbonate solution and water until neutral, dried over sodium sulfate and concentrated to a residual volume of about 15 cc., diluted with 200 cc. of ether and quickly filtered. The filtrate was decolorized with charcoal and evaporated to dryness. The residue, after addition of methanol, became solid. After two crystallizations from chloroform–methanol, 2 g. (39%) of white plates, m. p. 209–211° was obtained; $[\alpha]^{20}D$ + 177.3°, λ_{max} 232 mμ, log E_m 4.38.[23]

Anal. Calcd. for $C_{28}H_{34}O_3S$: C, 74.62; H, 7.60; S, 7.11. Found: C, 74.59; H, 7.62; S, 7.28.

3-Benzylthioenol Ether of Δ^4-Cholestenone (XIII).—This compound was prepared as described above under (b), using 5 g. (0.013 mole) of Δ^4-cholestenone in 100 cc. of benzene, 2.5 g. (0.02 mole) of benzyl mercaptan and 0.3 g. of *p*-toluenesulfonic acid. Crystallization from acetone yielded 3.2 g. (50%) of white needles of XIII, m. p. 121.5–122°, $[\alpha]^{20}D$ −105°, λ_{max} 268 mμ, log E_m 4.31.

Anal. Calcd. for $C_{34}H_{50}S$: C, 83.27; H, 10.26; S, 6.53. Found: C, 83.42; H, 10.14; S, 6.66.

3-Benzylthioenol Ether of Testosterone (II).—The flask of a Soxhlet extraction apparatus was charged with a solution containing 2 g. (0.053 mole) of lithium aluminum hydride in 800 cc. of anhydrous ether and 3 g. (0.008 mole) of I was placed in the extractor thimble. The solution was warmed until all the thioenol ether had been transferred to the reaction flask. The mixture was then cooled externally with ice and, under continuous stirring, water was added dropwise to decompose the excess hydride and the complex formed during the reaction. When decomposition was complete, 300 cc. of benzene was added in order to dissolve the product completely. The benzene–ether solution was washed with water, dried over sodium sulfate and evaporated to dryness. After recrystallization from methanol with a drop of pyridine, 2 g. (66%) of white needles, m. p. 168–169°, $[\alpha]^{20}D$ −126.2°, λ_{max} 268 mμ, log E_m 4.20 was obtained.

Anal. Calcd. for $C_{26}H_{34}OS$: C, 79.12; H, 8.68; S, 8.12. Found: C, 79.22; H, 8.68; S, 8.28.

The hydrolysis of II with hydrochloric acid was carried out as described above for I: To a solution of 1 g. of II in ethanol, 3 cc. of hydrochloric acid and 3 cc. of water were added. After two hours refluxing, the mixture was poured into water, the product extracted with ether and worked up as usual. By several recrystallizations from acetone–hexane, 0.5 g. (68%) of testosterone (III) m. p. 150–152°, $[\alpha]^{20}D$ +104.2° (in methanol) was obtained. The mixed melting point with an authentic sample of testosterone gave no depression. The sulfur test was negative.

To a solution of 2 g. of II in 250 cc. of acetone, 3 g. of cadmium carbonate and 3 g. of mercuric chloride were added. The mixture was refluxed for two hours and the reaction product worked up as in previous examples. By repeated recrystallizations from acetone–hexane 0.9 g. (61%) of testosterone (III), m. p. 150–51° mixed m. p. 150–153°, $[\alpha]^{20}D$ + 103.4° (in methanol) was obtained. The sulfur test was negative.

3-Benzylthioenol Ether of Testosterone Benzoate (IVa).—To a solution of 4 g. (0.01 mole) of II in 8 cc. of anhydrous pyridine, 5 g. (0.035 mole) of benzoyl chloride was added and the mixture was left standing at room temperature for fourteen hours. It was then diluted with chloroform, washed with 2% sulfuric acid, water, sodium carbonate solution and water until neutral, dried over sodium sulfate and concentrated to a residual volume of 20 cc. Ether was added and the solution was quickly filtered, decolorized with charcoal and evaporated to dryness. After crystallization from methanol, 2 g. (40%) of white needles was obtained which, after recrystallization from acetone–methanol, melted at 160–161°, $[\alpha]^{20}D$ −59.3°, λ_{max} 228, 268 mμ; log E_m 4.46, 4.32.

Anal. Calcd. for $C_{33}H_{38}O_2S$: C, 79.47; H, 7.68; S, 6.42. Found: C, 79.59; H, 7.80; S, 6.69.

To a solution of 0.7 g. of IVa in 200 cc. of alcohol, 3 drops of concentrated hydrochloric acid and 3 cc. of water were added. After two hours of refluxing, the product was worked up as in the previous example. By crystallization from methanol, 0.35 g. (64%) of testosterone benzoate (Va), m. p. 190–192° was obtained, which gave no depression when mixed with an authentic sample.

3-Benzylthioenol Ether of Testosterone Acetate (IVb).—A flask containing a mixture of 10 cc. of anhydrous dioxane and 10 cc. of pyridine was cooled externally with ice and 9 g. (0.11 mole) of acetyl chloride was added dropwise. To this mixture, which was kept in the ice-bath, a solution of 1.5 g. (0.004 mole) of II in 20 cc. of anhydrous dioxane was added dropwise. It was left standing at room temperature during one hour and then poured into water. It was extracted with ether and the ether solution washed with 2% sulfuric acid solution and water until neutral, dried over sodium sulfate and evaporated to dryness. After crystallization from methanol with a drop of pyridine, 1 g. (60%) of white needles, m. p. 110°, $[\alpha]^{20}D$ −134° was obtained.

Anal. Calcd. for $C_{28}H_{36}O_2S$: C, 77.01; H, 8.31; S, 7.34. Found: C, 76.98; H, 8.39; S, 7.19.

To a solution of 0.6 g. of IVb in 100 cc. of ethanol, 3 drops of concentrated hydrochloric acid and 3 cc. of water were added. After two hours of refluxing, the mixture was poured into water and worked up as usual. The residue was taken up in hexane and the solution decolorized with charcoal. By crystallization, 0.2 g. (44%) of testosterone acetate (Vb) m. p. 139–140°, $[\alpha]^{20}D$ + 89° was obtained, which gave no depression when mixed with an authentic sample. The sulfur test was negative.

3-(β-Hydroxyethyl)-thioenol Ether of Testosterone (X).—Under the same conditions as described above for I, 3 g. of VII was treated in a Soxhlet apparatus with an excess of lithium aluminum hydride yielding, after crystallization from methanol with a drop of pyridine, 2 g. (66%) of white needles m. p. 175–177°, $[\alpha]^{20}D$ −161.3°.

Anal. Calcd. for $C_{21}H_{32}O_2S$: C, 72.36; H, 9.25; S, 9.19. Found: C, 72.38; H, 9.46; S, 9.09.

Following the method described above for II, 1.5 g. of X was hydrolyzed with hydrochloric acid and 1 g. (80%) of testosterone m. p. 151–153°, $[\alpha]^{20}D$ +103° (in methanol), was obtained. The mixed m. p. gave no depression. The sulfur test was negative.

On hydrolysis with cadmium carbonate and mercuric chloride under the conditions described above for II, 2 g. of X yielded 1.4 g. (85%) of testosterone m. p. 151°,

(23) In view of this unexpected dextrorotation and the absence of the typical absorption maximum at 268 mμ, we abstain from assigning a structural formula to IX.

$[\alpha]^{20}D$ + 104.6° (in methanol) which gave no melting point depression.

The **dibenzoate (XI)** was prepared by applying to a solution of 1 g. of X in 5 cc. of pyridine, to which 3 g. of benzoyl chloride was added, the treatment described for II. After crystallization from methanol, 0.5 g. (31%) of tiny plates was obtained, m. p. 131–133°, $[\alpha]^{20}D$ −58.5°, λ_{max} 230, 268 mμ, log E_m 4.57, 4.22.

Anal. Calcd. for $C_{35}H_{40}O_4S$: C, 75.50; H, 7.24; S, 5.75. Found: C, 75.60; H, 7.30; S, 5.65.

Working as described for IVa, 2 g. of dibenzoate yielded 0.4 g. (28%) of testosterone benzoate, m. p. 188–193°. Mixed with an authentic sample of m. p. 192–194° the mixture melted at 188–193°.

Probable Hemithioketal of Δ^4-Androstene-3,17-dione: First Method.—Five grams (0.017 mole) of the diketone and 1.4 g. (0.17 mole) of monothioglycol were dissolved in 10 cc. of anhydrous dioxane. Seven grams of freshly fused and pulverized zinc chloride and 7 g. of anhydrous sodium sulfate were added and the mixture was left standing at room temperature for sixteen hours. It was then diluted with benzene, washed with water, dried and evaporated to dryness, leaving 5.5 g. of an oily residue, which was subsequently chromatographed on a column of 100 g. of aluminum oxide (Alorco F-20), using portions of 300 cc. of benzene–hexane 1:1 for each fraction of the elution. Fraction 1 yielded 0.9 g. and fraction 8 yielded 0.2 g. of an oil. The combined crystalline fractions 2–7 (3.7 g.) with melting points ranging from 178 to 193°, were recrystallized several times from methanol yielding 2.5 g. (41%) of white needles, m. p. 190–193°, λ_{max} 238 mμ, log E_m 4.30.

Anal. Calcd. for $C_{21}H_{30}O_2S$: C, 72.78; H, 8.72; S, 9.25. Found: C, 73.02; H, 8.86; S, 8.93; $[\alpha]^{20}D$ +52.4°.

Second Method.—Ten grams (0.035 mole) of the diketone was dissolved in 100 cc. of benzene and 3.5 g. (0.045 mole) of monothioglycol was added. The mixture was refluxed for six hours and every two hours 10 cc. of the azeotropic mixture was distilled off. Proceeding as described in previous examples, by several crystallizations from methanol 3 g. (25%) of white needles, m. p. 190–193° was obtained. An additional crop of 2 g. (16%) was obtained from the mother liquors.

The mixed m. p. of the crystals obtained by these two methods gave no depression.

On hydrolysis with hydrochloric acid, 2 g. of this product gave 1.3 g. of Δ^4-androstene-3,17-dione, m. p. 168–170°.

On hydrolysis with cadmium carbonate and mercuric chloride, 2 g. of the product gave 1.5 g. of Δ^4-androstene-3,17-dione.

Hydrogenolysis of 3-Benzylthioenol Ether of Δ^4-Androstene-3,17-dione (I). Method A with Fully Active Raney Nickel.—To a solution of 4 g. (0.01 mole) of I in 100 cc. of dioxane, a suspension of 30 g. of Raney nickel in 100 cc. of ethanol, prepared according to Mozingo[12] was added and the whole was refluxed for eight hours. The nickel was filtered off and the solvent was removed under reduced pressure leaving 3 g. of a solid residue, which was dissolved in 38 cc. of absolute ethanol and 3.8 cc. of acetic acid; 3 g. of Girard reagent T was added. After refluxing for one hour the mixture was poured into water, containing a quantity of sodium hydroxide sufficient to neutralize 9/10 of the acetic acid. From the aqueous mixture, the non-ketone fraction was extracted with ether, the ether solution was washed with water, dried and evaporated; by recrystallization from hexane, 0.3 g. (8%) of androstan-17(β)-ol, m. p. 163°, $[\alpha]^{20}D$ + 12° (in chloroform) was obtained. This compound has been prepared by Marker[24] who reports a m. p. 166°. Mixed with an authentic sample of 166° the mixture melted at 163–166°. The tetranitromethane test and the sulfur test were negative.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.55; H, 11.65. Found: C, 82.68; H, 11.74.

(24) Marker, THIS JOURNAL, **62**, 2523 (1940).

The androstan-17(β)-ol acetate was prepared by heating a solution of 0.5 g. of androstan-17(β)-ol in 20 cc. of acetic anhydride on a steam-bath for one hour. The excess anhydride was removed under reduced pressure and the residue crystallized from methanol–water, yielding 0.3 g. of androstan-17(β)-ol acetate, m. p. 72–75°, $[\alpha]^{20}D$ +5° (in chloroform).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.48; H, 10.52.

Kuwada and Miyasaki[25] describe a 17-acetoxyandrostane melting at 82°, but we did not have an opportunity to compare their product with ours.

The androstan-17(β)-ol benzoate was prepared by adding 3 g. of benzoyl chloride to a solution of 1 g. of androstanol in 8 cc. of anhydrous pyridine. The mixture was left standing at room temperature for sixteen hours, then diluted with chloroform, washed with 2% sulfuric acid and then with water until neutral, dried and evaporated. After recrystallization from methanol and acetone–methanol, 0.8 g. of white needles, m. p. 159–161°, $[\alpha]^{20}D$ + 51.7° (in chloroform) was obtained.

Anal. Calcd. for $C_{26}H_{36}O_2$: C, 82.05; H, 9.53. Found: C, 82.04; H, 9.64.

The aqueous mixture of the hydrogenolysis of I, which still contained the ketone fraction, was acidified with hydrochloric acid and extracted with ether. After the usual workup, 2.5 g. (66%) of white plates m. p. 85–87°, $[\alpha]^{20}D$ −21° (in chloroform) was obtained by crystallization from methanol–water. Mixed with a sample of $\Delta^{3,5}$-androstadien-17-one, obtained by dehydration of dehydroisoandrosterone with phosphorus pentoxide, following the method of Burrows, *et al.*,[26] no depression of the melting point was observed. The tetranitromethane test was positive; the sulfur test was negative.

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.24; H, 9.75.

$\Delta^{3,5}$-Androstadien-17-one has been isolated by Wolfe, Fieser and Friedgood[27] who report a m. p. 88–89° and has also been prepared by other authors.[28,29]

The oxime was prepared by dissolving 0.5 g. of the ketone in 50 cc. of methanol to which 0.3 g. of hydroxylamine hydrochloride and 0.5 g. of sodium acetate were added. After refluxing for three hours, the solution was poured into water and worked up as usual. By recrystallization from methanol–water, 0.3 g. of the oxime, m. p. 165–167°, was obtained. This compound has also been prepared by Wolfe, Fieser and Friedgood,[27] who report m. p. 164–166°.

Hydrogenolysis of I. Method B, with Partially Deactivated Raney Nickel.—A suspension of 20 g. of Raney nickel in 100 cc. of acetone was refluxed for one hour, 2 g. of I in 100 cc. of acetone was added and refluxing was continued for four hours. The nickel was filtered off and washed with acetone. The solution was evaporated to dryness and the residue was recrystallized from methanol–water, yielding 0.65 g. (48%) of white plates, m. p. 87–89°, of $\Delta^{3,5}$-androstadien-17-one. The mixed melting point with the above test compound gave no depression. The tetranitromethane test was positive; the sulfur test negative.

Hydrogenolysis of 3-Benzylthioenol Ether of Testosterone (II). Method A.—Two grams of II was dissolved in 100 cc. of alcohol and 20 g. of Raney nickel was added. After refluxing for four hours, the reaction mixture was worked up as described above for I, and by crystallization from hexane, 1.2 g. (86%) of androstan-17(β)-ol, m. p. 165–166°, was obtained. The tetranitromethane test and the sulfur test were negative.

(25) Kuwada and Miyasaki, *J. Pharm. Soc. Japan*, **57**, 870–880 (1937), quoted after *C. A.*, **32**, 1275 (1938).

(26) Burrows, Cook, Roe and Warren, *Biochem. J.*, **31**, 950–961 (1937).

(27) Wolfe, Fieser and Friedgood, THIS JOURNAL, **63**, 582 (1941).

(28) Butenandt, *et al.*, *Ber.* **71B**, 198–204 (1938), quoted after *C. A.*, **32**, 2538 (1938).

(29) Ross, *J. Chem. Soc.*, 25–27 (1945).

Method B.—Working as described for I, 3 g. of II yielded, after crystallization from ethanol, 1.8 g. (87%) of needles, m. p. 156°, $[\alpha]^{20}D$ −139° (in chloroform). The tetranitromethane test was positive and the sulfur test negative.

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.76; H, 10.35. Found: C, 83.79; H, 10.40.

This is the $\Delta^{3,5}$-androstadien-17(β)-ol previously described by Butenandt[28] and also by Kuwada and Miyasaki[25] who report m. p. 153–155°.

The acetate, prepared in the usual manner, melted at 128°. Kuwada and Miyasaki[25] report m. p. 126°, $[\alpha]^{20}D$ −155° (in chloroform).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.61. Found: C, 80.26; H, 9.64.

In order to obtain an authentic specimen for comparison, we also prepared $\Delta^{3,5}$-androstadien-17-ol by the following method, which is essentially the one followed by Butenandt[28] but with some modifications: one gram of testosterone was dissolved in 200 cc. of anhydrous ether. This solution was added dropwise to a boiling solution of 0.8 g. of lithium aluminum hydride in 200 cc. of anhydrous ether. After working up the reaction mixture as described in previous examples, a residue was obtained which was a mixture of isomeric androstenediols. These were dissolved in 300 cc. of ethanol and after addition of 10 cc. of hydrochloric acid, refluxed for two hours. The product was poured into water and worked up as usual. By crystallization from ether–hexane, 0.5 g. of $\Delta^{3,5}$-androstadien-17(β)-ol, m. p. 158° was obtained.

When mixed with a sample of the product obtained by method B (see above) the mixture melted at 156–158°.

Hydrogenolysis of the 3-(β-Hydroxyethyl)-thioenol Ether of Δ^4-Androstene-3,17-dione (VII). Method A.—Proceeding as described for I, 4 g. of VII yielded a crude reaction product of 2.7 g. (85%). After treatment with Girard reagent T, 0.7 g. (22%) of androstan-17(β)-ol, m. p. and mixed m. p. 162–164°, was obtained from the non-ketone fraction. The tetranitromethane test and the sulfur test were negative. The ketone fraction yielded 1 g. (32%) of $\Delta^{3,5}$-androstadien-17-one, m. p. 85–87°, $[\alpha]^{20}D$ −22° (in chloroform). The tetranitromethane test was positive; the sulfur test negative.

Method B.—Working as above, from 2 g. of VII, 1.3 g. (83%) of white plates of $\Delta^{3,5}$-androstadien-17-one, m. p. and mixed m. p. 87–88°, $[\alpha]^{20}D$ −21.5° (in chloroform) was obtained. The tetranitromethane test was positive; the sulfur test negative.

Hydrogenolysis of the 3-(β-Hydroxyethyl)-thioenol Ether of Testosterone (X). Method A.—Working as in previous examples, 2 g. of X yielded 1.3 g. (82%) of androstan-17(β)-ol, m. p. and mixed m. p. 164–166°. The tetranitromethane test and the sulfur test were negative.

The acetates prepared from this androstan-17(β)-ol and from the one obtained by hydrogenolysis of II were identical.

Androstan-17(β)-ol (0.5 g., 0.002 mole) was dissolved in 30 cc. of acetic acid. A solution of 1.5 g. (0.015 mole) of chromic anhydride in 10 cc. of 80% acetic acid was added. The mixture was left standing at room temperature for three hours, then poured into water and extracted with ether. After the usual workup and crystallization from methanol, 0.2 g. of white plates of androstan-17-one, m. p. 122°, $[\alpha]^{20}D$ + 103° (in chloroform) was obtained. The tetranitromethane test was negative.

Method B.—Working as in previous examples, 2 g. of X yielded 1.4 g. (90%) of needles of $\Delta^{3,5}$-androstadien-17-(β)-ol, m. p. and mixed m. p. 154–155°. The tetranitromethane test was positive, the sulfur test negative.

Hydrogenolysis of the 3-Benzylthioenol Ether of Δ^4-Cholestenone (XIII). Method A.—Working as in previous examples, 4 g. of XIII yielded after crystallization from methanol–ether, 2.5 g. (82%) of cholestane, m. p. 78–79°, $[\alpha]^{20}D$ + 23.7° (in chloroform). The tetranitromethane test and the sulfur test were negative.

Anal. Calcd. for $C_{27}H_{48}$: C, 87.01; H, 12.98. Found: C, 87.16; H, 12.72.

Method B.—Working as described above, 1.5 g. of XIII yielded 1 g. (88%) of crystals of $\Delta^{3,5}$-cholestadiene, m. p. 78–79°, $[\alpha]^{20}D$ −101° (in chloroform). The tetranitromethane test was positive and the sulfur test negative.

Anal. Calcd. for $C_{27}H_{44}$: C, 87.96; H, 12.03. Found: C, 87.82; H, 12.23.

The mixed melting point of the reaction products of method A and method B showed a marked depression.

Summary

1. Several thioenol ethers of Δ^4-3-keto steroids have been prepared.

2. The conversion of the thioenol ethers of Δ^4-androstene-3,17-dione and its esters to the corresponding testosterone derivatives has been accomplished by treatment with lithium aluminum hydride.

3. Evidence for the structure of the 3-thioenol ethers of Δ^4-3-ketosteroids has been given.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED, HUNGARY]

Synthetic and Degradative Studies in the Isoquinoline Series. IV

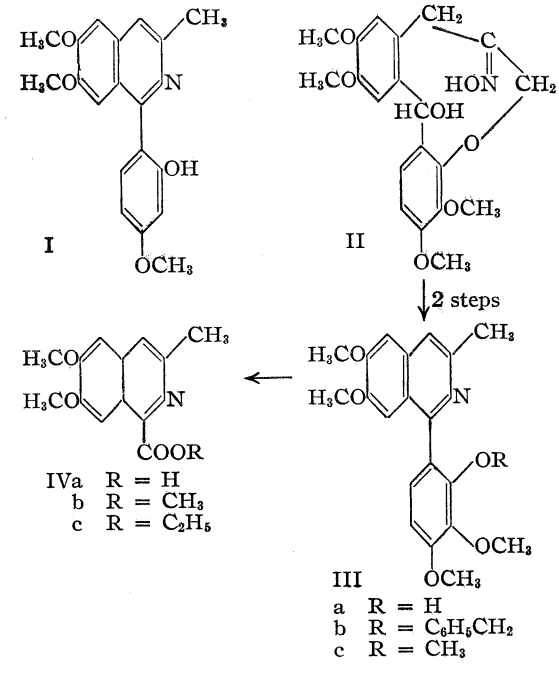
BY G. FODOR, V. BRUCKNER, J. KISS AND J. KOVÁCS

In our recent communication of this series[1] an unequivocal synthesis of I and the proof of its structure by oxidative degradation was described. This compound was isomeric, but not identical, with that prepared by Pfeiffer, *et al.*,[2] from brasilin and formulated as I; consequently the structure of their compound became doubtful.[1]

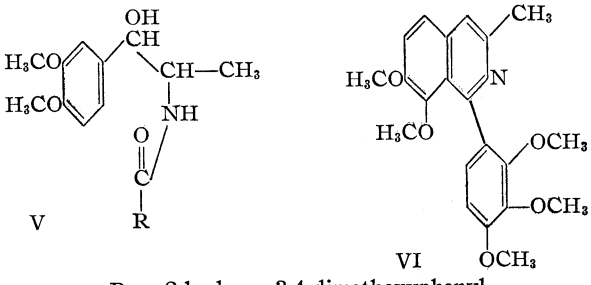
Tetramethyl hematoxylonol oxime (II) was converted by the same authors[2] in two steps into an amphoteric compound to which we will refer below as "H." Oxidation of "H" with permanganate yielded metahemipinic acid (3,4-dimethoxyphthalic acid). Degradation with nitric acid furnished an acid ("A") only isolated as picrate. Acid "A" reacted with diazomethane under formation of a monomethyl derivative, which was again only isolated as picrate. On the basis of these facts Pfeiffer, *et al.*,[2] suggested for "H" structure IIIa and for acid "A" formula IVa. These structures were not confirmed by synthesis. Although the synthesis of the methyl ether of "H" from amide Vb was attempted, the obtained synthetic

(1) Bruckner, Fodor, Kovács and Kiss, THIS JOURNAL **70**, 2697 (1948).

(2) Pfeiffer, Breitbach and Scholl, *J. prakt. Chem.*, **2**, 154, 157 (1940).



product was not identical with the methyl ether of "H," but only isomeric with it. Because of this failure Pfeiffer, *et al.*,[2] concluded that the intramolecular condensation of Vb, due to an unusual (o. m.) ring closure, led to the isoquinoline derivative (VI). However, this structure for the synthetic product was not proved by them through degradation.



The present publication deals with the synthesis and degradation of isoquinoline (IIIa) and with that of 3-methyl-6,7-dimethoxyisoquinoline-1-carboxylic acid (IVa).

The isoquinoline derivative (IIIa) was prepared by reaction of α-(3,4-dimethoxyphenyl)-β-aminopropanol with 2′-hydroxy-3,4-dimethoxybenzoyl chloride via the compound Va which was then benzylated to give Vc.[3]

This was then condensed to give the crystalline isoquinoline (IIIb). The latter was debenzylated by hydrogenolysis giving IIIa whose properties differed from "H," but which gave on treatment with diazomethane the methyl ether (IIIc) already obtained by Pfeiffer, *et al.*[2] The same compound was also obtained by us from the stereoisomeric form of Vb.[4]

The direction of the ring closure was elucidated by oxidative degradation of IIIa, leading to metahemipinic acid, so that there could be no further doubt as to the structure of the synthetic product. Obviously, the sole fact observed by Pfeiffer, *et al.*,[2] of "H" also giving an oxidative degradation metahemipinic acid, is no adequate proof for "H" possessing structure III, but only indicates the maintenance of the two carbon atoms, attached in *m*, *p* position to the methoxy groups of oxime II, during the two steps conversion into "H."

It remains to be decided whether the existing difference between IIIa and "H" is to be sought for in the different positions of the substituents in the aryl radical attached to carbon atom 1 of the isoquinoline system, or in the structure of the hetero ring. In the first case, both compounds ought to give on oxidation the same carboxylic acid (IVa). As we did not succeed in isolating on oxidation of IIIa with nitric acid either acid "A" or its picrate,[2] we attempted to approach the problem by a straightforward synthesis of IVa.

For this purpose the trichloroacetyl amide (Vd) was prepared which on condensation should yield a trichloromethylisoquinoline which on hydrolysis would be expected to give the desired acid (IVa) and on hydrogenolysis would give the known[5] 1,3-dimethyl-6,7-dimethoxyisoquinoline. Unfortunately, all attempts to form an isoquinoline derivative from Vd failed. Accordingly, we adopted another line of synthesis starting with the ethoxalyl derivative (Ve) preparable in good yield. Its intramolecular condensation by means of $POCl_3$ gave the 1-carbethoxyisoquinoline (IVc) and subsequent hydrolysis the crystalline acid (IVa). This acid, under the conditions reported by Pfeiffer, *et al.*,[2] did not give any precipitate with picric acid; moreover, on evaporating the solution only the picrate of 3-methyl-6,7-dimethoxyisoquinoline could be isolated, indicating the loss of the carboxylic group during the reaction. The identity of this unexpected product was shown by synthesis from the formamido compound (Vf).

Acid IVa gave with diazomethane a crystalline methyl ester (IVb, m. p. 151–153°), the picrate of which showed m. p. 168–170°. As Pfeiffer, *et al.*,[2] recorded for the picrate of their methyl ester, obtained from "A," m. p. 216°, IVa cannot be identical with "A." Furthermore, as structure IVa for our synthetic acid could be confirmed by its oxidative degradation leading to metahemipinic acid, "A" must have another structure, remaining still to be elucidated.

(3) Condensation of 2-benzyloxy-3,4-dimethoxybenzoyl chloride with the aminopropanol, in an analogous manner as described previously, did not go smoothly.

(4) The stereoisomer forms of acylamide (Vb) are in the same relation as ephedrine and ψ-ephedrine. Compare Bruckner, Fodor, Kiss and Kovács, *J. Chem. Soc.*, 885 (1948).

(5) Bruckner, Kovács and Kovács, *Ber.*, **77**, 610 (1944).

It is evident from the above facts that the difference between "H" and IIIa is not to be sought for in the difference of the aryl radicals attached to the carbon atom 1 of the isoquinoline ring, but perhaps in the difference of the position of both substituents of the hetero ring, or even in the structure of the entire hetero ring system of "H." To reach a decision in this matter the structure of "H" must be fully investigated.

Experimental

2-Benzyloxy-3,4-dimethoxybenzoic Acid.—Ten grams of methyl 2-hydroxy-3,4-dimethoxybenzoate, 1.1 g. of sodium and 6 ml. of benzyl chloride were condensed in 50 ml. of absolute ethanol[1] to yield colorless needles of the acid, melting at 95–96° after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.60. Found: C, 66.62; H, 5.30.

The acid was converted to the oily acid chloride by means of thionyl chloride.

α-(3,4-Dimethoxyphenyl)-β-(2-hydroxy-3,4-dimethoxybenzoylamino)-propanol (Va).—2-Hydroxy-3,4-dimethoxybenzoyl chloride, prepared from 11.5 g. of the acid was condensed in the usual manner[1] with 27 g. of α-(3,4-dimethoxyphenyl)-β-aminopropanol[6] to yield 18 g. of Va, m. p. 87–88°. Va, treated with ethereal diazomethane, was converted to Vb, melting at 107–108°, after recrystallization from toluene. Vb was also prepared by treating 2.2 g. of the aminopropanol with 1.06 g. of 2,3,4-trimethoxybenzoyl chloride.

Anal. Calcd. for $C_{21}H_{27}O_7N$ (Vb): C, 62.21; H, 6.71. Found: C, 62.26; H, 6.65.

Vb is stereoisomeric with the compound of Pfeiffer, m. p. 127–128°, obtained from the stereoisomeric aminopropanol.

1-(2'-Benzyloxy-3',4'-dimethoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline (IIIb).—To a solution of 18 g. of Va in 500 ml. of absolute ethanol was added a solution of 1.05 g. (0.046 mole) of sodium in 50 ml. of absolute alcohol. To this mixture was added 8 ml. (0.04 mole) of benzyl chloride and the solution refluxed for eight hours. The reaction mixture was filtered, the alcohol evaporated and the residue dissolved in 500 ml. of hot toluene. Addition of 25 ml. of phosphorus oxychloride yielded 8 g. of VIb, prisms melting at 147–148° after recrystallization from 50% ethanol.

Anal. Calcd for $C_{27}H_{27}O_5N$: C, 72.79; H, 6.09. Found: C, 72.91, 72.45; H, 6.41, 6.11.

1-(2'-Hydroxy-3',4'-dimethoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline (IIIa).—A solution of 6.5 g. of IIIb in 280 ml. of ethanol was subjected to hydrogenolysis using 2.5 g. palladium–charcoal (7% palladium). Absorption of hydrogen was quantitative in seventeen minutes and there was produced, as yellowish prisms, m. p. 158–60.5°, 5.1 g. (95.6% theoretical) of III, isolated by precipitation from alkaline solution by carbon dioxide. Recrystallization from ethanol afforded nearly colorless prisms, m. p. 168–169°.

Anal. Calcd. for $C_{20}H_{21}O_5N$: C, 67.57; H, 5.96. Found: C, 67.19; H, 6.41.

Pfeiffer[2] recorded for "H" m. p. 174°.

The **picrate** of IIIa was obtained as yellow crystals, m. p. 238–239° from ethanol.

Anal. Calcd. for $C_{26}H_{24}O_{12}N_4$: C, 53.40; H, 4.14. Found: C, 53.17; H, 4.35.

Pfeiffer[2] recorded for the picrate of "H" m. p. 210°.

The **methyl ether IIIc**, m. p. 105–107°, was obtained by treating a methanol solution of IIIa with ethereal diazomethane. Pfeiffer reported[2] the same melting point for the synthetic product from his Vb. We have obtained in the usual manner 0.76 g. of IIIc from 1 g. of our Vb (m. p. 109–110°) which is stereoisomeric with that of Pfeiffer.

The **picrate** of IIIc is obtained from methanol as yellow crystals, m. p. 184–185°.[2]

Anal. Calcd. for $C_{27}H_{26}O_{12}N_4$: C, 54.16; H, 4.38. Found: C, 54.15; H, 4.52.

Degradation of IIIa to 3,4-Dimethoxyphthalic Acid.—Three and seven-tenths grams (0.0107 mole) of IIIa dissolved in 525 ml. of hot 0.03% aqueous sodium hydroxide was treated with 23.7 g. of potassium permanganate dissolved in 475 ml. of hot water to obtain 3,4-dimethoxyphthalic acid.[1] The product weighed 200 mg. after recrystallization from water and melted at 175–177°[7] alone and when mixed with an authentic sample. The 3,4-dimethoxyphthalic acid was further characterized by converting it to metahemipinic ethylimide, m. p. 228–229°.[7]

Anal. Calcd. for $C_{12}H_{13}O_4N$: C, 61.25; H, 5.57. Found: C, 60.90; H, 5.57. Hemipinic ethylimide melts at 93°.[8]

α-(3,4-Dimethoxyphenyl)-β-N-ethoxalylaminopropanol (Ve).—Twenty-one and one-tenth grams (0.1 mole) of the corresponding aminopropanol[6] was dissolved in 100 ml. of hot chloroform, 6.8 g. (0.05 mole) of ethoxalyl chloride was added and the mixture allowed to stand overnight. The amino-propanol hydrochloride was collected, the filtrate washed with a total of 30 ml. of water, dried, the solvent blown off and the residue recrystallized from toluene; yield, 6.5 g.; m. p. 92–93°.

Anal. Calcd. for $C_{15}H_{20}O_6N$: C, 58.06; H, 6.50. Found: C, 57.93; H, 7.05.

α-(3,4-Dimethoxyphenyl)-β-N-trichloro-acetylamino-propanol (Vd).—From 2.11 g. of the amino-propanol[6] and 0.82 g. of trichloroacetyl chloride in 40 ml. of toluene, 0.8 g. of recrystallized amide (Vd) was obtained; needles from benzene–ligroin, m. p. 115–116°.

Anal. Calcd. for $C_{13}H_{16}O_4NCl_3$: C, 43.75; H, 4.52. Found: C, 43.89; H, 4.08.

3-Methyl-6,7-dimethoxyisoquinoline-1-carboxylic Acid (IVa).—To 0.94 g. of the amide Ve in 15 ml. of anhydrous toluene, 0.8 ml. of phosphorus oxychloride was added and the mixture refluxed for one hour. Then ice was added until phosphorus oxychloride decomposed, and the separated aqueous layer was made alkaline with ammonia and extracted with ether. The material recovered from the ether weighed 183 mg. and was hydrolyzed by boiling with 4 ml. of 10% sodium hydroxide solution and with 5 ml. of methanol for ninety minutes. The methanol was then evaporated, the alkaline aqueous solution extracted with ether, decolorized and acidified to congo red paper. The acid separated forming yellowish crystals; yield 57 mg., m. p. 203–204° (dec.). Recrystallized from water containing a drop of hydrochloric acid, its hydrate could be obtained (free of chlorine); from methanol the anhydrous acid could be obtained.

Anal. Calcd. for $C_{13}H_{13}O_4N \cdot H_2O$: C, 58.84; H, 5.70. Found: C, 58.80; H, 5.40. Calcd. for $C_{13}H_{13}O_4N$: C, 63.13; H, 5.30. Found: C, 62.80; H, 5.20.

Picrate.—By adding an aqueous solution of the acid to an alcoholic solution of picric acid, as reported by Pfeiffer,[2] the above acid did not give any precipitation. When a solution of 25 mg. of IVa and 23 mg. of picric acid in 1.5 ml. of methanol was heated and then allowed to stand, crystallization could not be observed. By evaporation of the solvent yellow crystals separated, m. p. 269–270° (shrinking from 200°). The analytical data showed that decarboxylation had taken place, yielding the picrate of 3-methyl-6,7-dimethoxyisoquinoline.

Anal. Calcd. for $C_{18}H_{16}O_9N_4$: C, 50.50; H, 3.76. Found: C, 50.30; H, 3.97.

3-Methyl-6,7-dimethoxyisoquinoline.—A solution of 4.5 g. of the aminopropanol[6] in 80 ml. of anhydrous formic

(6) Iwamoto and Hartung, *J. Org. Chem.*, **9**, 511 (1944).

(7) Goldschmiedt, *Monatsh.*, **9**, 722 (1888).

(8) Freund and Heim, *Ber.*, **23**, 2906 (1890).

acid was refluxed for forty-eight hours. Formic acid was then removed in a vacuum and the brownish glassy formamido compound (Vf) treated with 10 ml. of phosphorus oxychloride in 100 ml. of toluene in the usual manner. The isoquinoline was purified by repeated distillation under 1 mm. pressure; yield 1.2 g., m. p. 135–136°.

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45. Found: C, 71.21; H, 6.60.

Hydrochloride.—Long needles from ethanol–ether, m. p. 237–238°.

Picrate.—It is very poorly soluble in hot alcohol, m. p. 270°, and is identical with the picrate obtained from the acid (IVa).

Anal. Calcd. for $C_{18}H_{16}O_9N_4$: C, 50.5; H, 3.76. Found: C, 50.30; H, 4.02.

Decarboxylation of IVa.—Twenty-two mg. of the acid was heated under 1 mm. pressure in a Spaeth tube to 200° and the solid distillate converted into a picrate; crystals from methanol, m. p. 270°. It was identical with the picrate of the crystalline 3-methyl-6,7-dimethoxy-isoquinoline, obtained from the formamido compound, as described above.

Methyl Ester (IVb).—Five millimoles (123 mg.) of the acid (IVa) was dissolved in 23 ml. of methanol and 3 ml. of an ethereal diazomethane solution added. The solvent was evaporated under reduced pressure, the solid residue (53 mg.) treated with 10 ml. of ether and filtered. The filtrate was shaken with a dilute sodium bicarbonate solution, dried and the ether removed. The residue was 48 mg., m. p. after recrystallization from benzene–petroleum ether, m. p. 151–153°.

Anal. Calcd. for $C_{14}H_{15}O_4N$: C, 63.70; H, 5.98. Found: C, 63.80; H, 6.03.

Picrate.—Yellow needles from methanol, m. p. 168–170°. Pfeiffer recorded for the picrate of the methyl ester of the acid a melting point of 216°.

Anal. Calcd. for $C_{20}H_{18}O_8N_4$: OCH_3, 18.94. Found: OCH_3, 18.67.

1-Carbethoxy-3-methyl-6,7-dimethoxyisoquinoline (IVc).—This ester could be isolated by decomposing with absolute ethanol (instead of water) the excess of phosphoryl chloride in the mixture obtained on ring closure of the amide (Ve); yield 2.1 g. from 9.5 g. of ethoxyalylamide (Ve). Repeated distillation from a Spaeth tube under 1 mm. pressure afforded yellowish needles, m. p. 86–87°.

Anal. Calcd. for $C_{15}H_{17}O_4N$: N, 9.1. Found: N, 9.3.

Picrate.—Glistening gold-yellow needles (from 96% ethanol), m. p. 176–177°.

Anal. Calcd. for $C_{21}H_{20}O_{11}N_4$: C, 50.0; H, 4.0. Found: C, 50.1, 50.1; H, 4.4, 4.45.

Degradation of 1-Carboxy-3-methyl-6,7-dimethoxyisoquinoline (IVa) to 3,4-Dimethoxyphthalic Acid.—Two hundred and ten milligrams of potassium permanganate dissolved in 10 ml. of water was added to a solution of 247 mg. of 1-carboxy-3-methyl-6,7-dimethoxyisoquinoline in 40 ml. of dilute sodium hydroxide in fifteen minutes. The residue of evaporation (350 mg.) was extracted as described in previous degradation procedures and 144 mg. of crude crystals was obtained. Purification through the lead salt yielded 27 mg. of metahemipinic acid, m. p. after recrystallization from 0.5 ml. of water 176°, alone and mixed with an authentic specimen. The product was converted in the usual manner into its ethylimide which after sublimation and recrystallization showed m. p. 229° under the microscope.

Summary

The synthesis of 1-(2′-hydroxy-3′,4′-dimethoxyphenyl) - 3 - methyl - 6,7 - dimethoxyisoquinoline (IIIa) is described. Its structure has been confirmed by oxidative degradation. It differs from a compound obtained from hematoxyline, incorrectly assigned the same structure in the literature. The synthesis of 3-methyl-6,7-dimethoxyisoquinoline-1-carboxylic acid (IVa) and its methyl ester (IVb) was accomplished in a straightforward manner. They were found to be different from the compounds described earlier.

The recent results proved, in accordance with previous investigations, that the intramolecular condensation of acylamides of type V lead in every case to 6,7-dialkoxy isoquinoline derivatives and in no case to 7,8-dialkoxyisoquinolines, the latter possibility being assumed by earlier investigators.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FURMAN UNIVERSITY]

Formation of Bromine Addition Compounds with Some Condensed Ring Hydrocarbons

BY JOHN R. SAMPEY, JESSIE M. COX AND ANNE B. KING

The formation of intermediate addition compounds plays a prominent role in current theories on the mechanism of bromination.[1] Crystalline dibromide addition products of phenanthrene and anthracene have been isolated,[2] while more than fifty years ago Orndorff and Moyer[3] prepared a crystalline naphthalene tetrabromide in 3% yield. In the present study we increased the yield of the latter compound to 30% by photobromination, and we found all the above and other addition compounds stable when shaken with sodium sulfite solution to remove unreacted bromine, but each readily gave a test for active bromine when treated with an acetone solution of sodium iodide.

(1) Price, *Chem. Revs.*, **29**, 37–67 (1941); Kharasch, White and Mayo, *J. Org. Chem.*, **2**, 574–576 (1938).

(2) Price, THIS JOURNAL, **58**, 1834–1838 (1936).

(3) Orndorff and Moyer, *Am. Chem. J.*, **19**, 262–270 (1897).

Experimental

Preparation of Naphthalene Tetrabromide.—12.8 grams of pure naphthalene in 100 ml. of carbon tetrachloride was brominated under anhydrous conditions at 0° with one mole of bromine in 100 ml. of the same solvent during two hours with a 2″ arc at the distance of 2″; the solvent was evaporated and the product extracted with 95% alcohol and crystallized from chloroform; yield 30% of naphthalene tetrabromide, melting 111° and giving four atoms of bromine on a Rosanoff analysis. A sodium

iodide analysis[4] gave 72.4% bromine (theory 71.4%), showing all four bromines active.

Some Factors Influencing the Rate of Formation of Naphthalene Tetrabromide.—When 0.01 mole of naphthalene in 20.00 ml. of carbon tetrachloride was brominated under anhydrous conditions with 0.01 mole of bromine in 10.00 ml. of the same solvent in a darkened laboratory at room temperature, 5.1 ± 1% of the active bromine was found by the sodium iodide analysis. The presence of 0.029 g. of iodine did not change this percentage. Photobromination of 0.01 mole of the hydrocarbon in 20.00 ml. of carbon tetrachloride on a water-bath and under a 6″ mercury arc at 3″ distance with 10.00 ml. of molar bromine–carbon tetrachloride solution, during three hours, resulted in the formation of 21.1 ± 2% of active bromine; cooling the reaction to 0° and using a 2″ arc at 2″ for seventy minutes gave 61.0 ± 5% of active bromine.

With the aid of a Universal Spectrophotometer, Model 14, the effect of wave length on the formation of naphthalene tetrabromide has been determined. When 0.005 mole of naphthalene in 5.00 ml. carbon tetrachloride was brominated for twenty minutes at 41° with 10.00 ml. of half molar bromine solution in the same solvent under anhydrous conditions at 6000, 5250, 3700 Å. and no irradiation, the percentages of active bromine by sodium iodide analyses were respectively, 23.8 ± 0.2, 11.0 ± 1, 1.3 and 0%.

Rates of Formation of Bromine Addition Compounds with Other Condensed Ring Hydrocarbons.—The rates of formation of bromine addition compounds under dark-room conditions were carried out on 0.01 mole quantities of the hydrocarbons in 20.00 ml. carbon tetrachloride at 0° for a period of eighteen hours; 10.00 ml. of bromine–carbon tetrachloride solutions (molar) were added under anhydrous conditions. Sodium iodide analyses yielded the following percentages of active bromine: phenanthrene 55.2 ± 3%, naphthalene 11.2 ± 0.1% and diphenylmethane 2.0 ± 2%. Fluorene, benzene and diphenyl gave no active bromine even though the solutions were kept cold to prevent decomposition of any addition compounds during the treatment with sulfite and evaporation of the carbon tetrachloride. The addition of 0.029 g. iodine to the above reactions did not change by more than 2% the rates of bromine addition.

Since anthracene is insoluble in carbon tetrachloride 0.005 mole of this hydrocarbon was dissolved in 50.00 ml. of carbon disulfide, and the dark room brominations made with 10.00 ml. of half-molar bromine in the same solvent. Naphthalene solutions of the same strength were used for comparison. The results showed the presence of 13.0 ± 1.2% bromine with anthracene but none with naphthalene.

The photobrominations were carried out in carbon tetrachloride under anhydrous conditions at 0° with a 2″ arc at 2″ for sixty minutes; sodium iodide analyses indicated the following active bromine present: phenanthrene 84.1 ± 2%, naphthalene 55.3%, diphenyl 1% and benzene 1%. When 0.005 mole of anthracene and naphthalene were photobrominated in 50.00 ml. of carbon disulfide under similar conditions, they gave 74.0 ± 2% and 69.0% active bromine, respectively. These results demonstrate conclusively that larger amounts of active bromine addition products of the hydrocarbons are formed in photobromination than in dark room bromination.

Acknowledgments.—The authors are happy to acknowledge the helpful suggestions made by Dr. E. Emmet Reid in this research. Financial assistance was received from the Office of Naval Research.

Summary

1. Measurements have been made on the rates of formation of active bromine addition compounds under photo and dark room brominations of some condensed ring hydrocarbons.

2. Naphthalene tetrabromide has been prepared in 30% yield by photobromination.

GREENVILLE, SOUTH CAROLINA RECEIVED JUNE 6, 1949

(4) Sampey, Blitch and King, THIS JOURNAL, **70**, 2606 (1948).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

The Structure of Diphenylthiocarbazone (Dithizone)[1]

BY ALSOPH H. CORWIN AND GEORGE R. JACKSON[2,3]

Introduction

The compound diphenylthiocarbazone, known as "dithizone," is well known in analytical chemistry because of its colorimetric reactions with traces of metals. A search of the literature will show, however, that no direct attempt has been made to prove the structure arbitrarily assigned to it by Emil Fischer.[4a,b]

Because of increasing interest in dithizone derivatives, it was deemed advisable to attempt a structural determination of diphenylthiocarbazide, from which would follow the structure of its oxidation product, dithizone.

Diphenylthiocarbazide is prepared by the reaction of phenylhydrazine with carbon disulfide. In ether or benzene, the phenylhydrazine salt of phenyldithiocarbazic acid precipitates.[5,6] Heating this salt to 90–100° drives off hydrogen sulfide and leaves behind diphenylthiocarbazide. Treating this with alcoholic potassium hydroxide produces dithizone, for which the following equation has been proposed[4a]

$$2C_6H_5NHNHCNHNHC_6H_5 \longrightarrow \underset{\text{I}}{\underset{\|}{\underset{S}{}}}$$

$$C_6H_5N{=}NCNHNHC_6H_5 + C_6H_5NH_2 + \underset{\text{II}}{\underset{\|}{\underset{S}{}}}$$

$$C_6H_5NHNHCNH_2 \quad \underset{\text{III}}{\underset{\|}{\underset{S}{}}}$$

(1) From the doctoral dissertation of G. R. Jackson, The Johns Hopkins University.

(2) Chemical Foundation Fellow, 1942–1943; Standard Oil Company of Indiana Fellow, 1946–1947.

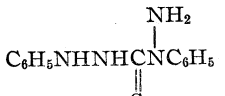
(3) Present address: Chemistry Department, Western Reserve University, Cleveland, Ohio.

(4) (a) E. Fischer, *Ann.*, **190**, 114 (1878); (b) **212**, 320 (1882).

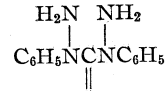
(5) Grummitt and Stickle, *Ind. Eng. Chem., Anal. Ed.*, **14**, 953 (1942).

(6) Billman and Cleland, THIS JOURNAL, **65**, 1300 (1943).

On the basis of analysis, structure I was assigned to diphenylthiocarbazide. Structures IV and V should be considered as alternatives, however.



IV



V

These differ from Fischer's structure with respect to the point of attachment of the nitrogens to the carbon. Compound IV would be formed by the α,β condensation of carbon disulfide with phenylhydrazine, compound V by the β,β condensation.

The structural investigation of diphenylthiocarbazide (I) is divided into two parts; (1) the reduction to phenylthiosemicarbazide and (2) the investigation of the structure of the latter compound which has been formulated as III but for which the alternative β formulation has not been excluded.

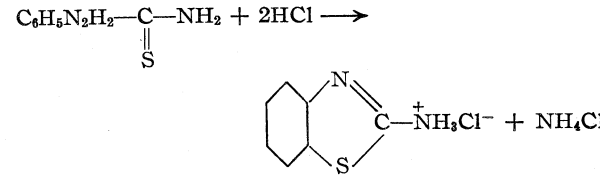
Upon reduction with stannous chloride and hydrochloric acid,[7] diphenylthiocarbazide gave one mole of aniline and one mole of phenylthiosemicarbazide. The reduction was also performed catalytically, using Raney nickel. The reaction stopped after one mole of hydrogen was consumed and additional shaking had no effect. The products were again aniline and phenylthiosemicarbazide.

Since compound V cannot yield the $S{=}C{-}NH_2$ grouping on reduction, the reductions show that one half of the diphenylthiocarbazide molecule has the structure $C_6H_5{-}NH{-}NH{-}C$, an observation which excludes formula V. The problem is thus reduced to that of ascertaining the structure of phenylthiosemicarbazide.

Phenylthiosemicarbazide was prepared from phenylhydrazine hydrochloride and ammonium thiocyanate according to the procedure given by Fischer and Besthorn,[8] but since the compound obtained from the reduction and the synthetic product both decomposed on heating, mixed melting points could not be used to establish identity. Proof of identity was obtained by the mixed solubility method, using the absorption in the ultraviolet as the criterion of solubility.

Reductions of phenylcarbazide with tin in hydrochloric acid, zinc in glacial acid, zinc in hydrochloric acid and sodium hydrosulfite were tried, but only starting material was recovered in each case.

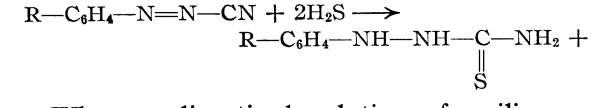
The acid used in the stannous chloride reductions was approximately 5 normal. It was found that when concentrated hydrochloric acid was used, with or without the reducing agent, 2-aminobenzothiazole hydrochloride was formed according to the equation



Thus it was found that strong reducing agents had no effect on phenylthiosemicarbazide, and concentrated hydrochloric acid converted it to 2-aminobenzothiazole, which did not conclusively prove the structure. The resistance of this class of hydrazine derivatives toward reduction will be investigated further.

Aqueous cyanide solutions will react with diazonium salts to precipitate colored compounds referred to as diazocyanides, the reaction differing from the normal coupling reaction in that the solution must remain acid during the addition.[9,10] It has generally been accepted that the structure of the aromatic diazocyanides is of the form $R{-}C_6H_4{-}N{=}N{-}CN$, and that labile and stable isomers which have been isolated represent *syn* and *anti* forms of this general structure.

The substituted benzene diazocyanides are easily converted to the thioamides by treatment with hydrogen sulfide. Either the *syn* or the *anti* form of the diazocyanide may be used



When a diazotized solution of aniline was treated with aqueous potassium cyanide at $-5°$ a red, unstable oil was obtained. The ether extract was treated with hydrogen sulfide. The product obtained melted with decomposition at 200° and had all the physical properties of the phenylthiosemicarbazide obtained from the reduction of diphenylthiocarbazide.

If the structure of benzenediazocyanide is accepted as $C_6H_5N{=}NCN$, the C–N–N–C grouping is established. From the reaction with H_2S it follows that the structure of phenyl thiosemicarbazide is $C_6H_5NHNHCNH_2$ (with S). This observation excludes formula IV and thus establishes Fischer's formulation of the structure of diphenylthiocarbazide.

A simple formulation of the mechanism of the condensation between phenylhydrazine and carbon disulfide is rendered improbable by the observation that this condensation does not proceed in the absence of air. It might be postulated that the catalytic effect of air is due to the fact that the essential reagent is a free radical.

To shed some light on the mechanism of the condensation, the reaction of cyanogen bromide with phenylhydrazine was studied in ether and in aqueous solution at different acidities.

(7) Fierz-David, "Technologie der Textilfasern," Julius Springer, Berlin, 1926, Vol. III, p. 660.

(8) Fischer and Besthorn, *Ann.*, **212**, 316 (1882).

(9) Gabriel, *Ber.*, **12**, 1637 (1879).

(10) Hantzsch and Schultze, *ibid.*, **28**, 666 (1895).

Pelazzari and Tivoli[11] have shown that cyanogen halides react with phenylhydrazine to give cyanophenylhydrazines. In ether β-cyanophenylhydrazine is formed. This is an unstable oil which forms a reasonably stable hydrochloride. Ammonium hydrosulfide converts this to β-phenylthiosemicarbazide. Water, on the other hand, converts it to β-phenylsemicarbazide. We have established the identity of the β-phenylthiosemicarbazide by intercomparison with material prepared according to Fischer's method.[8]

If the reaction between phenylhydrazine and cyanogen bromide is carried out in aqueous solution using a twofold excess of phenylhydrazine, two products are formed. The first is β-cyanophenylhydrazine. The main product is an isomer, α-cyanophenylhydrazine. This reacts with ammonium hydrosulfide to give α-phenylthiosemicarbazide, decomposing at 153°, and with water to give α-phenylsemicarbazide.

We have found that both α and β substitutions can occur in aqueous solution. At *p*H 0.6 the yield was quite low but more than half of the product was β-phenylsemicarbazide obtained from the β-isomer and less than half was α. At *p*H 3.5 the yield was higher and the proportion was much greater in favor of the α-isomer. At *p*H 5.6 the yield of α-isomer appears to be still higher but the results are complicated by the fact that a secondary reaction, perhaps polymerization, sets in. These condensations must be regarded as anomalous since the β-position of phenylhydrazine should be the more reactive in the case of the free base while increasing salt formation should either block the reaction or should favor condensation in the α-position. The contrary results observed show the need for an investigation of the mechanism of the reaction.

Experimental

Preparation and Purification of Diphenylthiocarbazide.—The procedure given by Grummitt and Stickle[5] was followed for the preparation of crude diphenylthiocarbazide. When crystallized from alcohol in the manner directed, the crystals obtained are slate-gray in color. It is necessary to wash these crystals with three portions of benzene to obtain an "almost colorless product." Attempts to purify the slate-gray material by means of further recrystallizations from alcohol do not give a better looking product.

A much more satisfactory method of purification consists of heating 95% alcohol to boiling, pouring it on the crude carbazide, and filtering hot. On cooling, the crystals are invariably snow white, except if one uses as starting material the slate-gray product referred to above. This method consumes more alcohol than the other but a product suitable for analysis is obtained.

Anal. Calcd. for $C_{13}H_{14}N_4S$: C, 60.41; H, 5.47. Found: C, 60.35; H, 5.43.

It was found that the crude diphenylthiocarbazide consists of two materials, one of which is extremely soluble in alcohol. This can be extracted from the main product by boiling with benzene, in which diphenylthiocarbazide is very slightly soluble. The suspension is filtered hot and on cooling the second product comes out as a white, amorphous mass. The yield averaged 10 g. for 54 g. of phenylhydrazine. Further investigations on this substance are in progress.

Reduction of Diphenylthiocarbazide with Stannous Chloride.—A solution of 10 g. of $SnCl_2 \cdot 2H_2O$ in 20 cc. of concentrated hydrochloric acid was added to a mixture of 10 g. of diphenylthiocarbazide and 60 cc. of water. This was stirred for fifteen minutes at room temperature, heated on the steam-bath for three hours with stirring, and then allowed to cool. The crystalline product was filtered, mixed with 50 cc. of water and filtered again. This was repeated with another 50-cc. portion of water, and finally the product was washed with 25 cc. of water. The crystals remaining were sucked as dry as possible and recrystallized once from 95% ethanol, to obtain 6.0 g. (95% of theoretical) of material melting with decomposition sharply at 200°.

To recover the aniline, hydrogen sulfide was passed into the combined filtrates from above until precipitation ceased, and the tin sulfides removed and washed with water containing a little hydrochloric acid. Ammonium sulfide was then added to complete the precipitation of tin. This was filtered and washed as before. The filtrate was made strongly basic and extracted five times with 50–75 cc. portions of ether. The ether was then removed from the combined extracts and finally pale yellow aniline was collected, b. p. 183–183.5°. This was acetylated to give a derivative melting at 113.5–114°. The yield of aniline was 3.1 cc. or 86% of the theoretical.

Catalytic Hydrogenation.—Three cubic centimeters of Raney nickel catalyst was added to 4 g. of pure diphenylthiocarbazide in 200 cc. of 95% ethanol. The diphenylthiocarbazide did not dissolve completely. The suspension was placed on the shaker and hydrogen was introduced under a pressure of 50 lb. p.s.i. After forty-five minutes no hydrogen had been absorbed. Five cubic centimeters more catalyst was added at this point and shaking was resumed. Hydrogen was absorbed rapidly and after two hours the theoretical amount for one mole had been taken up. The hydrogenation was allowed to continue overnight but no more hydrogen was absorbed.

The catalyst was filtered off and phenylthiosemicarbazide was isolated as a white crystalline solid melting with decomposition at 200°. Aniline was isolated as acetanilide, m. p. 113.5–113.8°.

Spectrophotometric Identification of Phenylthiosemicarbazide.—Saturated solutions were made of the substance prepared by reduction of diphenylthiocarbazide and by synthesis from phenylhydrazine and ammonium thiocyanate by mixing 350 mg. of material with 10 cc. of 95% ethanol. A solution saturated with respect to both compounds was also made by mixing 350 mg. of each compound with 10 cc. of 95% alcohol. These were allowed to stand for three hours before measurements were begun, to insure complete equilibration. The absorptions of the three solutions at 312 mμ were 29.2, 29.0 and 29.4, proving the identity of the two compounds.

Attempted Reductions of Phenylthiosemicarbazide.

1. **Tin and Hydrochloric Acid.**—One gram of phenylthiosemicarbazide was added to a solution of 10 cc. of concentrated hydrochloric acid and 10 cc. of water. To this was added 2 g. of mossy zinc and the mixture heated on the steam-bath. The phenylthiosemicarbazide did not go into solution and was recovered on cooling.

2. **Zinc and Glacial Acetic Acid.**—One gram of phenylthiosemicarbazide was added to 10 cc. of glacial acetic acid and warmed until it went into solution. This was heated on the steam-bath for two hours with zinc dust. The excess zinc dust was filtered off and water added to the acetic acid solution, at which time almost 1 g. of starting material crystallized.

3. **Zinc and Hydrochloric Acid.**—One gram of phenylthiosemicarbazide was mixed with 10 cc. of concentrated hydrochloric acid and 10 cc. of water, and zinc dust added. Hydrogen was evolved but the phenylthiosemicarbazide was recovered unchanged.

4. **Sodium Hydrosulfite.**—A mixture of 1 g. of phenylthiosemicarbazide, 5 cc. of water, and 2 g. of sodium hydrosulfite was heated on the steam-bath for two hours, the

(11) Pelazzari and Tivoli, *Gazz. chim. ital.*, **22**, 226 (1892); Pelazzari, *ibid.*, **37**, 611 (1907).

phenylthiosemicarbazide remaining suspended in the colorless solution the entire time. When cooled, washed with water, and dried, more than 0.9 g. of starting material was recovered.

Preparation of 2-Aminobenzothiazole from Phenylthiosemicarbazide.—Four grams of phenylthiosemicarbazide was added to 40 cc. of concentrated hydrochloric acid and heated on the steam-bath for two hours. On cooling, the hydrochloride crystallized. The free base obtained by neutralizing the hydrochloride was recrystallized from water to give white shining platelets which melted reversibly at 130–131°. Warming with acetic anhydride and recrystallizing from alcohol produced thick prisms melting sharply at 187°. The acetyl derivative of 2-aminobenzothiazole is reported as melting at 186–187° and 2-aminobenzothiazole as melting at 130–131°.[12]

Preparation of 1-Phenylthiosemicarbazide from Benzenediazocyanide.—Almost water-white aniline was prepared by fractional distillation of aniline which had been twice steam distilled, collecting the fraction coming over at 181.5–182° (uncor.). A mixture of 28 cc. of this aniline, 90 cc. of concentrated hydrochloric acid and 180 cc. of water was cooled to −5° and a solution of 21 g. of sodium nitrite in 60 cc. of water slowly added until diazotization was complete. Then 350 cc. of ether that had been freshly distilled from a weakly acidic ferrous sulfate solution to remove peroxides was slowly added, keeping the temperature below 0°. To this was slowly added a solution of 39 g. of potassium cyanide in 75 cc. of water, the mixture being well stirred and the temperature maintained below 0°. When addition was complete, the mixture was poured into a large separatory funnel and the aqueous portion separated and discarded. Preliminary tests showed that the crude diazocyanide decomposed on warming to room temperature so it was not isolated. The ether extract was quickly cooled in an ice-bath and hydrogen sulfide passed through. The red solution turned dark very slowly, and then suddenly changed to light straw color. The crude precipitate melted with decomposition over a wide range from 185–195°. After recrystallizing from alcohol once a pure product was obtained which melted with decomposition sharply at 200°.

The same product was obtained when the ether extract from the diazonium mixture was dried with sodium sulfate before introducing the hydrogen sulfide, and since there was a considerable loss due to adsorption on the sodium sulfate, this step was omitted. The best yield of pure 1-phenylthiosemicarbazide was approximately 20 g., or 40% of theoretical.

Reaction between Phenylhydrazine and Cyanogen Bromide at Various Acidities. 1. **At *p*H 0.6.**—A mixture of 2.8 g. of phenylhydrazine hydrochloride (0.02 mole), 5 g. of sodium bisulfate and 3 g. of sodium sulfate was dissolved in 50 cc. of water to give a solution whose *p*H was observed to be 0.6. Two and two-tenths grams (0.02 mole) of cyanogen bromide in 5 cc. of 95% ethanol was added slowly. After standing for fifteen minutes the solution was warmed slightly and then allowed to cool. A crop of 0.4 g. of α-cyanophenylhydrazine in the form of thin white platelets was obtained. The filtrate was again warmed for a few minutes and then thoroughly cooled. 0.4 g. of the hydrolysis product of β-cyanophenylhydrazine, β-phenylsemicarbazide, was obtained. On evaporation an additional 0.2 g. of this substance was obtained.

2. **At *p*H 3.5.**—A mixture of 2.8 g. of phenylhydrazine hydrochloride and 15 g. of sodium sulfate was dissolved in 100 cc. of water giving a solution whose *p*H was 3.5. Two and two-tenths grams of cyanogen bromide in 5 cc. of 95% ethanol was added slowly. After standing four hours the crystals of α-cyanophenylhydrazine were removed, washed with water and dried, yield 0.8 g. The filtrate was evaporated to two-thirds of its original volume and allowed to cool. The precipitate was 1.0 g. additional α-isomer. Upon further evaporation and cooling 0.7 g. of β-phenylsemicarbazide was obtained.

3. **At *p*H 5.6.**—A mixture of 2.8 g. of phenylhydrazine hydrochloride and 15 g. of sodium acetate was dissolved in 100 cc. of water to give a solution whose *p*H was 5.6. Two and two-tenths grams of cyanogen bromide was added as before. An abundant white precipitate of α-cyanophenylhydrazine came down almost immediately. Within a few minutes this started to turn yellow and after thirty minutes it was almost completely transformed to tar.

Reaction of Phenylhydrazine with Carbon Disulfide with and without Air.—A solution of 10 cc. of phenylhydrazine in 40 cc. of benzene was added to each of two 100-cc. three-neck flasks equipped with stirrers and condensers. Three and two-tenths cubic centimeters of carbon disulfide was dropped into each with stirring, producing a light-yellow, practically solid sludge. The third neck of flask A was then plugged but air was not excluded. Nitrogen was introduced through the third neck of flask B to remove air. Both were heated on steam cones and B was continually swept with nitrogen. It was necessary to make periodic additions of benzene to B to compensate for evaporation. Parallel observations are recorded.

Time, min.	Flask A (with air)	Flask B (with nitrogen)
15	Thick suspension	Yellow solution
30	H_2S being evolved	Green color. Trace of H_2S
35	H_2S	No H_2S. Removed to ice-box
50	Solution H_2S still evolved	Cooling overnight gave no ppt.
120	H_2S test negative, heavy ppt.; removed to ice-box; obtained solid mass of diphenylthiocarbazide	Next day air admitted, white ppt. formed slowly

Summary

1. Diphenylthiocarbazide has been reduced catalytically and chemically to produce aniline and phenylthiosemicarbazide, proving that one half of the molecule has the grouping C_6H_5—NH—NH—C.

2. Attempts to reduce phenylthiosemicarbazide to thiourea and aniline were unsuccessful.

3. 1-Phenylthiosemicarbazide obtained from benzene diazocyanide and hydrogen sulfide was found to be identical to the phenylthiosemicarbazide obtained from the reduction of diphenylthiocarbazide.

4. Assuming that benzene diazocyanide is $C_6H_5N{=}N{-}CN$, it follows that phenylthiosemicarbazide and therefore diphenylthiocarbazide have the C—N—NC grouping of benzene diazocyanide.

5. From this evidence it is concluded that the structure of diphenylthiocarbazide used in the preparation of dithizone is

$$C_6H_5{-}NH{-}NH{-}\underset{\underset{S}{\|}}{C}{-}NH{-}NH{-}C_6H_5.$$

(12) Hugershoff, *Ber.*, **36**, 3134 (1903).

BALTIMORE 18, MD. RECEIVED APRIL 18, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WELLESLEY COLLEGE]

Absorption Spectra of Certain α,β-Unsaturated Ketones. II.[1] Effect of Size of Ring and of Position of Double Bond

BY HELEN S. FRENCH AND LOIS WILEY

Definite and reliable rules have been formulated by Woodward[2] for the relations between structure and absorption spectrum of α,β-unsaturated cyclohexanones. These have been very useful already in determining the structures of complex naturally-occurring compounds. Comparatively little has been done for corresponding compounds of α,β-unsaturated cyclopentanones. Gillam[3] postulated a shift of 110 Å. toward the violet for the high-frequency high-intensity band of such cyclopentenones as compared with that of cyclohexenones based upon experimental results on a small number of such compounds. In our first paper of this series[1] we found indications that the shift occurred in the opposite direction, toward the red, for such α,β-unsaturated cyclopentanones with an exocyclic rather than an endocyclic double bond, and more work on such compounds was promised. Since such five-atom ring ketones also occur frequently in complex naturally-occurring compounds, it seems important to formulate any possible "rules" connecting their structures and absorption spectra.

Closely related and relatively simple derivatives of cyclohexanone and cyclopentanone, with α,β-exocyclic ethylene bonds have therefore been prepared and their absorption spectra studied.

Experimental

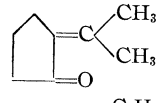
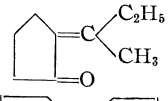
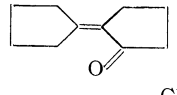
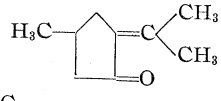
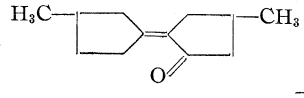
Preparations.—Since all the compounds were prepared according to previously published methods, references to those methods are given in Table I. All compounds were carefully purified by recrystallizations from the appropriate solvents, or by redistillations *in vacuo*, until their melting points (or boiling points) were as recorded in the literature, and until two successive purifications gave identical absorption spectra.

Absorption Measurements.—The method was the same as that previously reported from this Laboratory,[4] with the substitution of a Spekker photometer for the sector photometer. The results are recorded as curves in Figs. 1–4, and the absorption maxima are listed in Table I.

The first eleven compounds in Table I were prepared and purified as above described. For purposes of comparison, Table I also includes the previously published data for the absorption maxima of nine closely related compounds. The data in the table refer only to the short-wave length, high-intensity bands.

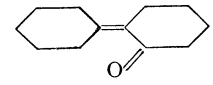
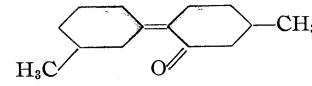
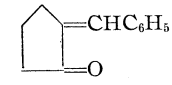
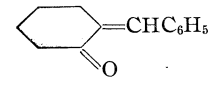
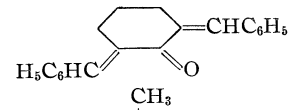
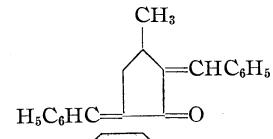
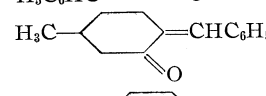
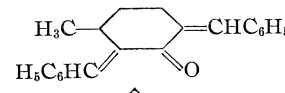
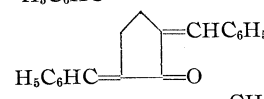
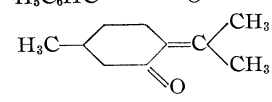
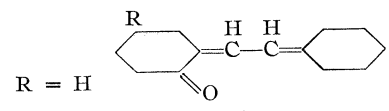
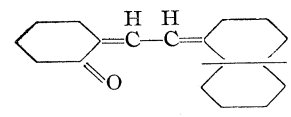
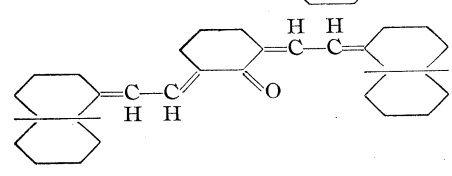
Discussion.—From a study of Fisher–Hirschfelder models, it is clear that 6-atom rings are very little changed by the introduction of one double bond. Cyclohexanone and cyclohexenone are both strainless to about the same degree, since both rings are non-planar. This helps account for the validity of Woodward's[2] rules, which allow very little difference in absorption for equal substitution on an exocyclic double bond and on an endocyclic double bond. The permitted regions for absorption maxima overlap in such cases, *e. g.*, 2350 ± 50 Å. for an endocyclic double bond and 2400 ± 50 Å. for an exocyclic double bond, when two substituents are on the doubly-bound carbons.[2]

TABLE I

Compound	Formula	$\lambda_{max.}$ Å.	$\log_{10}\epsilon$	Solvent
I[5,6]		2520	3.56	Alcohol
II[5,6]		2530	3.52	Alcohol
III[5,6]		2590	4.03	Alcohol
IV[7]		2540 2468	3.98 3.98	Alcohol Hexane
V[7]		2590 2510	3.82 3.92	Alcohol Hexane

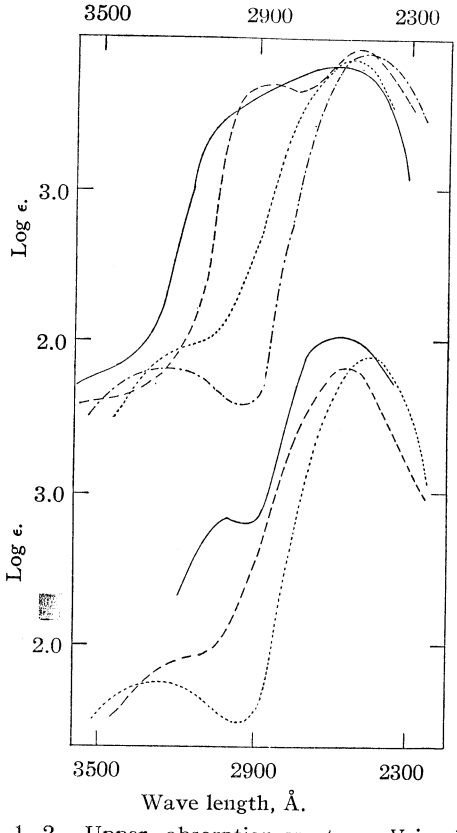
(1) Previous publication in this series: Helen S. French and Muriel E. T. Holden, THIS JOURNAL, **67**, 1239 (1945).
(2) Woodward, *ibid.*, **64**, 76 (1942).
(3) Gillam and West, *J. Chem. Soc.*, 486 (1942).
(4) French and Gens, THIS JOURNAL, **59**, 2600 (1937).
(5) Vavon and Apchié, *Bull. soc. chim.*, **43**, 667 (1928).
(6) Cornubert and Borrel, *ibid.*, **47**, 958 (1930).
(7) Wallach, *Ann.*, **394**, 362 (1912).

TABLE I (*Continued*)

Compound	Formula	$\lambda_{max.}$, Å.	$\log_{10} \epsilon$	Solvent
VI[8]		2550 2460	3.80 3.90	Alcohol Hexane
VII[8]		2540 2481	3.83 3.90	Alcohol Hexane
VIII[9]		2985	4.23	Alcohol
IX[9]		2900	4.05	Alcohol
X[10]		3300	4.40	Alcohol
XI[11]		3525	4.20	Alcohol
XII[1]		2885	4.20	Alcohol
XIII[1]		3280	4.54	Alcohol
XIV[1]		3440	4.44	Alcohol
XV[12,13]		2520 2420	3.81 3.95	Alcohol Hexane
XVI[14]		2970	4.40	Ether
XVII[14]	R = OCH_3	3065 2970	4.39 4.40	Alcohol Ether
XVIII[15]	R = $OCCH_3$	3060	4.14	Alcohol
XIX[14]		3000	4.44	Ether
XX[14]		3420	4.96	Ether

Models show, however, great differences in corresponding five-atom rings. Cyclopentanone and its derivatives with α,β-exocyclic double bonds are planar, with the four conjugated atoms in the same plane. When a double bond is introduced into the ring, the struggle for the ring to be preserved at all upsets the coplanarity of the conjugated atoms. This may account for the shift of absorption maxima of 110 Å. to shorter wave lengths noted by Gillam and West.[3] The complete planarity of the four conjugated atoms in the cyclopentanones with α,β-exocyclic bonds, how-

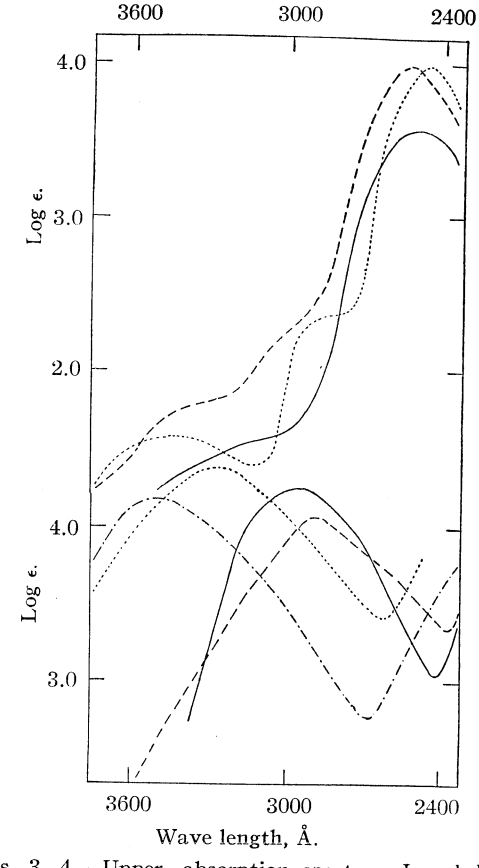
(8) Reese, *Ber.*, **75**, 384 (1942).
(9) Vorländer and Kunze, *ibid.*, **59**, 2078 (1926).
(10) Weiss and Ebert, *Monatsh.*, **65**, 399 (1935).
(11) Wallach, *Ber.*, **29**, 1601 (1896).
(12) Gillam, Lynas-Gray, Penfold and Simonsen, *J. Chem. Soc.*, 60 (1941).
(13) Savard, *Bull. soc. chim.*, **43**, 524 (1928).
(14) Dimroth and Jonsson, *Ber.*, **71**, 2658 (1938).
(15) Aldersley and Burkhardt, *J. Chem. Soc.*, 545 (1938).



Figs. 1, 2.—Upper, absorption spectra: V in alcohol —; V in hexane — — —; VII in alcohol - - - - -; VII in hexane —·—·—; lower, absorption spectra: III in alcohol —; VI in alcohol — — —; VI in hexane - - - - -.

ever (more complete than in either of the 6-atom ring types), results in a shift of the absorption toward the red. The relations among (1) co-planarity of conjugated atoms, (2) the completeness of the resonance of the system and (3) the region of maximum absorption are well-known, and have been frequently emphasized.[16] Our results show this shift to be small and to vary from 20 to 50 Å. when the substituents on the exocyclic double bonds are saturated groups. Note the corresponding cyclohexanone and cyclopentanone pairs of compounds VI and III, VII and V, XV and IV, the latter two pairs in both alcohol and hexane. The shift to the red is greater when the phenyl group is a substituent, 85 Å. for IX and VIII, 140 Å. for X and XIV, and 250 Å. for XIII and XI. The smallest shift (20 Å.) means a difference of approximately 130 Å. between the effects of an exocyclic and an endocyclic double bond in cyclopentanones, which is admittedly within the largest limit (150 Å.) allowed for cyclohexanones. However, if the absorption maxima of four corresponding compounds are considered, those of *both* cyclohexanones lie between those of the two more widely differing cyclopentanones.

(16) Wheland, "Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 161.



Figs. 3, 4.—Upper, absorption spectra: I and II in alcohol —; IV in alcohol — — —; IV in hexane - - - - -. Lower, absorption spectra in alcohol: VIII —; IX — — —; X - - - - -; XI —·—·—.

An unexplained but consistent shift to the red is caused by the change from two alkyl radicals to an alicyclic ring on the exocyclic double bond in both cyclopentanones and cyclohexanones. The models show less tendency to steric interference when the alicyclic rings are present, which may be a sufficient explanation. (Compare the pairs I and III, IV and V, XV and VII.)

The very large shifts to the red caused by extending the conjugation are to be expected, and show consistent regularities. (1) When one α-sidechain is extended to include a second double bond conjugated with the first, but with only saturated substituents, the shift is about 500 Å. to the red. (Compare VI with XVI, XVII, XVIII, and XIX.) (2) When the conjugation is extended by the substitution of a phenyl group for a saturated ring, the shift to the red is 375 ± 25 Å. (Compare VI and IX, VII and XII, III and VIII.) The phenyl group has been variously described under such circumstances as being equivalent to one double bond[17] and to 1.5 double bonds.[18] From these few examples, it would seem

(17) Wilds, Beck, Close, Djerassi, Johnson, Johnson and Shunk, THIS JOURNAL, **69**, 1991 (1947).

(18) Dimroth, *Angew. Chem.*, **52**, 545 (1939).

to be not quite equivalent to one double bond in these compounds. (3) When the conjugation is crossed by the introduction of a second exo-α,β-double bond on the other side of the ketone group, the shift to the red is 400–450 Å. (Compare IX and X, XII and XIII, VIII and XIV, XIX and XX.) This *shift* is independent of whether the substituted groups are saturated or aromatic.

Finally, several pairs of compounds (III and V, I and IV, VI and VII, IX and XII, X and XIII, XI and XIV) differ only by a methyl radical which is on the ring but not on a doubly-bound carbon. The effect of this methyl group on the absorption maxima is negligible with the exception of the last pair. The shift of 85 Å. to the red on the introduction of the methyl group into the 2,5-dibenzalcyclopentanone was surprising. The study of models shows, however, that only in this case would the phenyl group be forced to take the position toward the carbonyl oxygen. The shift of absorption may therefore be an effect of *cis–trans* isomerism. Without the methyl group, the phenyl group has more room away from the carbonyl oxygen. More evidence would certainly be needed to establish this point. The methyl group seems not in any way to inhibit the complete coplanarity of the conjugated system in these molecules.

The effect of change of solvent from alcohol to hexane is the usual one for this high-intensity band, a shift of about 70 Å.[2] to shorter wave lengths. In the curves for IV, V, VI and VII is shown the further effect of hexane in changing the "step-out" in the longer wave length region into a definite low-intensity maximum. This effect agrees with Ramart-Lucas and Hoch's[19] observation that alcohol shifts the low-intensity C=O band toward the violet and the high-intensity C=C—C=O band toward the red, resulting in a mere step-out for the former in alcohol solution instead of the definite maximum in hexane.

It will be noted that the cyclopentanone compounds III, IV, V, VIII, XI, XII and XIV all have analogous cyclohexanone compounds, VI, XV, VII, IX, XIII, XII and X. I and II are conspicuously without analogs. This emphasizes the fact, known at least since 1912,[20] that cyclopentanones and cyclohexanones react very differently with aliphatic ketones. Under the same conditions which give I with cyclopentanone and acetone, cyclohexanone and acetone form cyclohexylidene acetone.[20] Even this compound is unstable and forms an equilibrium mixture with the isomeric cyclohexenyl acetone.[21] The double bond exocyclic to a 6-atom ring is unstable by 3.5 kcal. with respect to the corresponding endocyclic compound.[22] The reason for an analog for IV is that pulegone is a naturally occurring compound! It must be emphasized in this connection that VI and VII must be prepared with great care, in order to keep the double bond exocyclic to the 6-atom ring. Reese[7] was the first to isolate the 2-cyclohexylidene cyclohexanone as a pure compound in 1942, a white crystalline solid, m. p. 57°. Before that time and even after 1942 reports of its preparation described the product as an oil boiling at 142–145° at 15 mm. (or at corresponding boiling points at various other low pressures).[23] It was the absorption spectrum of this liquid product that was reported by Evans and Gillam[24] with the comment that the low intensity of the absorption maximum indicated contamination by an unconjugated isomer. Unless kept *in vacuo*, the solid rearranges to the liquid, as would be expected from the foregoing discussion. To confirm the identity of the crystals as the conjugated α,β-unsaturated ketone, and the liquid as the unconjugated β,γ-unsaturated ketone, Reese[7] measured the molecular refractivities of both. The absorption spectra of these compounds VI and VII reported here confirm Reese's conclusions.

The benzal derivatives of cyclohexanone have the exocyclic double bond stabilized by conjugation with the aromatic ring.

In conclusion, α,β-unsaturated cyclopentanones have not been as widely investigated as the corresponding cyclohexanones. It is therefore not possible as yet to formulate for them rules such as Woodward's.[2] The following statements, however, can be made with a fair degree of confidence concerning cyclopentanones with an α,β-exocyclic double bond.

1. Their absorption is shifted farther to the red than that of the corresponding cyclohexanones, in constrast to cyclopentenones with endocyclic double bonds, whose absorption is shifted to the blue from that of the corresponding cyclohexanones.

2. Alkyl radicals on the ring carbon alpha to the exocyclic double bond cause a red shift which is unnoticeable in the cyclohexanones.

3. The exocyclic double bond is more stable and more completely conjugated with the carbonyl group than in the cyclohexanones.

4. The shifts toward the red caused by extension of conjugation by the phenyl radical are about 50 Å. greater than in the corresponding cyclohexanones.

Work is in progress in this Laboratory to determine the further effect on absorption of α,β-exocyclic double bonds on cyclic ketones already containing α,β-endocyclic double bonds.

Summary

1. The absorption spectra of seven α,β-unsaturated cyclopentanones and four α,β-unsaturated cyclohexanones are recorded in curves and a table.

(19) Ramart-Lucas and Hoch, *Bull. soc. chim.*, [5] **2**, 327 (1935).

(20) Wallach, *Ann.*, **394**, 362 (1912).

(21) Kon and Linstead, *J. Chem. Soc.*, 1269 (1929).

(22) Hückel, "Theor. Grundlagen der org. Chem.," 2nd ed. Akad. Verlag., Leipzig, 1934, p. 72.

(23) Mannich, *Ber.*, **40**, 157 (1907); Wallach, *Ann.*, **381**, 97 (1911); Garland and Reid, THIS JOURNAL, **47**, 2333 (1925); Hurd, Greengard and Roe, *ibid.*, **61**, 3359 (1939); Wayne and Adkins, *ibid.*, **62**, 3401 (1940); Price, Knell and West, *ibid.*, **65**, 2469 (1943); Gault, Daltroff and Eck-Tridon, *Bull. soc. chim.*, **12**, 952 (1945).

(24) Evans and Gillam, *J. Chem. Soc.*, 816 (1941).

2. The results are discussed in an attempt to formulate generalizations for cyclopentanones analogous to those formulated for cyclohexanones by Woodward.[2]

3. The most important of such generalizations is that the conjugated *exo*-cyclic double bond in the cyclopentanones shifts the absorption maximum to the red from that of the corresponding cyclohexanones and in contrast to the shift to the blue of the conjugated *endo*-cyclic double bond in the cyclopentenones.

WELLESLEY 81, MASS. RECEIVED MARCH 25, 1949

[CONTRIBUTION FROM THE BALLISTIC RESEARCH LABORATORIES, ABERDEEN PROVING GROUND]

The Explosion of Nitrous Oxide–Hydrogen Mixtures

BY CHARLES P. FENIMORE AND JOHN R. KELSO

This paper presents explosive limits for the nitrous oxide–hydrogen system. When combined with Melville's[1] interpretation of his slow reaction data between these gases, the explosive data strongly indicate the presence of the radical HO_2 in the reacting system. Although a detailed reaction mechanism cannot be based on these findings, it is of some interest that the processes forming HO_2 occur at temperatures 200° or more higher in this system than they previously have been known to occur in other reaction systems.[2]

Since Melville encountered explosions in his studies of the slow reaction but did not observe reproducible limits, it is necessary to state at the outset that reproducible limits can be readily obtained. To do so, the gases must be oxygen-free, however, and their entry into the reaction vessel must be rapid. The second requirement is necessary presumably so that not much molecular oxygen can be formed by the thermal decomposition of nitrous oxide before the pressure builds up to the explosion limit. Hence, the second requirement is only a restatement of the first, that the gases must be oxygen free.

Experimental

Hydrogen and nitrous oxide, freed from oxygen by treatment with aqueous alkaline pyrogallol and dried, were mixed in a previously evacuated vessel in the desired proportions. Proportions were estimated by an attached mercury manometer. The mixing vessel communicated to the reaction vessel through a stopcock of 2-mm. bore. The reaction vessel was heated in an electric resistance furnace and fitted with two chromel alumel thermocouples whose readings did not differ by more than 1°. Adequate temperature constancy could be maintained through a Sorensen voltage regulator and variable transformers with only occasional manual control. Two cylindrical quartz reaction vessels 30 cm. long were used; one measured 0.9 cm. inside diameter, the other 2.5 cm. These two vessels were new and manufactured at the same time and place, and presumably possessed similar surfaces. In addition, runs were made in a cylindrical vycor vessel of 1.5 cm. inside diameter. The findings obtained in the vycor vessel showed the same features as those in quartz up to 830° and are not reported in detail.

After the mixing vessel had been filled at a pressure such that the pressure would rise to the desired value in the previously evacuated reaction vessel when the gas was partitioned between them, the stopcock was opened rapidly. An explosion ensued immediately or not at all. No perceptible induction period was ever noted. Explosions were indicated by a sharp click and a bright flash of light which propagated back through the stopcock into the mixing vessel. The color of the light was dependent on temperature and composition. Explosions at low temperatures or of compositions rich in hydrogen appeared reddish; those at higher temperatures or of mixtures rich in nitrous oxide yellowish or white. At 800° only compositions containing over 50% hydrogen appeared at all reddish.

At a given temperature and gas composition, observations were repeated at varying pressures until the lower pressure limit was bracketed within 1–2 mm. The measurements were taken over a fairly extended period of time and frequent returns to limits measured weeks or months before proved the values, at temperatures $\leqslant 830°$, reproducible to 3–5 mm. The results obtained in vycor between 900 and 980° were less reproducible ($\simeq \pm 10$ mm.).

Results and Discussion

In Figs. 1 and 2, the lower limiting explosion pressure for nitrous oxide–hydrogen mixtures is plotted as a function of temperature and gas composition for vessels of two different sizes. The decimal point serves a double purpose in these contour maps. In addition to pointing off tenths of a cm. of a pressure determination, each point places the temperature and composition at which that determination was made. At temperatures below 720° in the small vessel (or 670° in the larger one) the explosion pressure was too high to observe in a quartz and glass apparatus. For the same reason, the minimum explosion pressure escaped capture in either vessel above 820°. In a vycor vessel of 1.5-cm. inside diameter, very similar results

(1) Melville, *Proc. Roy. Soc.* (London), **142A**, 524 (1933); **146A**, 737, 760 (1934).

(2) For a discussion and for references, see Minkoff, *Faraday Soc. Discussions*, **2**, 151 (1947).

were obtained; the explosive region extended from 670 to 820°, the minimum explosion pressure (6.6 cm.) occurred with 69% nitrous oxide at 740°.

The most striking feature of these data is that in any section of fixed composition the pressure *versus* temperature curve possesses a minimum; although if no change occurred in the reaction mechanism, a continuous decrease of the lower limit would be anticipated with increasing temperature. The nature of the reaction which intrudes to upset a steady decrease of the explosion limit becomes evident when a small amount of oxygen is added to the reactants. We have found oxygen to be an efficient poison for the explosive reaction, although Melville found it an effective catalyst for the slow reaction. Extensive tests proved that the addition of 2 mm. of oxygen raised the explosion limit above 20 cm. wherever it was less than this value in Figs. 1 and 2. This quantity of oxygen was much greater than the amount necessary to inhibit the reaction, however. Nitrogen was prepared containing 3% of oxygen, and it was found that the addition of 5 mm. of this mixture to the reactant gas drove the explosion pressure above 20 cm. for any composition at 780 and 820° in the large reaction vessel and at 760 and 800° in the smaller vessel.

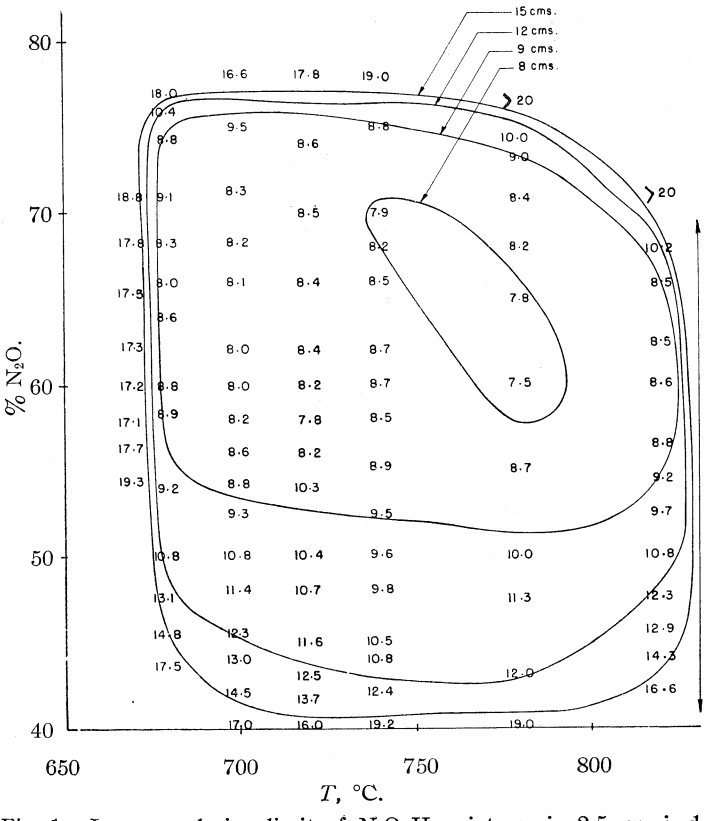


Fig. 1.—Lower explosion limit of N_2O–H_2 mixtures in 2.5-cm. i. d. quartz vessel.

The effect of added oxygen must be ascribed to the chemical nature of the additive since nitrogen (free from oxygen) did not inhibit the explosions. In general, the effect of 2–12 mm. of added nitrogen was to depress slightly or to leave unaltered the pressure of nitrous oxide plus hydrogen required for explosion. Added in still larger amounts, nitrogen increased the limiting pressure of the reactants. It might be conceived that the effect of oxygen could depend only on its paramagnetism and that nitric oxide would also inhibit the explosive reaction. This was proved false. The addition of 3 mm. of nitric oxide slightly shifted the minimum pressure toward the stoichiometric ratio, but left the main features of Fig. 1 unchanged.

The inhibition of explosions by added oxygen suggests an explanation for the existence of a minimum in the explosion limit in the absence of added oxygen. Nitrous oxide undergoes thermal decomposition to nitrogen and oxygen and the obvious conclusion is that at a high enough temperature the decomposition furnishes oxygen enough to inhibit the explosive reaction between nitrous oxide and hydrogen.

For a more detailed statement of this view, we consider the following sequence of reactions by which Melville interpreted his studies of the slow reaction and note that if these equations are valid

$$N_2O \longrightarrow N_2 + O \quad (1)$$
$$O + H_2 \longrightarrow OH + H \quad (2)$$
$$H + N_2O \longrightarrow OH + N_2 \quad (3)$$
$$OH + H_2 \longrightarrow H_2O + H \quad (4)$$
$$H \longrightarrow \text{recombination on wall or third body} \quad (5)$$

for the explosive as well as for the slow reaction, it appears inevitable that the mechanism of poisoning by added oxygen must be

$$H + O_2 + M \longrightarrow HO_2 + M \ (HO_2 \text{ is inert}) \quad (6)$$

because the hydrogen atom is the only labile particle in Melville's sequence which could react with molecular oxygen. The natural assumption is that the inhibition of the explosive reaction even without added oxygen is also caused by (6), and this because nitrous oxide decomposes to give chiefly molecular oxygen and nitrogen, although the decomposition is not allowed for in Melville's sequence.

The success of (6) as a poisoning reaction is founded on the stability of HO_2 or, more precisely, on the fact that HO_2 is destroyed without the generation of free radicals which can re-enter the gas phase reaction. While this is the only fate permitted above, it is obvious that the reaction

$$HO_2 + H_2 \longrightarrow H_2O_2 + H \quad (7)$$

might proceed in the nitrous oxide–hydrogen system since it does so in the oxygen–hydrogen system where its occurrence permits the third explo-

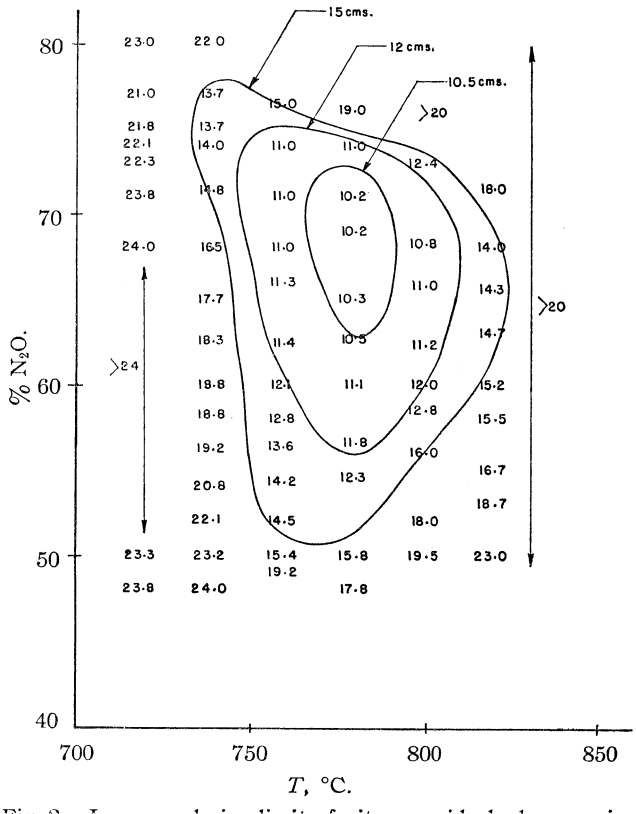


Fig. 2.—Lower explosion limit of nitrous oxide–hydrogen mixtures in 0.9-cm. i. d. quartz vessel.

sion limit.[3] A comparison of Figs. 1 and 2 hints that this reaction does in fact take place. In the larger vessel, the explosive region extends much farther toward hydrogen-rich mixtures than in the smaller vessel, while the limit toward nitrous-oxide-rich mixtures is only slightly extended. In view of the weak dependance of explosion pressure on vessel size (the minimum explosion pressure in the two vessels varies inversely with the cube root of the diameter) this strong feature could not result from a greater diffusion path alone. It might be expected, however, if reaction (7) occurred because the greater diffusion path to the wall allows greater opportunity for the regeneration of the hydrogen atom before destruction of the HO_2 radical at the wall in the larger than in the smaller vessel, and hence a greater extension of the explosive region toward hydrogen-rich mixtures is permitted.

It is of interest to ask whether HO_2 will remain a quasi-inert body as temperature is increased. In the absence of any major change of reaction mechanism, it would be expected that if HO_2 became unstable or more reactive at higher temperatures the explosion limit would decrease again because a chain-breaking mechanism would have ceased to operate. Furthermore, if such an effect were observed it should be accompanied by a cessation or at least a great diminution of the poisoning effect of added molecular oxygen. We have not been able to recapture the explosion limit in either of the quartz vessels between 830 (where it vanished) and 960°. In the vycor vessel, on the other hand, the explosion limit reappeared at 900° and slowly decreased as the temperature was raised further. At the higher temperatures (above 900°) the minimum explosion pressure occurred much nearer the stoichiometric ratio than in the lower temperature region. In Fig. 3, the explosion limit is plotted for equimolar mixtures in a 1.5-cm. inside diameter vycor vessel. The addition of 2 mm. of molecular oxygen to this mixture produced only a slight effect in the temperature range from 900 to 980° (increased the explosion pressure by an amount $\leqslant 10$ mm.) although the low temperature lobe was destroyed by a similar addition of oxygen, just as it was in either quartz vessel.

It will be recalled that the vycor vessel gave lower explosion limits than those obtained in even a larger quartz vessel in the low temperature range as well, $T < 830°$, and this may be due either to the greater facility of hydrogen atom recombination on quartz than on vycor or to a difference in the fate of HO_2 on quartz and on vycor. The first alternative appears the simpler, and it is probable that a more rugged or larger apparatus would allow the recapture of the explosion limit in quartz above 900°. The major constitutive difference between vycor and quartz is the presence of approximately 4% of boric oxide and small amounts of sodium, iron, aluminum and arsenic in the latter; and the larger quartz vessel was treated with boric oxide and with sodium borate in an attempt to force the reappearance of the explosion limit.

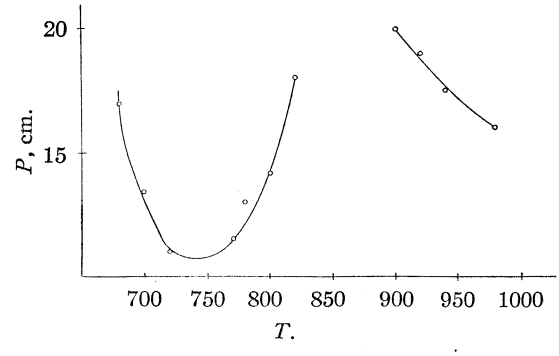


Fig. 3.—Lower explosion limit of 1:1 nitrous oxide–hydrogen mixtures in 1.5-cm. i. d. vycor vessel.

However, neither treatment was effective in promoting explosions in the temperature range 830–960° in quartz. On the contrary, the only effect observed from these surface treatments was a moderate elevation of the explosion limit in the low temperature range, $T < 830°$.

(3) Von Elbe and Lewis, *J. Chem. Phys.*, **10**, 366 (1942).

Acknowledgment.—The authors are indebted to Dr. Bernard Lewis for suggestive discussions preceding and during the course of this work.

Summary

A study of the lower explosion limit of the nitrous oxide–hydrogen system reveals the existence of a minimum in the pressure *versus* temperature curve for mixtures of any fixed compositions. The addition of molecular oxygen poisons the explosive reaction, and this suggests that the minimum is due to the poisoning of the reaction by oxygen from the thermal decomposition of nitrous oxide. In view of the results of Melville's study of the slow reaction, the mechanism of poisoning must be $H + O_2 + M \rightarrow HO_2 + M$.

After passing through the minimum, the explosion limit does not increase indefinitely as the temperature is raised. Above 900° it decreases again in a vycor vessel, but could not be observed to decrease in quartz vessels of the size employed. In vycor above 900°, the explosion is not strongly affected by added oxygen and this insensitivity would be expected from the interpretation of the low temperature results.

ABERDEEN PROVING GROUND, MD.

RECEIVED APRIL 21, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF ETHYL CORPORATION]

Studies in the Lead Chloride–Lead Bromide System[1]

BY GEORGE CALINGAERT, FRANCES W. LAMB AND FRED MEYER

The published information on the lead chloride–lead bromide system is incomplete and contradictory, and after a preliminary examination of its X-ray diffraction characteristics it became obvious that previously reported work would have to be repeated in order to arrive at a reliable description of the system. This paper covers an investigation of this system which, in addition to a thorough X-ray diffraction analysis, includes a repetition and an extension of the work of other investigators by thermal analysis, by conductivity and by aqueous preparations.

In a recently published study of the binary and ternary systems of lead halides, Mlle. Delgery,[2] contrary to the conclusions of previous investigators,[3] reported the existence of several compounds and eutectics. Her first two papers gave the results of thermal analyses on the three binary systems of lead chloride, lead bromide and lead iodide,[2a] and on the ternary system of these lead halides.[2b] These thermal analyses were supported in a third publication[2c] on six series of unsaturated aqueous solutions, each containing two of the four halides. In each series, the composition of the solute was varied from that of one halide to that of the other, while the total concentration was kept constant. All the conductivity–composition curves reported showed broad minima and sharp maxima, which latter were interpreted by the author as indicating the existence in solution of compounds of the corresponding solute compositions. Furthermore, Delgery proposed such measurements as a valuable adjunct to thermal analysis, reporting that peritectic compounds difficult to detect by thermal analysis were readily detected by such conductance measurements.[2c,2d]

For the lead chloride–lead bromide system Delgery's results indicated the existence of a stable compound, PbClBr, a peritectic compound, $PbBr_2 \cdot 3PbCl_2$, a eutectic close to $9PbBr_2 \cdot 16PbCl_2$, and several series of solid solutions, two of which had limited miscibility. These results contradicted the earlier thermal analysis of Mönkemeyer,[3a] who found that this system was one in which there was a continuous series of solid solutions with the melting (liquidus) points of all intermediate compositions lying on a straight line joining the melting points of the pure components. The work of Mönkemeyer was directly confirmed by Favorskii,[3b] and indirectly by Matthes[3c] in a study of the ternary system, lead chloride–lead bromide–lead iodide. A comparison of the results obtained by Delgery, Mönkemeyer and Favorskii is given in Fig. 1.

On the other hand, Thomas,[4] in 1898, claimed, like Delgery, to have prepared both $PbBr_2 \cdot 3PbCl_2$ and PbClBr. His evidence that $PbBr_2 \cdot 3PbCl_2$ was a compound rather than a solid solution was based on the constancy of the composition of the material crystallizing out of a hot solution of lead chloride to which potassium bromide had been added. His evidence for the existence of PbClBr was even less satisfactory, since his material was obtained only by heating PbClI in a current of bromine.

Experimental

Materials.—Except for lead bromide, these were of analytical reagent quality; all were used without further purification. Spectrographic analysis of the potassium chloride, lead chloride and lead bromide showed a total metallic impurity of less than 0.007, 0.01 and 0.01%, respectively. Chemical analysis of the lead chloride gave

(1) The X-ray diffraction portion of this study was presented before the Sixth Annual Pittsburgh Conference on X-Ray and Electron Diffraction on November 19, 1948.

(2) (a) Delgery, *Compt. rend.*, **222**, 886 (1946); (b) **223**, 401 (1946); (c) **224**, 274 (1947); (d) **224**, 915 (1947).

(3) (a) Mönkemeyer, *Neues Jahrb. Mineral. Geol.* (Beilage Bd.), **22**, 1 (1906); (b) Favorskii, *Ann. secteur. anal. phys.-chim., Inst. chim. gén. (U. S. S. R.)*, **13**, 281 (1940); (c) Matthes, *Neues Jahrb. Mineral. Geol.* (Beilage. Bd.), **31**, 342 (1911).

(4) Thomas, *Bull. soc. chem.*, [3] **19**, 598 (1898); [3] **21**, 532 (1899); *Compt. rend.*, **128**, 1234 (1899).

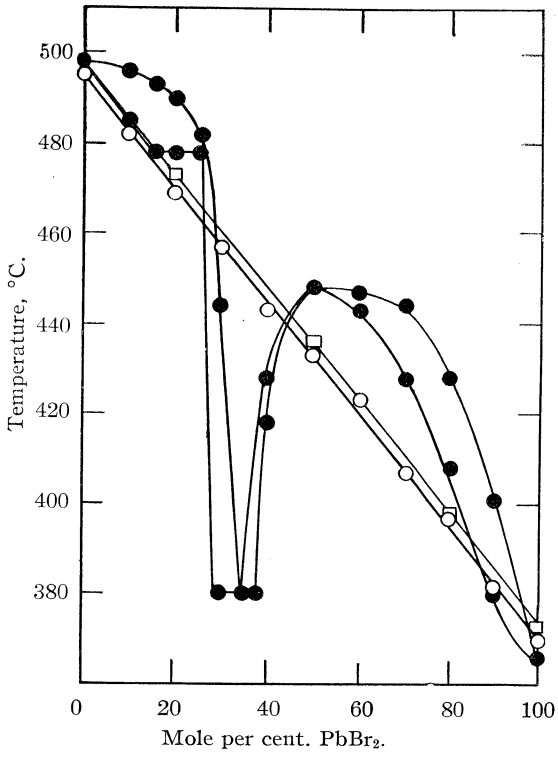


Fig. 1.—Thermal diagram of the lead chloride–lead bromide system as reported in the literature: O, Mönkemeyer; □, Favorskii; ⊜, Delgery.

the calculated composition; chemical analysis of the lead bromide indicated the presence of less than 0.8% of a basic bromide.

Thermal Analysis.—All cooling and heating curves were run *in vacuo* in a Vycor tube in which was supported a Vitreosil thermal well having a thin-walled capillary end. The runs were made on 40- to 50-g. samples which were vacuum dried for several hours before starting the run. Cooling and heating rates of 1°/minute ± 10% were maintained by manual control of the furnace voltage. Temperatures were measured with an L. & N. glass-fiber insulated iron–constantan thermocouple and a K-2 potentiometer. Throughout each run, the Vycor tube was vibrated continuously with a Burgess Vitro-Tool; this gave improved heating and cooling curves and minimized supercooling.

One cooling curve and two heating curves were obtained on each sample. One heating curve was run on an intimate mechanical mixture and the other on the solidified melt, after it had been finely ground. The two heating curves always gave comparable results; that is, in the heating curve run on the mixture, only one thermal arrest, characteristic of the solidus temperature of the corresponding solid solution, was observed. The duration of arrests obtained ordinarily varied from thirty to almost fifty minutes for a 40-g. sample.

Conductivity Measurements. A. Equipment.—Conductance measurements were made at 1000 cycles from a bridge assembled from an L & N precision type slide wire, a shielded 11,111 ohm a. c. decade resistance box, a 1000 mmf. variable air condenser, a Wagner ground and appropriate shielding. The slide wire was used as fixed unit-ratio arms by maintaining the slide wire contact at its effective a. c. center. Two Jones-type conductivity cells were made of 16-mm. Pyrex tubing with platinized electrodes approximately 10 cm. apart. The cells were calibrated at 25° with the 0.01 demal KCl solution of Jones and Bradshaw, and the measurements were made at 25.00 ± 0.01°. The *p*H was measured with a glass electrode and a Model G Beckman *p*H meter.

B. Preparation of Solutions.—Two sets of stock solutions of lead chloride and lead bromide were prepared, corresponding to the two series of solutions whose conductivities were to be measured.

In the first set, sufficient lead halides were dissolved in carbon dioxide-free, hot conductivity water, in calibrated Pyrex volumetric flasks, so that after hydrolysis products were removed, the solutions would be exactly 0.02 molar in lead ion. After solution of the halides was complete, the solutions were allowed to reach hydrolytic equilibrium at 25°, adjusted to final volume and filtered through a Jena sintered-glass filter. The final concentration of the lead bromide solution was calculated from the weight of Pb(OH)Br recovered, and the final concentration of the lead chloride solution was computed on the basis of *p*H. The second set of stock solutions was prepared by dissolving the desired amount of each lead halide in a hot dilute solution of its hydrohalic acid. The *p*H's of both hydrobromic and hydrochloric acid solutions, prepared by dilution of concentrated acids with conductivity water, were close to 3.30, this being nearly the maximum *p*H at which the more easily hydrolyzed lead bromide would dissolve completely. The compositions of both sets of stock solutions were finally confirmed by analysis.

Solutions for conductivity measurements were prepared by mixing at room temperature appropriate volumes of each stock solution from calibrated Pyrex burets into Pyrex volumetric flasks. No appreciable change in volume occurred on mixing. This method of preparation insured that both the relative composition (Cl/Br) and the actual total concentration (0.0200 molar lead halides at 25°) were accurately controlled.

C. Conductance measurements on each solution were made in both cells, and were considered satisfactory when consecutive measurements of the cell resistance were constant to 3 parts in 10,000 and the resistance ratio of the cells was within 5 parts in 10,000 of the value found in calibration.

Aqueous Preparations. A. The Preparation of $PbBr_2 \cdot 3PbCl_2$ was attempted according to the method of Thomas,[4] using four times his scale, and by collecting the entire crystalline product for three temperature intervals. A Glas-Col electrical beaker jacket was used to maintain close temperature control. Forty ml. of a 10% potassium bromide solution was added slowly with stirring at 95° to one liter of carbon dioxide-free water containing 20 g. lead chloride. The resulting clear solution was slowly cooled with constant stirring, and crystallization began at 90°. The solution was further cooled to 70°, where it was maintained for two hours before removing the first crop of crystals. A second crop of crystals was similarly obtained from the supernatant solution for the interval from 70 to 50°. The resulting supernatant solution was then allowed to cool overnight to room temperature (approx. 23°) for the last crop. Each crop of crystals was separated from adhering mother liquor by washing with 95% ethyl alcohol, transferring to a Buchner funnel and draining as completely as possible. The crystal meals were then ground, and dried overnight at 75° *in vacuo* with constant pumping.

B. Other solid solutions of lead chloride and bromide of predetermined composition were attempted. The appropriate volumes of standardized hydrochloric and hydrobromic acids (approx. 1.1 *N*) required to prepare 1.021 equivalents of mixed acid (equivalent to 900 ml. of the hydrobromic acid solution) of the desired chlorine-bromine ratio were placed in "Low-Actinic" flasks and 66.7 ml. of a 1.5 *M* lead acetate solution was added dropwise with stirring. The flasks were stoppered and kept for three weeks at room temperature (approx. 23°), with occasional shaking. The products recovered were found to be well-formed tiny crystals which were drained as completely as possible on a filter, and then vacuum-dried at 110° to remove the final traces of acids.

X-Ray Diffraction.—The following is a description of the samples used and the technique of specimen preparation:

A. Fused preparations were obtained by heating under nitrogen an intimate mixture of the appropriate weights of lead chloride and lead bromide at about 525° in fused alumina crucibles. After melting, they were stirred for ten or fifteen minutes and allowed to cool.

B. Heat-treated Preparations: H 1.—One of the 50 mole % compositions used for thermal analysis, and having a forty-minute crystallization period, was kept at 420 ± 3° for sixty hours, and then allowed to cool in air.

H 2.—This is a 50 mole % lead bromide melt which had a three-hour crystallization period and was cooled to room temperature in the furnace.

H 3.—The same as H 2 except that, following the three-hour crystallization period, the sample was annealed at 416 ± 3° for forty-six hours, after which it was cooled to 100° over a period of ten hours.

H 4.—The same as H 2 except that the crystallization and annealing times were fifteen hours each, and the cooling time three hours.

C. The preparation of specimens which would show a minimum of preferred orientation and give patterns of reproducible relative intensities was a problem of major importance, which is inherently more difficult with the Geiger-Counter Spectrometer than with camera units. Lead chloride and lead bromide crystallize in long needles along their a axes, and there is a tendency for these axes to line up parallel to the surface on which they are mounted. A method was developed for making reproducible collodion films of 30-mg. samples on microscope slides, as follows:

(1) The 200-mesh material was ground an additional ten minutes. Grinding is important not only for particle size reduction but also to obtain particles of equal dimensions in all three directions in order to avoid possible orientation during the drying of the collodion film.

(2) Two drops of dilute collodion (1 part collodion in 2 parts of a 3:1 absolute alcohol–ether solution) was added to 30 mg. of the fine powder placed in a small glass cone. The mixture was worked with a stirring rod (the end of which was shaped to fit the bottom of the cone) until the solvent evaporated, leaving a fine powder coated with collodion. About 0.5 ml. of dilute collodion was added, and the dried powder was suspended by stirring, forming a fine, stable suspension.

(3) This suspension was poured on a microscope slide to cover the full width of the slide for one inch of its length, and was stirred rapidly until it became tacky and formed a thick gel. After drying, the preparation was ready for use.

The reproducibility of this method of specimen preparation was checked on nine lead chloride and ten lead bromide preparations. The average deviation from the mean relative intensity of 31 of the lead chloride reflections and 29 of the lead bromide reflections was found to be approximately 10% for each of the reflections.

Collodion films are also well suited for use with the back-reflection camera, since they can be readily removed from the glass slide, are smooth, flexible and may be accurately held to the curvature of the focusing circle of the camera. For this purpose a denser film was prepared by using 100 mg. of sample and 1 ml. of dilute collodion.

D. A calibration of the goniometer was made before and after each series of 2 θ measurements, using alpha-quartz. The lattice constants, a = 4.91310 Å. and c = 5.40461 Å., given by Wilson and Lipson,[5] were used to calculate the 2 θ values of suitable lines occurring in the forward-reflection region. These are listed in Table I. The calibration of the goniometer readings showed very little variation throughout the series of measurements made in this study.

[a] Calculations were made using 1.5418 Å. as the wave length of the weighted mean of the CuKα radiation, except for the indicated reflections where 1.54050 and 1.54435 Å. were used as the wave lengths of α_1 and α_2, respectively.

E. Lattice constants were computed for each fused composition from measured angles of reflection (2 θ) found for five planes in the forward-reflection region by manual scanning measurements after correcting for systematic errors (based on the previous calibration), using a weighted least squares solution of the equation

$$d^{-2} = (2/n\lambda)^2\sin^2\theta = h^2a^{-2} + k^2b^{-2} + l^2c^{-2} \quad (1)$$

The weighting factor, determined by least squares theory, is proportional to $\csc^2 2\theta$. Since the numerical solution of simultaneous equations obtained from Eq. (1) by least squares is not sensitive to small variations in weights, it was possible to assign an average relative weight for each plane satisfactory for all compositions (Table II) and, consequently, to obtain by matrix algebra a general solution of the least squares equations for the lattice constants for all compositions.

(5) Wilson and Lipson, *Proc. Phys. Soc.*, (*London*), **53**, 245 (1941).

TABLE I

ALPHA-QUARTZ CALIBRATION DATA[a]

hkl	2 θ calcd.	*hkl*	2 θ calcd.
100	20.877°[a]	103	55.381°
101	26.663°	121	60.017°
110	36.578°	121α_1	59.961°
102	39.504°	121α_2	60.126°
200	42.490°	302	75.738°
112	50.187°	302α_1	75.662°
202	54.927°	302α_2	75.886°

TABLE II

RELATIVE WEIGHTS USED IN CALCULATION OF LATTICE CONSTANTS

Plane	$\csc^2 2\theta/\csc^2 2\theta_{026}$ PbCl$_2$	50% PbBr$_2$	PbBr$_2$	w
002	7.51	7.58	7.77	7.6
020	5.40	5.51	5.61	5.5
103	2.47	2.50	2.53	2.5
123	1.81	1.82	1.85	1.8
026	1.00	1.00	1.00	1.0

Results

Thermal Analysis.—Liquidus and solidus temperatures were determined from cooling and heating curves, respectively, on nine compositions ranging from pure lead chloride to pure lead bromide in steps of one-eighth mole fraction except that the 37.5 mole % lead bromide was replaced by 35 mole % lead bromide which is the eutectic composition of Delgery's thermal diagram.

A summary of the data obtained is given in Table III and Fig. 2. Where more than one run

TABLE III

THERMAL ANALYSIS OF PbCl$_2$–PbBr$_2$ SYSTEM

Composition in mole % PbBr$_2$[a]	Liquidus, T, °C.	Solidus, T, °C.
0	496.3[b]	496.0[b]
12.5	478.9	474.6
25	464.0	457.5
35	452.3	443.3
50	435.9	425.0
62.5	420.7	410.2
75	403.4	394.2
87.5	386.5	381.5
100	370.1[c]	369.8[c]

[a] The compositions are based on the weights of reagents used. [b] Mönkemeyer, Favorskii and Delgery give 495, 498 and 498°, respectively. [c] Mönkemeyer, Favorskii and Delgery give 370, 373 and 366, respectively.

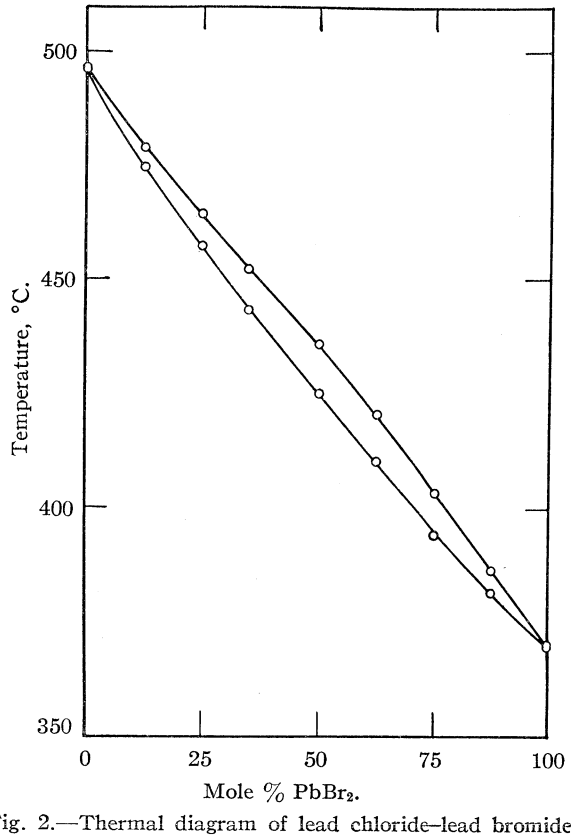


Fig. 2.—Thermal diagram of lead chloride–lead bromide system obtained in the present work.

was made, the values shown represent an average of those values for which the extrapolation of the thermal breaks was the least arbitrary. For this reason, solidus values from cooling curves and liquidus values from heating curves were ignored. The points given in this Table are believed to be precise to one degree; but judging from a calibration with zinc, they may be from zero to 2.5° low.

The thermal diagram obtained for this system is an ideal example of the diagram obtained for a binary system in which the two components form a continuous series of solid solutions, where all the melting points are intermediate between those of the pure components. As a consequence, no compounds exist in the lead chloride–lead bromide system; at least, not in the temperature–composition region above and possibly somewhat below the solidus curve of the system. This is in complete agreement with Mönkemeyer[3a] and Favorskii,[3b] and in complete disagreement with Delgery.[2a,2b]

Conductivity Measurements.—The variations in conductivity with varying anion composition which Delgery observed[2c,2d] are considerably different in character from those observed by Sandonnini[6] for similar systems in which complex compounds are known to exist, and are in such complete contradiction with accepted theories of conductivity that we decided to subject them to extremely careful experimental verification.

Because no experimental details, other than the concentrations used, were given in Delgery's brief communication,[2c] it was not possible to carry out these measurements under conditions identical with those which she employed; nor, did it seem desirable to do so on the basis of the following considerations. First, it was estimated from a study of the system $PbCl_2$–$PbBr_2$–H_2O,[7] that the minimum solubility of this system at 20° is 0.020 mole of lead halides per liter.[8] Therefore, nearly saturated solutions were avoided by using a total halide concentration of 0.020 molar at 25° rather than 0.0245 molar as used by Delgery. Second, because of the appreciable hydrolysis of both lead chloride and lead bromide, some free acid is always present in their solutions, and the solution of either halide in water is always accompanied by the separation of some insoluble hydrolysis products. Variations in the composition of the solutions and, consequently, in their conductivities would depend, therefore, on the method used to prepare the solutions.

Two methods were used; each involved mixing appropriate volumes of stock solutions of lead chloride and lead bromide. In the first, the stock solutions were prepared with the minimum amount of free acid by dissolving the proper excess of lead halide in conductivity water so that after the products of hydrolysis were removed the solutions were of the desired concentration. This method has the principal disadvantage that a solution of lead bromide is more acidic than a solution of lead chloride of the same concentration (about 1 *p*H unit for 0.020 molar solutions at 25°), so that the *p*H of a series of solutions prepared from them varies continuously. Also some investigation of the nature and degree of the hydrolysis of these lead halides was required.[9] This method was used only because it seems similar to Delgery's. Since she does not mention hydrolysis, it was assumed that her stock solutions were prepared by dilution from saturated solutions. In the second method, the lead bromide stock solution was prepared by using as the solvent the most dilute hydrobromic acid solution which would prevent the precipitation of hydrolysis products. The lead chloride stock solution was prepared by using a hydrochloric acid solution of the same *p*H as the hydrobromic acid. These lead halide solutions form a series of isohydric solutions and so do the hydrohalic acid solutions used to prepare them.

The results of the conductivity measurements

(6) Sandonnini, *Gass. chim. ital.*, **46**, II, 205–219 (1916).

(7) Meyer, *Rec. trav. chim.*, **42**, 301 (1923).

(8) The temperature of this study was not stated, but assuming that the work was done at constant temperature, it was estimated from the ratio of solubilities reported by G. Meyer for the lead halides and from the solubility–temperature data of these compounds reported in the "International Critical Tables."

(9) The products of hydrolysis were identified as the basic salts Pb(OH)X, and 0.020 molar lead bromide and lead chloride solutions were found to be 2.1 and 0.2% hydrolyzed at 25°, respectively.

are given in Table IV and are plotted against composition in Fig. 3. Series A, varying pH, is the series of solutions for which the lead halide stock solutions were prepared with water, and where the acidity, due to hydrolysis, is the minimum possible for each solution of the series. Series C, constant pH, is the series of solutions for which the lead halide stock solutions were prepared with their respective dilute acids, each of the same pH. Series B, constant pH, is a series of solutions made by mixing the hydrochloric and hydrobromic acid solutions used for preparing the stock solutions of Series C. The conductivities of all three series show very slight positive deviations from a simple additive relation with composition, and no evidence whatever of the sharp maxima reported by Delgery. The results for the two halide series can be shown to be consistent by evaluating the contribution of the acids present in each solution of each series, assuming as a first approximation that the conductivities of these solutions are an additive function of all the ions present, and that the ionization equilibria of the lead halides are independent of the acid concentration.

TABLE IV

CONDUCTIVITY MEASUREMENTS FOR THE LEAD CHLORIDE–LEAD BROMIDE AND HYDROCHLORIC–HYDROBROMIC ACID SERIES

Solution	Vol. % $PbBr_2$ soln.	Spec. cond.[a] ohm^{-1} cm.$^{-1}$ × 10^3	pH	Solution	Vol. % $PbBr_2$ soln.	Spec. cond.[a] ohm^{-1} cm.$^{-1}$ × 10^3	pH
Series A, 25.00 ± 0.01 °C. 0.02003 M $PbBr_2$, 0.02000 M $PbCl_2$							
1	0	3.761	4.41	6	50.03	3.721	3.63
2	20.00	3.746	3.97	7	59.99	3.712	3.56
3	25.01	3.742	3.90	8	79.98	3.695	3.43
4	30.03	3.737	3.83	9	100.00	3.676	3.36
5	40.04	3.729	3.71				
Series C, 25.00 ± 0.01 °C. 0.02000 M $PbCl_2$ in HCl, 0.02000 M $PbBr_2$ in HBr							
1	0	3.942	3.27	6	50.03	3.828	3.27
2	20.00	3.897	3.28	7	59.99	3.804	3.27
3	25.01	3.886	3.27	8	79.98	3.756	3.27
4	30.03	3.874	3.27	9	100.00	3.707	3.28
5	40.04	3.851	3.27				
Series B, 25.00 ± 0.01 °C. HBr, HCl approx. 5.4 × 10^{-4} N							
	Vol. % HBr soln.	Spec. cond.[a] × 10^4			Vol. % HBr soln.	Spec. cond.[a] × 10^4	
1	0	2.194	3.29	6	50.03	2.209	3.30
2	20.00	2.204	3.30	7	59.99	2.209	3.30
4	29.98	2.204	3.31	8	79.97	2.217	3.34
5	39.98	2.207	3.31	9	100.00	2.217	3.30

[a] Measurements were made in each case on two cells and their average and maximum deviation from the average value shown above was 0.015 and 0.025%, respectively.

Corrections for solutions of Series C were obtained directly from the smooth curve drawn through the conductivity values obtained for Series B as in Fig. 3. The curve of these corrected values for Series C (C minus B), shown in Fig. 3 as C − B, is almost exactly parallel to the original curve C.

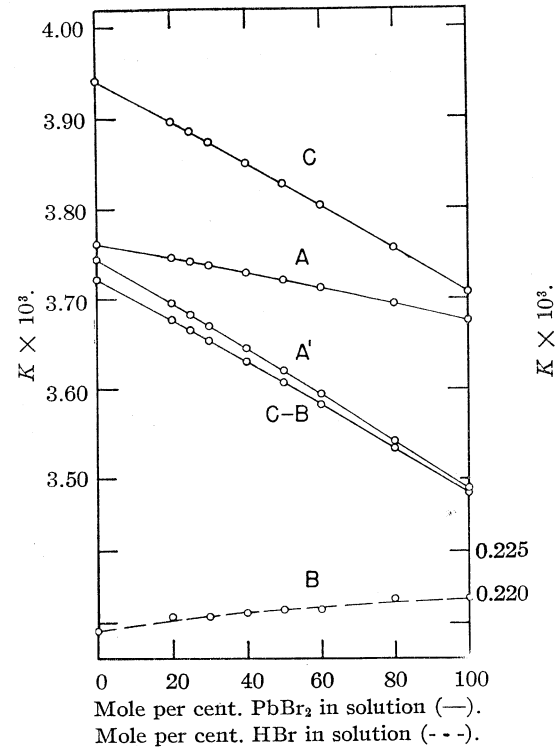


Fig. 3.—Conductivity of aqueous solutions of $PbCl_2$–$PbBr_2$ system, and of HCl–HBr system (pH 3.30).

The corresponding corrections for solutions of Series A were made from an estimate of the total acid present, using the value of 425 as a composite equivalent conductance for both acids. That no appreciable change in the amount of each acid occurred on mixing the stock solutions is shown in Table V by the agreement between the values of the pH calculated and observed for each Series A solution. The corrected conductivities for Series A are shown in Table V and in Fig. 3, as A′.

TABLE V

CORRECTED CONDUCTIVITIES OF SERIES A SOLUTIONS

Solution	Estimated acidity N × 10^4 HCl	HBr	pH Calcd.	pH Found	Specific conductivity × 10^3 Mixed acid	Corrected
A1	0.39	..	(4.41)	4.41	0.017	3.744
A2	.31	0.87	3.93	3.97	.050	3.696
A3	.29	1.09	3.86	3.90	.059	3.683
A4	.27	1.31	3.80	3.83	.067	3.670
A5	.23	1.74	3.70	3.71	.084	3.645
A6	.20	2.18	3.62	3.63	.101	3.620
A7	.16	2.62	3.56	3.56	.118	3.594
A8	.08	3.49	3.45	3.43	.152	3.543
A9	..	4.36	(3.36)	3.36	.185	3.480

The failure of the two corrected curves, A′ and C − B, to superimpose exactly must be attributed

to the fact that the ionic equilibria involved in each series, particularly with regard to intermediate ions formed from the lead halides, are influenced by the amount of halogen acids present. The closer agreement obtained for the lead bromide end is, of course, due to the similarity of the compositions of the two lead bromide solutions, so that there is really no assurance that these corrected conductivities are a measure of the "conductivity of lead bromide" independent of the *p*H of the solutions used.

Another interesting point is that, for both series, the conductivity of the lead bromide solution was lower than that of the lead chloride solution. This was unexpected, inasmuch as the Br^- ion has a higher limiting ionic conductivity than the Cl^- ion. It is also contrary to the report of Delgery,[2c] who, strangely enough, shows the bromide to be more conducting than the chloride in the two more concentrated solutions, and less conducting in the most dilute solution she measured.

For comparison, the conductivity results reported by Delgery[2c] for the lead chloride–lead bromide system are shown in Fig. 4 for 0.0245 molar Pb, together with the present results. These results, as well as those for the other binary halide solution systems, which seemed improbable, must now be considered erroneous and should be disregarded.

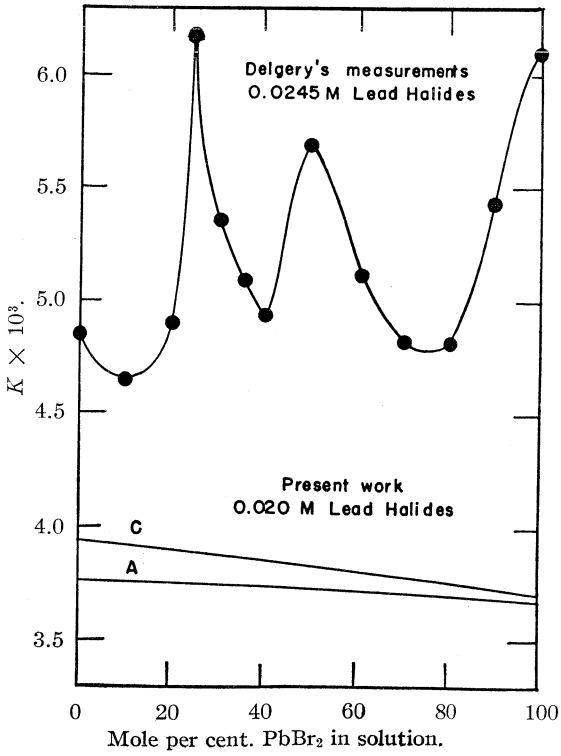


Fig. 4.—Comparison of conductivity of aqueous solutions of the lead chloride–lead bromide system.

Aqueous Preparations.—These were undertaken to check the claim by Thomas[4] that a compound $PbBr_2 \cdot 3PbCl_2$ could be prepared from an aqueous solution; to determine whether it was possible to prepare from aqueous solutions any given solid solution of this system; and to determine whether the X-ray diffraction characteristics of solid solutions of this system prepared from aqueous solution were different from those of solid solutions prepared by fusion.

A. The preparation of $PbBr_2 \cdot 3PbCl_2$ was attempted using the method of Thomas[4] but on a larger scale and by collecting the entire crystalline product for three temperature intervals (see Experimental Part). The results are given in Table VI. The estimated ranges of composition of the solid solutions are given in the last column, where the smallest figure is based on the assumption that the contaminant is entirely potassium bromide and the largest on the more plausible assumption that it is entirely potassium chloride. These results show that the composition of the solid solution crystallizing out is not constant as Thomas claimed.

TABLE VI

ATTEMPTED PREPARATION OF $PbBr_2 \cdot 3PbCl_2$ USING THOMAS' METHOD

Fraction	Temp. range, °C.	Yield, g.	Analyses, % Pb	Br	Cl	K	Composition, mole % $PbBr_2$
1	90–70	7.3	68.21	14.96	16.55	0.10	28.3–28.7
2	70–50	5.4	68.56	14.34	17.01	.08	27.0–27.3
3	50–23	4.0	69.22	12.33	18.23	.09	22.8–23.2

X-Ray diffraction patterns in the back-reflection region of these samples were among the sharpest obtained for solid solutions of this system, and a comparison of these patterns clearly showed a progressive shift in lines, again demonstrating the difference in composition of these samples. The non-existence of this "compound" is further supported by the fact that except for very slight line shifts, forward-reflection patterns of the first and third samples were identical with those of the fused 25 mole % preparation.

B. The Preparation of Solid Solutions of Predetermined Composition.—It has been shown in a study of the effect of alkali and alkaline earth chlorides and bromides on the solubility of lead chloride and lead bromide,[10] that all the solubility curves obtained possess a common minimum for a range of concentration of soluble halides from about 0.3 to about 0.7 *N*. It was therefore expected that if no compounds or favored composition existed, the addition of lead ion to a solution containing both bromide and chloride ions in this concentration range would result in the precipitation of a solid solution containing the same chlorine–bromine ratio as the solution. To simplify the problem of purification of the product, hydrobromic and hydrochloric acids were selected as the soluble halides and lead acetate as the soluble lead salt. (Even if salts were used for the

(10) Herz and Hellabrant, *Z. anorg. allgem. Chem.*, **130**, 188 (1923).

halides, some acid would have been necessary to avoid hydrolysis.) The effect of hydrochloric acid on the solubility of lead chloride[10,11] fits into the same general picture. As far as the authors are aware, no comparable data exist for the effect of hydrobromic acid on the solubility of lead bromides.

The actual preparations are described in the Experimental Part. The preparations were analyzed chemically and studied by X-ray diffraction. The results of analysis showed the products to vary in composition from 48.3 to 57.5 instead of from 35 to 65 mole % lead bromide, as expected. The data for these experiments are summarized in Table VII. The last column of Table VII gives the estimated composition of the mixed acid remaining after the addition of lead acetate and is based on the estimate made from Herz and Hellabrant's data[10] that 0.004 mole of lead ion remains in solution. That aging was not an important factor in determining composition was shown in an experiment in which the initial precipitate from a solution of the same composition as that used for Aq 1 was immediately recovered and was found, by X-ray diffraction, to be close to 50 mole % lead bromide.

TABLE VII

COMPOSITION OF SOLID SOLUTIONS OF LEAD CHLORIDE AND LEAD BROMIDE OBTAINED BY PRECIPITATION FROM MIXED HCl–HBr SOLUTIONS

Solid solution	Initial mole % HBr of mixed acid	Analysis of precipitates % Br	% Cl	Mole % $PbBr_2$ in precipitates	Calcd. mole % HBr in soln. in equil. with precipitate
Aq 1	35	23.96	11.39	48.3	32.0
Aq 2	45	25.60	10.40	52.2	43.3
Aq 3	50	25.73	10.39	52.4	49.5
Aq 4	50	25.64	10.40	52.2	49.5
Aq 5	55	26.29	10.09	53.6	55.3
Aq 6	65	27.88	9.14	57.5	66.7

The last two columns of Table VII correspond to the equilibrium compositions obtained by G. Meyer[7] for the solid solution and the solute in the system $PbCl_2$–$PbBr_2$–H_2O. For comparison, the two sets of data are shown in Fig. 5. The similarity between the two systems is striking. In fact, the only effect of the presence of 0.85 *N* mixed acids (considering the 0.21 *N* acetic acid present to be without influence) is to shift the equilibrium compositions of the solid solutions about 2% toward the lead bromide axis. This effect may in part be ascribed to the greater acid strength of hydrobromic acid, and is apparently superimposed on the tendency to form the 50 mole % lead bromide solid solution.

While G. Meyer pointed out that this relationship between the equilibrium compositions of solute and solid solution of the $PbCl_2$–$PbBr_2$–H_2O system is exactly similar to that found for the

(11) Kendall and Sloan, THIS JOURNAL, **47**, 2306 (1925).

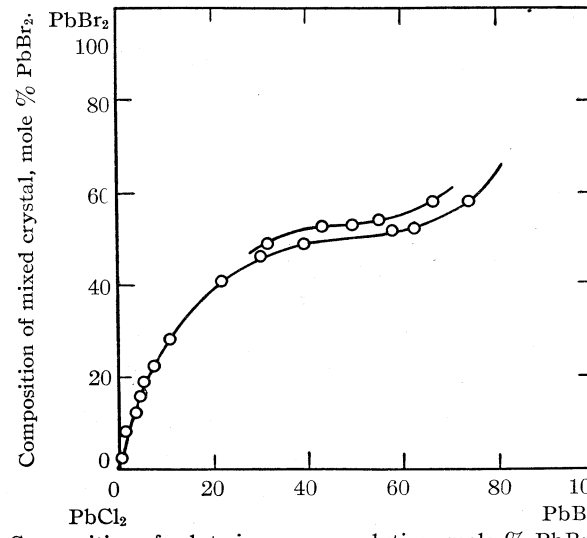


Fig. 5.—Lead chloride–lead bromide mixed crystals in equilibrium with their aqueous solution: lower curve, $PbCl_2$–$PbBr_2$–H_2O system from G. Meyer; estimated temperature, 20°; upper curve, present data for 0.85 *N* mixed acid; approximate temperature, 23°.

permutites by Hisschemöller[12] and was therefore explainable on the basis that a compound, $PbCl_2 \cdot PbBr_2$, existed, he felt that it could also be due to physical forces alone. The present results, however, clearly demonstrate that not all compositions of solid solutions of lead chloride and lead bromide are equally likely to form; in other words, chloride and bromide ions do not enter the crystal lattice on the basis of statistical probability alone.

The results obtained in repeating Thomas' preparation of the 25 mole % lead bromide solid solution can now be qualitatively explained on the basis of the tendency to form the 50 mole % composition, if the same relationship between the composition of the solid solution and the solute in aqueous solution is assumed to hold for the system $PbCl_2$–KBr–H_2O at the various temperatures used as for the $PbCl_2$–$PbBr_2$–H_2O system at 20°. On this basis, the composition of the solid solutions for the various fractions would have been 34.5, 28 and 19 mole %, respectively, instead of the 28.5, 27, and 23 mole % lead bromide actually obtained.

X-Ray Diffraction.—Lead chloride and lead bromide[13] are orthorhombic, with four molecules per unit cell, and belong to space group V_h^{16}, with all atoms occurring in special positions (c). Their lattice constants (Table IX) differ from their mean value by less than 3%, and they would be expected to form a continuous series of solid solutions and to obey Vegard's law for solid solutions.

An X-ray diffraction study was made of nine

(12) Hisschemöller, *Rec. trav. chim.*, **40**, 394 (1921).

(13) (a) Bräkken, *Z. Krist.*, **83**, 222 (1932); (b) Bräkken and Harang, *ibid.*, **68**, 123 (1928); (c) Döll and Klemm, *Z. anorg. Chem.*, **241**, 247 (1939); (d) Nieuwenkamp and Bijvoet, *Z. Krist.*, **84**, 49 (1933); (e) Wyckoff, "The Structure of Crystals," 2nd ed., suppl., Chemical Catalog Co., New York, N. Y., 1935, p. 27.

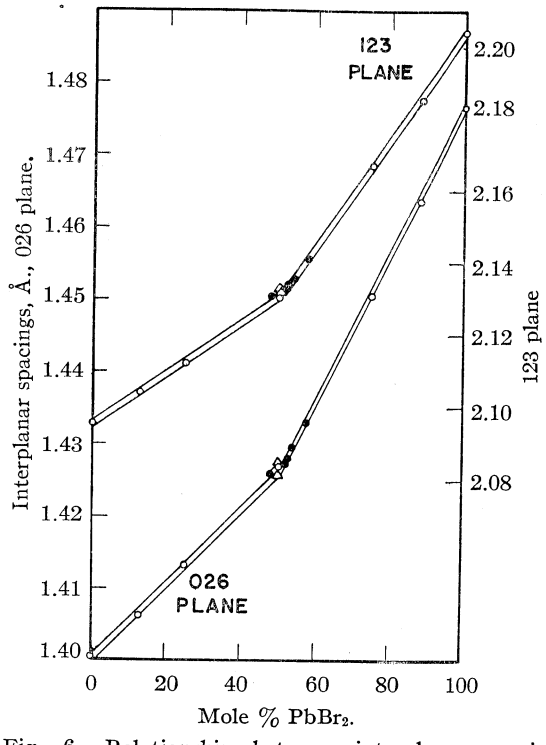


Fig. 6.—Relationship between interplanar spacings and compositions for the 123 and 026 planes in the $PbCl_2$–$PbBr_2$ system. The lines show the effect of an error of $\pm 0.02°$ in 2θ. Legend: ○, fused; ●, aqueous; △, heat-treated preparations.

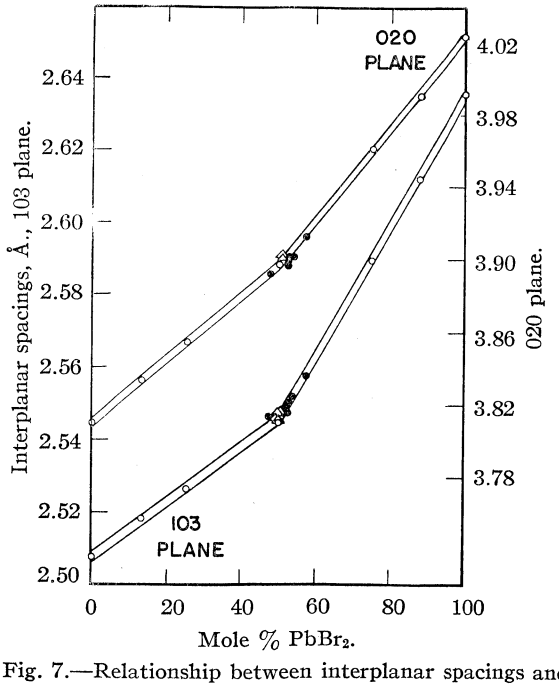


Fig. 7.—Relationship between interplanar spacings and compositions for the 020 and 103 planes in the $PbCl_2$–$PbBr_2$ system. The lines show the effect of an error of $\pm 0.02°$ in 2θ. Legend: ○, fused; ●, aqueous; △, heat-treated preparations.

fused preparations of the lead chloride–lead bromide system. In a preliminary examination of 2 r. p. m. automatic recordings in the forward-reflection region obtained with a Norelco Geiger-counter X-ray spectrometer using Cu K_α radiation, line-shift measurements showed a discontinuity at the 50 mole % composition indicative of a compound, PbClBr, isomorphic with lead chloride and lead bromide and forming a complete series of solid solutions with each of these compounds. The preliminary investigation also reveals discontinuities in the progressive changes in relative intensities of a number of lines at the 50 mole % composition, which gave further support to the above hypothesis.

In view of these unexpected results more accurate determinations of the Bragg angles were made by manual scanning measurements, which gave 2 θ values reproducible to $\pm 0.01°$. Making allowance for error in applying the calibration data, the total experimental error in 2 θ measurement should not be over $\pm 0.02°$.

Manual scanning data were obtained for the 002, 020, 026, 103, 123 and the unresolved 212, 114 planes of most of the fused preparations. The average d values in Ångström units for the first five planes are given in Table VIII. The interplanar spacings–composition data are shown in Figs. 6 and 7 for the 123, 026, 020 and 103 planes. From

TABLE VIII

INTERPLANAR SPACING VALUES FOR LEAD CHLORIDE–LEAD BROMIDE SYSTEM

Sample	Mole % $PbBr_2$	Interplanar spacing values in Å. Plane 026	Plane 123	Plane 103	Plane 020	Plane 002
F 0	0.00	1.4008	2.0958	2.5079	3.8101	4.5193
F 1	12.8	1.4071	2.1044	2.5182	3.8324	4.5393
F 2	25.2	1.4133	2.1128	2.5262	3.8536	4.5564
F 4	50.0	1.4268	2.1307	2.5448	3.8971	4.5944
F 6	74.9	1.4503	2.1672	2.5897	3.9611	4.6796
F 7	88.1	1.4635	2.1850	2.6122	3.9902	4.7164
F 8	100.0	1.4768	2.2040	2.6360	4.0238	4.7612
Av. dev.[a]		±0.0001	0.0004	0.0005	0.0006	0.0028
H 1	49.9			2.5451		
H 2	50.2	1.4264	2.1322	2.5473	3.8992	
H 3	50.3	1.4273	2.1321	2.5483	3.8995	
H 4	50.0			2.5463		
Aq 1	48.3	1.4260	2.1310	2.5458	3.8921	
Aq 2	52.2	1.4277	2.1337	2.5483	3.8989	
Aq 3	52.4	1.4280	2.1342	2.5504	3.9001	
Aq 4	52.2	1.4284	2.1341	2.5496	3.8973	
Aq 5	53.6	1.4295	2.1360	2.5525	3.9008	
Aq 6	57.5	1.4329	2.1413	2.5581	3.9123	
Av. dev.[a]		±0.0002	0.0003	0.0004	0.0006	
Calcd. ± exptl. error[b]		0.0004	0.0010	0.0013	0.0031	0.0046

[a] Each of the individual interplanar spacing values represents the average of 2 or 3 determinations. The average deviation for each plane is based on 18 to 20 individual determinations for the fused preparations and 24 to 29 for the heat-treated and aqueous preparations. [b] The calculated experimental error is based on a $\Delta 2\theta$ of $\pm 0.02°$.

these figures, discontinuities in interplanar spacings can be seen at the 50 mole % composition, which is in agreement with the preliminary observations made from the automatic scanning records.

In order to determine whether the results of X-ray diffraction were in any way due to a distortion of the crystal lattice in the fused preparations, an investigation was made of heat-treated and aqueous preparations. The compositions of the heat-treated preparations were held close to the 50 mole % composition, since the effect of line-shift measurements should be most pronounced at this composition. Heat treatment included slow crystallization, prolonged annealing and slow cooling. Manual scanning data were obtained for the heat-treated and aqueous preparations. The average interplanar spacing values are given in Table VIII, and Figs. 6 and 7. It is evident that any changes produced in interplanar spacing values for the 026, 123 and 020 planes by heat treatment are within the experimental error. The increases in d values noted for the 103 plane are only slightly greater than the experimental error and may or may not be real. If real, a possible explanation might be that the adjustment of the crystal lattice took place primarily along the a-axis. Preparations from aqueous solution likewise show no significant differences.

A least squares treatment was used to calculate the lattice constants for each composition from the manual scanning data obtained on the 002, 020, 026, 103 and 123 planes. The lattice constants, axial ratios and unit cell volumes are given in Table IX. The lattice constants for lead chloride and lead bromide show good agreement with the literature values.

TABLE IX

LATTICE CONSTANTS, AXIAL RATIOS AND UNIT CELL VOLUMES FOR LEAD CHLORIDE–LEAD BROMIDE SYSTEM

Mole % $PbBr_2$	Lattice constants in Å. a	b	c	Axial ratios a	b	c	Unit cell vol., Å.^{3}
0.0	4.5301	7.6220	9.0375	0.594	1	1.186	312.1
12.8	4.5424	7.6644	9.0767	.593	1	1.184	316.0
25.2	4.5477	7.7074	9.1147	.590	1	1.183	319.5
50.0	4.5616	7.7949	9.1985	.585	1	1.180	327.1
74.9	4.6511	7.9209	9.3520	.587	1	1.181	344.5
88.1	4.6850	7.9798	9.4384	.587	1	1.183	352.9
100.0	4.7249	8.0461	9.5255	.587	1	1.184	362.1
VALUES CALCULATED FROM THE LITERATURE[a]							
$PbCl_2$	4.534	7.623	9.048	0.595	1	1.187	(B.[13c] 1932)
$PbCl_2$	4.529	7.620	9.045	.594	1	1.187	(D. & K.[13c] 1939)
$PbBr_2$	4.725	8.036	9.504	.588	1	1.183	(N. & B.[13d] 1933)
$PbBr_2$	4.727	8.054	9.537	.587	1	1.184	(D. & K.[13c] 1939)

[a] Lattice constants converted from kX. units to Ångström units.

The relationships of lattice constants and unit cell volume with composition are shown in Fig. 8.

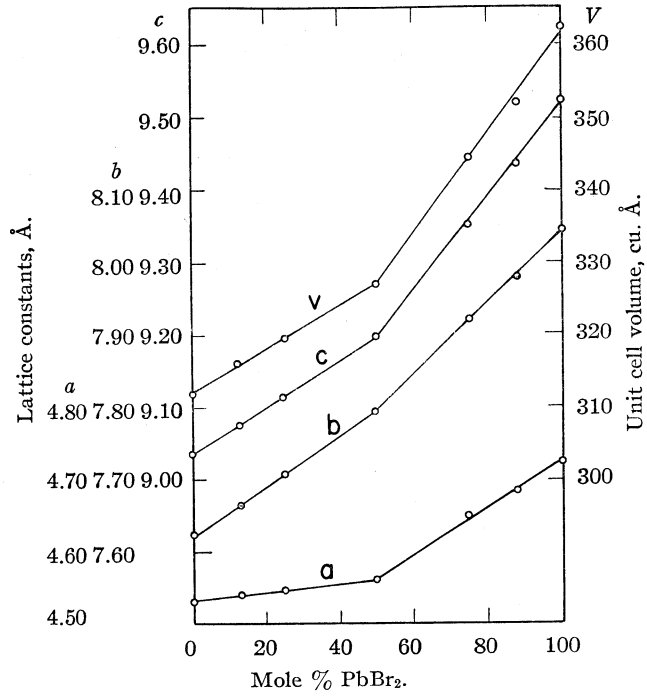


Fig. 8.—Relationship of lattice constants and unit cell volume with composition for the $PbCl_2$–$PbBr_2$ system.

As would be expected from the interplanar spacings-composition relationships, these data are best represented by two straight lines intersecting at the 50 mole % composition. From this it may be concluded: (1) that the replacement of chloride ions by bromide ions expands the crystal lattice at a slower rate from 0 to 50 than from 50 to 100 mole % lead bromide. This difference in rate of expansion is most pronounced for the a-axis and least for the b-axis (Fig. 8; also the 020 plane, Fig. 7); (2) that the compound or ordered structure at the 50 mole % composition has definite axial ratios independent of the method of preparation. These axial ratios are unique, being minimum values for the system.

According to Nieuwenkamp and Bijvoet,[13d] the halide ions of the isomorphic compounds lead chloride and lead bromide occupy two inequivalent positions in the crystal lattice, designated as X′ and X″. Also, the Cl″ and Br″ ions have a slightly larger space volume around them in their respective lattices than the Cl′ and Br′ ions. From this it was theorized that a preferential replacement of the Cl″ ions is taking place from the 0 to 50 mole % lead bromide compositions, leaving only the Cl′ ions for replacement from the 50 to 100 mole % compositions. This would explain the lower rate of expansion of the unit cell from 0 to 50, since there is more space for the larger bromide ion at the Cl″ ion positions than at the Cl′ ion positions in the crystal lattice. On the basis of this theory, the 50 mole % composition might then be considered to be a preferential-replace-

TABLE X

RELATIVE INTENSITIES FOR LEAD CHLORIDE–LEAD BROMIDE SYSTEM

Mole % $PbBr_2$	Miller indices 002	101	012	020	111	121	103	113	032	123	212, 114
0.0	0.30	0.42	1.00	0.42	0.94	0.56	0.65	0.09	0.27	0.45	0.31
12.8	.21	.34	0.91	.47	1.00	.72	.62	.09	.35	.43	.32
25.2	.18	.29	.99	.46	0.98	.86	.63	.12	.37	.43	.33
36.0	.15	.28	.92	.39	.98	.96	.58	.14	.39	.42	.36
50.0	.07	.22	.93	.35	.90	1.00	.57	.18	.42	.38	.34
62.5	.11	.21	.75	.35	.80	1.00	.58	.15	.41	.38	.32
74.9	.20	.24	.74	.40	.84	1.00	.66	.13	.39	.42	.28
88.1	.28	.26	.68	.35	.78	1.00	.82	.13	.43	.48	.26
100.0	.64	.37	.74	.45	.70	0.94	1.00	.17	.41	.55	.22

TABLE XI

COMPARISON OF CALCULATED AND EXPERIMENTAL INTENSITIES FOR LEAD CHLORIDE–LEAD BROMIDE SYSTEM

Plane	Observed relative intensities,[a] I/I $PbCl_2$	50 mole %	$PbBr_2$	Calculated intensities[a] $I \times 10^{-5}$ $PbCl_2$	$PbCl'Br''$	$PbCl''Br'$	Random	$PbBr_2$
002	0.30	0.07	0.64	0.20	0.12	0.33	0.21	0.21
101	0.43	.22	.37	.17	.05	.25	.13	.10
012	1.00	.93	.74	.47	.44	.32	.38	.29
020	0.42	.35	.45	.80	.71	.87	.79	.78
111	.94	.90	.70	.63	.64	.43	.53	.44
121	.56	1.00	.95	.34	.55	.36	.45	.57
103	.65	0.57	1.00	.95	.98	1.34	1.15	1.37
113	.09	.18	0.17	.008	.012	0.011	0.012	0.016
032	.27	.42	.41	.60	.70	.72	.71	.82
212, 114	.31	.34	.22					
212				.33	.31	.21	.26	.19
114				.009	.068	.0003	.015	.022
212 + 114				.329	.378	.210	.275	.212
123	.45	.38	.55	.61	.59	.66	.63	.65

[a] The experimentally determined relative intensities have not been corrected, and the calculated intensities have not been converted to relative intensities, so that while comparisons of intensities may be made for any one plane for various structures, they cannot be made from plane to plane for any one structure.

ment structure, $PbCl'Br''$, and would explain the discontinuity observed in the lattice constant–composition relationships.

As a further check on the existence of the preferential-replacement form $PbCl'Br''$, a comparison was made of calculated and experimental relative intensities of a number of the reflections. This was of particular interest since discontinuities were noted in the progressive changes in relative intensities of several lines at the 50 mole % composition. The relative intensities (I/I_1) of 11 lines were evaluated for the fused compositions from 1 r. p. m. automatic recordings taken on quadruplicate specimen preparations. A rotating sample mount was used to decrease preferred orientation effects. A summary of the average observed relative intensities for each composition is given in Table X, from which it is noted that at the 50 mole % composition there is either an actual reversal in the progressive changes of relative intensities, as for the 002 plane, or there is an abrupt change in their rate, as for the 121 plane.

Using the structure factor formula[14] for lead chloride and lead bromide, the intensities for the above 11 reflections were calculated for lead chloride, lead bromide and the three possible forms at the 50 mole % composition: namely, the form in which there is random replacement of Cl′ and Cl″ by Br′ and Br″ and the two forms in which there is preferential replacement, $PbCl'Br''$ and $PbBr'Cl''$. The calculated intensities and the experimental relative intensities are given in Table XI. The calculated intensity values for the "ordered" form, $PbCl'Br''$, fit the trend of the experimental relative intensities at the 50 mole % composition better than either the "ordered" form $PbBr'Cl''$, or the random form. This is true for each of the planes calculated except the 113 and 032 planes where the calculated intensities for the three forms are nearly the same. It is interesting to note that the sum of the calculated intensities for the 212 and 114 planes of the "ordered" form, $PbCl'Br''$, is in good agreement with the trend of the observed relative intensity for the 212, 114 plane (not resolved) at the 50 mole % composition. The results of the intensity study thus support the theory that a preferential-replacement structure occurs at the 50 mole % composition and indicate that it is $PbCl'Br''$. Thus, the line-shift and intensity data both indicate that the "ordered" form is a "compound"

(14) "Internationale Tabellen zur Bestimmung von Kristallstrukturen," Vol. I, rev. ed., The Chemical Catalog Co., New York, N. Y., 1944, p. 138.

stable at room temperature, isomorphic with lead chloride and lead bromide and forming a complete series of solid solutions with both pure components.

Discussion

The present thorough study of the lead chloride–lead bromide system shows it to be a somewhat unique salt system, containing an "ordered" structure at the 50 mole % composition, stable at room temperature. Since the lattices of the two isomorphous components possess two sets of halogen positions with different space volumes, the opportunity arises for the formation of a unique type of ordering as one halogen is replaced by the other in such a way as to cause the least dimensional change in the lattice. Consequently, as bromine is substituted for chlorine in the lead chloride lattice, it preferentially replaces the chlorine from the more spacious Cl″ positions until these are completely replaced, forming a continuous series of solid solutions culminating in the formation of the "ordered" structure, PbCl′Br″. Upon further substitution of bromine for chlorine, the less spacious Cl′ positions are occupied, and this forms another continuous series of solid solutions ending with lead bromide. In this second series, the rate of expansion of the unit cell with change in composition is necessarily greater than in the first series of solid solutions. This interpretation not only accounts for the discontinuities observed in the lattice constants–composition relationships for the system, but it has also been shown to account for the discontinuities observed in the relative intensities–composition data.

If the structure PbCl′Br″ were a compound which was at all stable in the range of temperatures defined by the thermal diagram of the system, one would expect the liquidus and solidus curves to approach or meet at the 50 mole % composition, as in the bromine–iodine system.[15] Since this is not the case (Fig. 2), it is clear that PbCl′Br″ does not exist as a compound in this temperature range. For this reason, the preferential-replacement structure may be considered a borderline compound which is stable only at lower temperatures.

The fact that no transition temperature was observed, even in the annealing and slow-cooling of the 50 mole % composition may be due either to the fact that the heat of transition is too small for detection with the present method, or to the fact that the transition occurs over a range of temperatures.[16] Furthermore, two samples of 50 mole % composition which were quenched from the solidus temperature, where they had been held for an hour, to that of a Dry-Ice–chloroform bath, showed no measurable degree of randomness at room temperature. If the transition to the preferential-replacement structure does not occur in the temperature–composition region immediately below the solidus curve for the system, it occurs rapidly and completely at lower temperatures, since the X-ray diffraction characteristics of any solid solution of this system appear to be independent of sample history.

The results obtained in the attempted preparation of solid solutions of lead chloride and lead bromide of predetermined composition by precipitation from solutions containing excess hydrochloric and hydrobromic acid, and those of G. Meyer on the lead chloride–lead bromide–water system, demonstrated the definite tendency of the 50 mole % composition to crystallize out, which appears to further support the existence of the "ordered" structure PbCl′Br″ as a borderline compound.

The results and conclusions of the present study are completely at variance with those reported by Delgery for this system.[2] Furthermore, we are unable to account for the striking differences which exist between her thermal analysis and those of other investigators[3] (Fig. 1), including the present one (Fig. 2). Based on her thermal analysis, Delgery claimed the existence of a high-temperature stable compound, PbClBr, and a peritectic compound, $PbBr_2 \cdot 3PbCl_2$, both of which Thomas[4] had previously claimed to prepare. Thomas' preparation of the first composition by heating PbClI in a current of bromine is obviously no evidence for a compound, and we were unable to confirm his preparation of the second. Likewise, we are unable to account for the striking differences which exist between Delgery's conductivities for this system and our own (Fig. 4). We have shown that hydrolysis does not account for the unexpected variations in conductivity which she reported; neither would the possible presence of excess solid phase in her lead chloride–lead bromide solutions, since the system possesses only one minimum in solubility. All her conductivity-composition curves for solutions of binary lead halide systems show sharp conductivity maxima, of a type never observed before, and not readily interpretable on the basis of accepted theories. It is also noteworthy that these maxima are reported at compositions which were precisely the same as those of compounds which she had initially observed or was able to confirm afterward by thermal analysis.

Acknowledgment.—It is a pleasure to acknowledge the assistance of Loren M. Knowles in making the thermal runs and completing several aqueous preparations, and of Gordon E. Noakes and Berol L. Robinson in securing X-ray diffraction data. We are also indebted to Profs. Lewis S. Ramsdel and A. L. Ferguson, University of Michigan, respectively for valuable suggestions in the interpretation of the X-ray diffraction data and for making electrochemical equipment available for the conductometric studies.

(15) Terwogt, *Z. anorg. Chem.*, **47**, 203 (1905).

(16) See, for example, the discussion of ordered and disordered phases for Seitz, "Modern Theory of Solids," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 35–36 and 502–511.

Summary

The lead chloride–lead bromide system has been studied by means of thermal analysis, conductivity, aqueous preparations and X-ray diffraction. No binary compounds exist in this system other than the preferential-replacement structure, PbCl′Br″, whose existence was demonstrated by the X-ray diffraction data. This "ordered" structure is stable at room temperature but not at the melting point, is isomorphous with lead chloride and lead bromide, and forms a complete series of solid solutions with both.

DETROIT, MICHIGAN RECEIVED APRIL 25, 1949

[CONTRIBUTION FROM THE LABORATORIES OF DISTILLATION PRODUCTS, INC.]

Vapor Pressures of Phlegmatic Liquids. I. Simple and Mixed Triglycerides[1]

BY E. S. PERRY, W. H. WEBER AND B. F. DAUBERT[2]

The vapor pressure measurements of phlegmatic[3] liquids, such as the triglycerides, require a method which imposes a minimum of thermal hazard to the substance under examination. Of the available methods capable of accommodating materials of this kind, the static method of Hickman, Hecker and Embree[4] employing the pendulum tensimeter appeared to be more promising than the dynamic methods proposed by Verhoek and Marshall[5] and Kapff and Jacobs.[6] In application, the dynamic methods have been limited to the vapor pressure measurements of plasticizer-type esters in the range of 10^{-2} to 10^{-4} mm. at 40 to 160°. The pendulum-tensimeter method, however, has been used with substances of lower volatilities which have perhaps even less thermal stability than the ester materials, such as, for example, 1,4-dipropyldiaminoanthraquinone. In addition, the method gives absolute pressure measurements in that the pressure of the vapor is measured directly as a force per unit area. In contrast to the dynamic methods, therefore, the results are independent of the theoretical equations of the kinetic theory and errors introduced by inaccuracies in accommodation coefficients are obviated. For these reasons the pendulum-tensimeter method seemed most generally applicable for the measurements reported below. In the present paper are presented the vapor pressures for a large number of triglycerides, including all of those having an even number of carbon atoms in the acid radical from tributyrin to tristearin; for mixed triglycerides, both saturated and unsaturated; and for several fractionated natural fats. In a subsequent paper[7] there will be presented the vapor pressures of a number of high molecular weight esters of the plasticizer and diffusion pump fluid types.

The theory for the pendulum-tensimeter method has been reported by the original authors,[4] therefore only the final equations will be reproduced here for convenience. The vapor pressure P is calculated from the effective weight of the pendulum M, the area of the orifice A, and the angular displacement θ, according to the relationship: $P = M/A \times \sin \theta$. For our specific apparatus the vapor pressure in mm. mercury is: $P = 1.075/8.96 \times 13.6 \times 10 \times \sin \theta = 0.0882 \times \sin \theta$.

Experimental

Apparatus.—A pendulum-tensimeter similar to that of Hickman, Hecker and Embree,[4] but incorporating the orifice heater recommended by Verhoek and Marshall,[5] was used. A small liquid trap was added to the reflux line to prevent loss of vapor from the boiler. The usual oil-bath was replaced by an air-bath so that the temperature range could be extended. This consisted of an aluminum box approximately 9″ × 9″ × 5″, lagged with asbestos paper. The first air-bath contained a single heater element wound in a flat coil and mounted just off the floor of the box. The heater was shielded and baffled to prevent irregular heating by radiation. Heat distribution in the box was examined by placing 8 thermometers at various points and recording the temperatures of each as the heat was progressively increased to 300°. A satisfactory heat distribution was not obtained by this method regardless of the baffle used and it was finally discarded in favor of one which responded better to the test. The new heater element consisted of a glass rod frame on which was wound asbestos-covered resistance wire equivalent to 1000 watts. The glass frame was cubical in shape and dimensioned so as to leave a half-inch space between it and the walls of the box on all sides. Resistance wire was wound evenly on all 12 rods of the frame. Power was controlled by a variable transformer. Air temperatures measured at various points in the box by means of thermometers as discussed above showed that the total disparity in temperatures was not over 2°. The bath was therefore used as such without any further attempts to better distribute the heat.

The aluminum box with heating element hung from a yoke which straddled the tensimeter and was supported so that it could rotate with the tensimeter. Two Pyrex windows were provided for better illumination and direct observation of the pendulum at the orifice. One window was located on the front wall of the box and the other on the rear wall. The use of the air-bath greatly facilitated the observation of the equilibrium point of the pendulum and thereby increased the reproducibility of the readings. It also extended the effective temperature range to well over 300°.

While collecting data, temperature measurements were made with a well-thermometer which protruded into the

(1) Communication No. 151 from Laboratories of Distillation Products, Inc.

(2) Department of Chemistry, The University of Pittsburgh.

(3) Hickman and Weyerts, THIS JOURNAL, **52**, 4714 (1930).

(4) Hickman, Hecker and Embree, *Ind. Eng. Chem.*, **9**, 264 (1937).

(5) Verhoek and Marshall, THIS JOURNAL, **61**, 2737 (1939).

(6) Kapff and Jacobs, *Rev. Sci. Instruments*, **18**, 581 (1947).

(7) Perry and Weber, THIS JOURNAL, **71**, 3726 (1949).

TABLE I

EXPERIMENTAL DATA AND CALCULATED CONSTANTS OF THE TRIGLYCERIDES

	Material	Temp. (P_1 = 50μ) °C.	°K.	Temp. (P_2 = 1μ) °C.	°K.	A	B	L (cal./mole)	M. p., °C.	Carbon atoms in acid groups	Dühring's rule constant
1	Tributyrin	91	364	45	318	4250	13.37	19,450	.....	12	0.920
2	Tricaproin	135	408	85	358	4950	13.82	22,650	.....	18	.980
3	Tricaprylin	179	452	128	401	6060	15.12	27,800	.....	24	.963
4	Tribenzoin	201	474	148	421	6450	15.30	29,500	75 –76	21	.981
5	Tricaprin	213	486	159	432	6510	15.08	29,800	31.5–32.0	30	.964
6	Trilaurin	244	517	188	461	7190	15.58	32,500	45 –46.5	36	.949
7	Trimyristin	275	548	216	489	7720	15.78	35,300	56 –57	42	1.000
8	Tripalmitin	298	571	239	512	8400	16.40	38,400	64.5–65.5	48	0.983
9	Tristearin	313	586	253	526	8750	16.60	40,000	71 –72	54	
10	1-Capryl-2-lauryl-3-myristin[8]	249	522	189	462	6880	14.90	31,500	36.5–37	36	1.020
11	1-Lauryl-2-myristyl-3-palmitin[8]	275	548	216	489	7720	15.80	35,300	49.5–50	42	0.983
12	1-Myristyl-2-palmityl-3-stearin[8]	297	570	237	510	8250	16.18	37,800	57 –58	48	0.983
13	2-Oleyl-1,3-distearin[9]	315	588	254	527	8660	16.42	39,600	44 –44.5	54	1.033
14	1-Myristyl-2-capryl-3-stearin[8]	274	547	215	488	7750	15.88	35,400	50.5–51.5	42	1.000
15	1-Myristyl-2-lauryl-3-stearin[8]	282	555	223	496	7860	15.84	36,000	53.5–54.5	44	1.034
16	1-Palmityl-2-capryl-3-stearin[8]	280	553	223	496	8090	16.30	37,000	53 –54	44	0.983
17	1-Palmityl-2-lauryl-3-stearin[8]	290	563	232	505	8360	16.55	38,200	56 –57	46	
18	Soybean oil	308	581	254	527	9650	18.30	44,200	.....	54	
19	Olive oil	308	581	253	526	9430	17.92	43,100	.....	54	

boiler and dipped below the surface of the liquid when the usual charge of 20–30 g. of material was used. With smaller charges of 3 to 10 g., the well was slightly above the liquid surface. However, the stem was entirely within the air-bath and the temperatures of the well-thermometer were in agreement with other calibrated thermometers located in the immediate vicinity, although outside of the well. The temperature of the oil layer in the boiler was thus assumed to be at the temperature of the bath.

Materials.—Most of the simple triglycerides were obtained from the Eastman Kodak Company. The mixed triglycerides, tricaprylin and tricaprin, were synthesized and purified at the University of Pittsburgh.[8,9] The simple triglycerides were further purified by molecular distillation and in some cases the distillation was preceded by a recrystallization from solvents. Because the amounts of the mixed triglycerides available were so small, purification had to be limited to recrystallization only. Distillation in the cyclic molecular still consisted of removing three strip cuts, the first of which amounted to 5% of the original charge and the others 10% each. The 2 succeeding 25% fractions were used for the vapor pressure measurements. The natural fats were also prepared by molecular distillation. The olive oil was an imported U. S. P. grade packaged by Magnus, Mabee and Reynard, Inc. Castor oil from several sources was used; two were refined commercial grades and the third was a U. S. P. grade. The corn and soybean oils were refined commercial products. In all cases, the original oil was first distilled into four equal fractions. The two middle fractions were again molecularly distilled, first removing a 25% strip cut and then collecting the succeeding 50% for examination in the tensimeter.

Melting points for most of the triglycerides used are given in Table I.

Procedure.—Most details of the procedure were similar to those recommended by the original authors.[4] Readings were taken after the temperature had reached and maintained a constant value for at least three minutes. Best results were obtained by adjusting the pendulum until it just appeared to float on the vapor, not quite touching the orifice. When sufficient sample was available, a 20- to 30-g. portion was used. With the mixed triglycerides where only limited amounts of material were available, the measurements were made with as little as 3 g. of sample. When using the smaller samples it was necessary to make the readings rapidly so that the material would not all evaporate before the desired temperature range was covered. It was found that results obtained by taking measurements while the temperature rose at the rate of 0.5 to 1° per minute were as good as those taken after the three-minute equilibrating period. This can be verified by an inspection of the results plotted in the figures of the next section. Measurements with all mixed triglycerides were done using this method of temperature increase. Individual temperature readings were taken to 0.5° values. More accurate measurements were not warranted in view of the reproducibility obtained as shown in Figs. 1 to 5.

(8) Chen and Daubert, THIS JOURNAL, **67**, 1256 (1945).

(9) Jackson, Daubert, King and Longenecker, *ibid.*, **66**, 289 (1944).

Results and Discussion

The experimental data for the measurement of all the triglycerides are plotted in Figs. 1 to 5 on the usual log P *vs.* $1/T$ chart. The temperature data given in Table I are not necessarily determined points. These are the temperatures at which the straight lines drawn through the experimental points for each triglyceride intersect the 1- and 50-μ pressure values. This method of listing data was chosen merely as a convenience for permitting accurate reproduction of the vapor pressure curves and thus obviating the necessity of tabulating all of the experimental data in this report. The accuracy of the data, however, can be seen from the curves. In most every case the individual temperature measurements lie on a straight line, with deviations usually not greater than 2° from the line, and in many cases 1°. Data resulting from several independent sets of measurements with the same sample showed that the reproducibility of the curve was within 1°. A 1° variation in the slope of the line corresponds

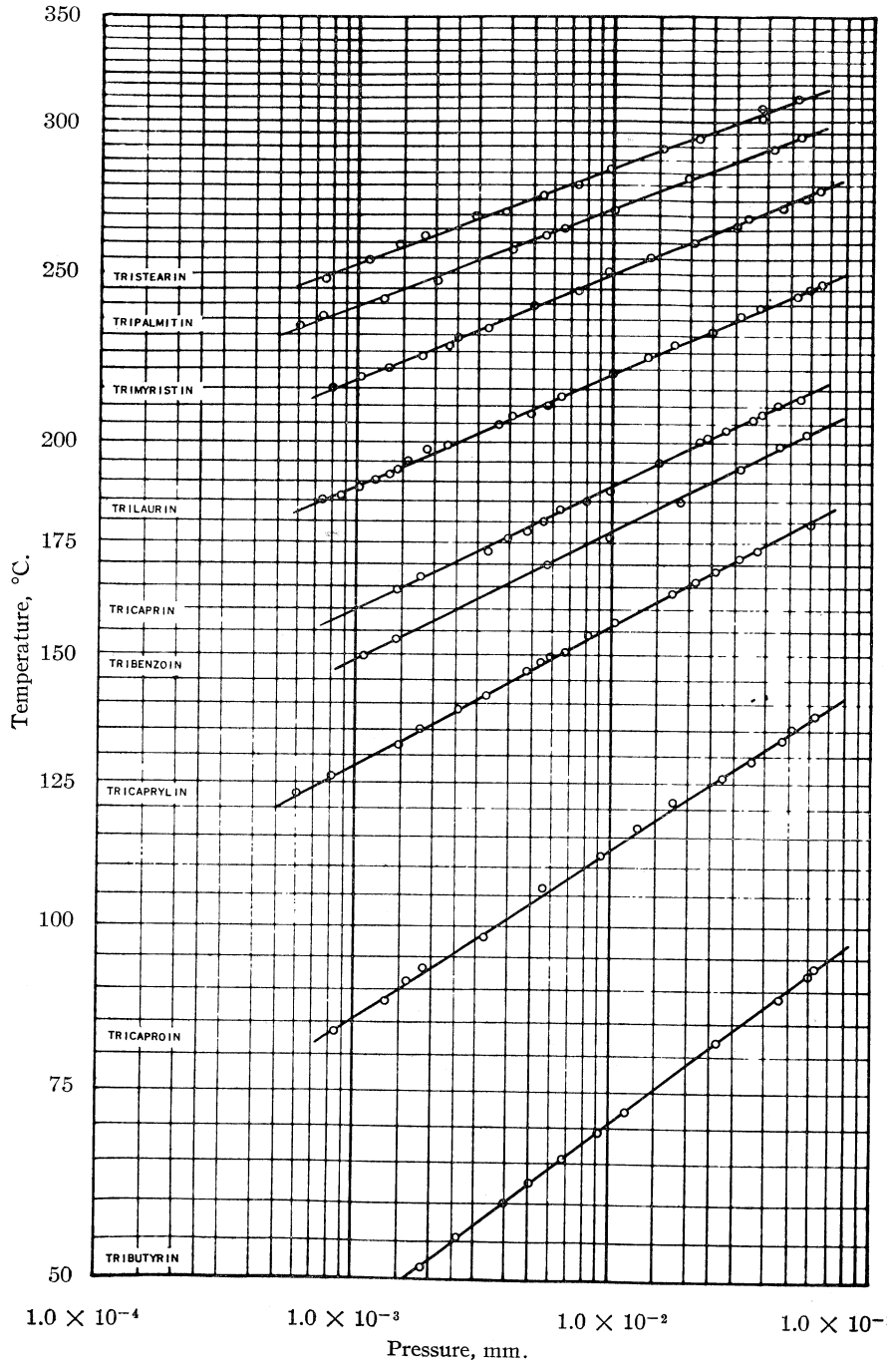


Fig. 1.—Experimental vapor pressure data.

to about a 2% change in the latent heats of vaporizations.

The curves connecting the points for each triglyceride can be expressed by the general equation: $\log P = -A/T + B$, where A represents the slope of the line and B is the y-intercept. These constants have been calculated for each material using the temperatures corresponding to pressures at 50 and 1 μ. The values are recorded in Table I. The latent heats of vaporization L in cal./mole are related to A as follows: $A = L/2.3R$, where R is the universal gas constant. The latent heats for each material have been calculated and are given in column 6 of Table I.

It will be noticed that the slopes of the curves for all triglycerides show a gradual increase as the number of carbon atoms in the acid chain increase. The degree of linearity obtained between latent heats of vaporization and molecular weight is shown by the plot of Fig. 6 in which the computed latent heats for the triglycerides are plotted against the total number of carbon atoms of the fatty acid side-chains. The points on the curve are numbered in accordance with the listing of Table I for the purpose of reference to the triglyceride in question. The adherence to straight line agreement is only fair but the general trend is clearly shown. Tribenzoin (point 4), containing 7 carbon atoms per acid group, 6 of which form an aromatic ring, shows a definite departure from the curve. This is not unexpected since it is known that aromatic groupings usually have lower vapor pressures than do the same number of carbon atoms arranged in open-chains. The vapor pressure–temperature relationship of tribenzoin lies between that for tricaprylin and tricaprin, perhaps being very close to that for an aliphatic triglyceride having 9 carbons in the acid chains.

The vapor pressure curves for the mixed triglycerides are given in Figs. 2, 3 and 4, according to the sequence of the acid groupings in each molecule. These data indicate that the vapor pressure appears to be independent of the group

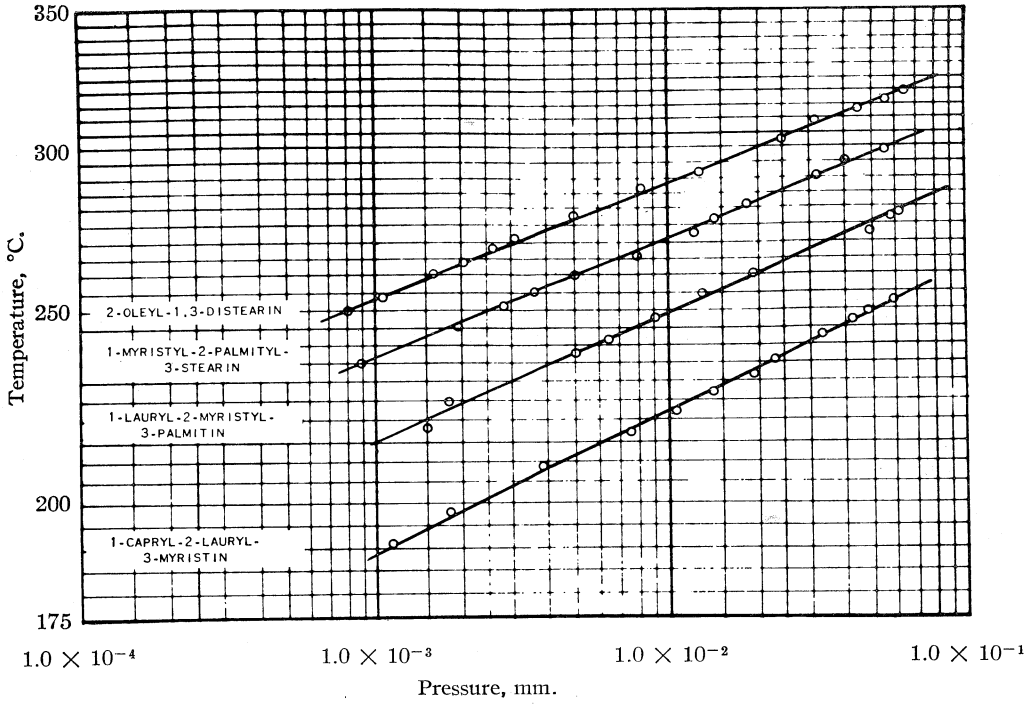


Fig. 2.—Experimental vapor pressure data.

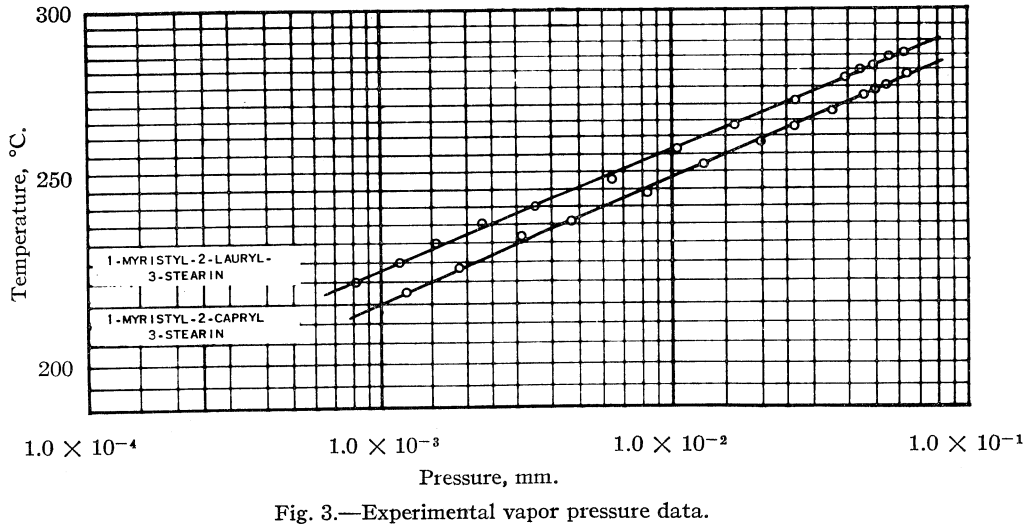


Fig. 3.—Experimental vapor pressure data.

arrangement and the individual chain-length of the acid groups. The principal influence is, perhaps, the total number of carbons in the molecule. For example, the three compounds: trimyristin, 1-lauryl-2-myristyl-3-palmitin and 1-myristyl-2-capryl, 3-stearin—all of which have a total of 42 carbon atoms in the acid groups—have comparable latent heats, as shown by the coincidence of points 7, 11 and 14 of Fig. 6. Likewise, the latent heat for tripalmitin is comparable to that for 1-myristyl-2-palmityl-3-stearin —points 8 and 12. Other correlations of this kind are evident from Fig. 6 or Table I. The effect of one double bond per triglyceride molecule has very little, if any, influence on the vapor pressure, as is shown by comparison of results for 2-oleyl-1,3-distearin with tristearin. The vapor pressure values for tristearin are very slightly higher than those for the oleyl distearin which, if significant, is at variance with the relative order of vapor pressures as would be deduced from boiling point data of saturated compounds and their unsaturated analogs. From the distillation of mixtures of quite pure methyl oleate and methyl stearate, Weitkampf and Brunstrun[10] have shown

(10) Weitkampf and Brunstrun, *Oil and Soap*, **18**, 47 (1941).

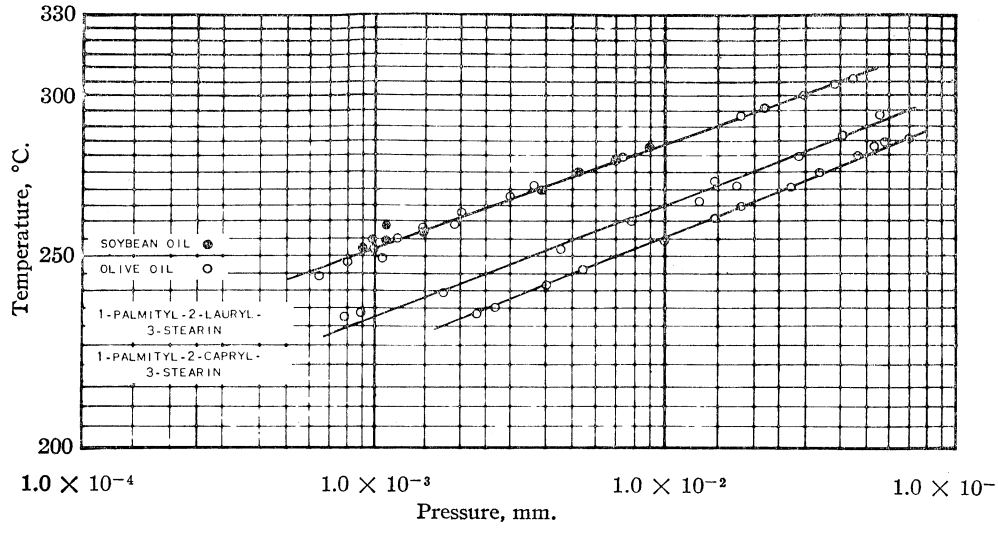


Fig. 4.—Experimental vapor pressure data.

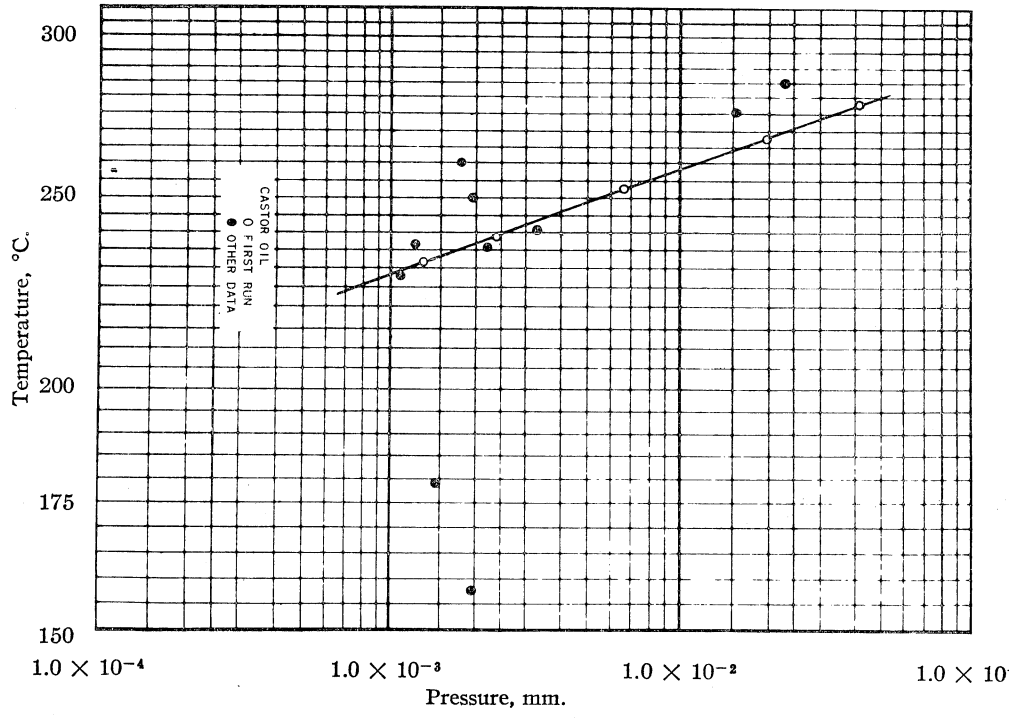


Fig. 5.—Experimental vapor pressure data.

that the boiling points of the unsaturated acids appear to be perhaps 2 to 3° lower than those of the corresponding saturated acids. The more recent work of Norris and Terry[11] shows conclusively that the vapor pressures of the methyl ester of fatty acid of equal carbon atoms increase with increasing unsaturation. For example, the vapor pressure of methyl stearate is lower than that of its unsaturated analog, methyl oleate, and the latter, in turn, is lower than that of methyl linoleate. It would be expected, therefore, that the vapor pressure of tristearin should be lower than that of the oleyl distearin. The influence of only one double bond in the large oleyl distearin molecule may not be as effective in altering its vapor pressure as one double bond would be in a smaller molecule like the fatty acid molecule.

The attempt to determine the effect of additional unsaturation on vapor pressure was not successful with synthetic triglycerides owing to the abnormal behavior encountered with triolein and its *trans*-isomer, trielaidin, in the tensimeter. Although synthesized and purified by the

(11) Norris and Terry, *Oil and Soap*, **22**, 41 (1945).

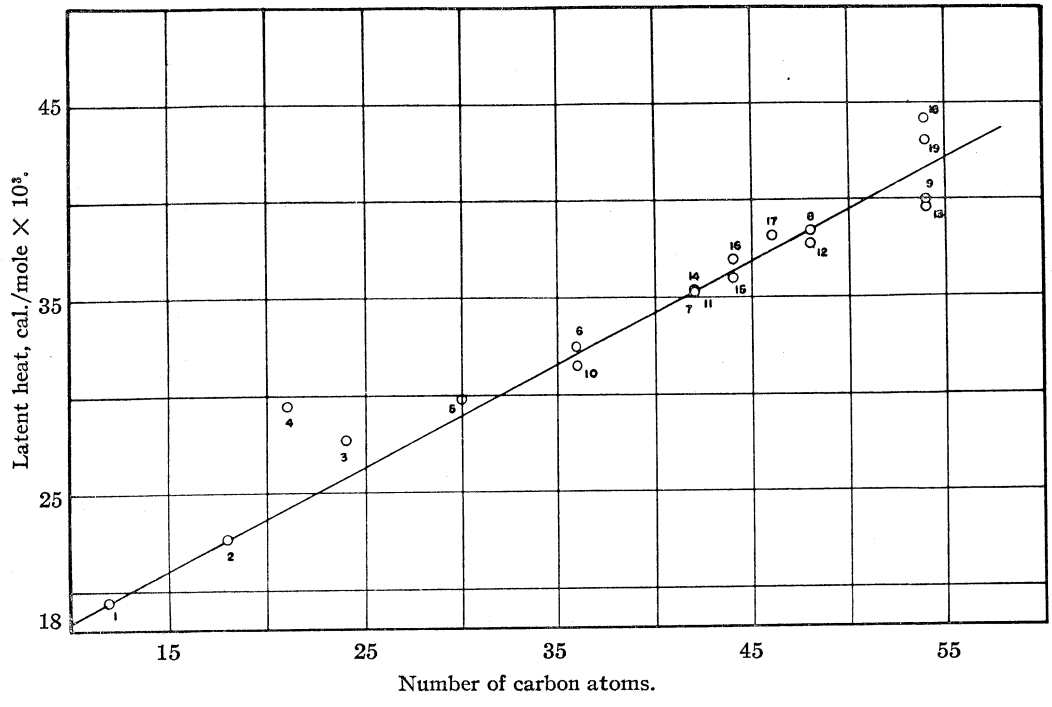


Fig. 6.—Relationship between molecular weights and latent heats.

same general methods used for the other triglycerides, these substances appeared to decompose in the tensimeter. The data followed no general trend and variations of 25 to 50° at one temperature were not uncommon. This was indeed surprising because of the known thermal stability of triolein in regard to its distillability. Since similar results were obtained from three individual preparations it appeared that the difficulty could be inherent in this type of triglyceride.

Of interest, however, is the fact that distilled olive oil responds normally to measurement by the method. Although the principal fatty acid constituent of this fat is oleic acid which makes it very similar to triolein, good reproducible vapor pressure data can be obtained with it by the tensimeter method. The pressure–temperature relationship for olive oil is plotted in Fig. 4. The regularity with which the points fall on a straight line is not only evidence of the accuracy of the data but shows that the olive oil triglycerides sustain the treatment of the tensimeter and hereby differ from the behavior of the synthetic triolein or trielaidin. The vapor pressures for olive oil are higher than those for tristearin which, on the basis of its unsaturation, is in agreement with the results of Norris and Terry.[11]

There was cause to surmise from these results that perhaps the olive oil fractions contained a natural inhibitor which protects it. Olive oil, however, is known to contain only minute quantities of tocopherols, its natural stability being due to the high percentage of stable fatty acids, such as oleic, which comprise its structure. The fractionation in the molecular still, in addition, would have completely removed any tocopherols from the fractions tested. In spite of these facts, an experiment was undertaken in which 25 mg. of tocopherols was added to 6 g. of the synthetic triolein in hopes of arresting the undesirable reactions taking place in the tensimeter. The presence of the tocopherols, however, made no improvement over the previous results.

The vapor pressures obtained with the fractionated soybean oil are also plotted in Fig. 4. The data fall on a straight line which, within experimental limits, follows the course of the olive oil line and thereby exhibits identical vapor pressures. The greater degree of unsaturation which exists in soybean oil, however, is not manifested in showing higher vapor pressures for this fat over the more saturated olive oil, which would be expected. When compared to tristearin, the two lines are not parallel but cross at the lower range and diverge 5° at 50 μ. Tristearin, in general, has lower vapor pressures over this range than soybean oil, but not of the order which would be expected from the differences in saturation. Perhaps these differences expected from pure substances are minimized in natural material where the molecules are heterogeneous combinations of many related constituents such as the number of different triglycerides which can exist in a natural fat.

Abnormal behavior was encountered with castor oil. The first experiments with a commerical grade of castor oil of unknown origin

labeled "Stripped" gave results which fell with good regularity on a straight line, as shown in Fig. 5. The position of the line, however, was some 25° below that for soybean oil or tristearin which did not seem reasonable in view of the structure of the castor oil molecule. Assuming that the sample used had received some unknown treatment either by the refiner or in stripping, several other samples were tried. A commercial grade of refined oil (Baker Castor Oil Co.) having acetyl values of 146.5 and 146.3 before and after distillation, respectively, gave very erratic results which extended over an abnormal temperature range, as can be seen from the plot in Fig. 5. After treatment in the tensimeter, the acetyl value was found to be 143 ± 2%, the uncertainty being due to errors introduced because of the small sample available for analysis. The degree of dehydration, however, seemed small to account for the large disparity in the data. Other undesirable reactions must occur, although the fact that the greatest variations are at the lower temperatures makes it difficult to offer an explanation on the basis of thermal effects. The examination of two other samples of castor oil, one a U.S.P. product and the other a refined grade, yielded similar results.

It was not possible to get data when using corn oil because of the tendency of the pendulum to stick to the orifice. Apparently the corn oil polymerized too rapidly to be successfully handled in the tensimeter and that oil which reached the orifice was sufficiently tacky to cause the diaphragm of the pendulum to stick. The orifice heater aggravated this condition perhaps by even further overheating the oil. After several attempts to collect data with fresh samples of corn oil, these measurements were abandoned.

The constants for Dühring's rule[12] for the triglycerides have been determined and are listed in the last column of Table I. The constants were computed from the absolute temperatures at the 2 pressures, 50 μ and 1 μ for contiguous members of the series in the order listed in Table I. The constant as determined is the ratio of the absolute temperature difference for one triglyceride at 2 pressures to that for the other triglyceride at the same 2 pressure values. Expressed more precisely, the relationship has the following form: $T'_A - T_A/T'_B - T_B = \text{constant}$, where $(T'_A - T_A)$ equals the absolute temperature of one triglyceride at 50 and 1 μ, respectively, and $(T'_B - T_B)$ equals the corresponding temperatures for the other triglycerides. The Dühring constant is calculated from the temperature data of the indicated material with that of the material next lower in the list. For example, the value 0.920 is the ratio of the difference of the two temperatures for tributyrin to that for tricaproin. The constancy of this quantity is good over the entire series investigated, as can be noted from the computed values in Table I.

Summary

The vapor pressure–temperature relationships for 9 simple triglycerides, 10 mixed triglycerides and 4 natural fats have been determined by the pendulum-tensimeter method. In most every instance a straight-line relationship between temperature and pressure was obtained. Abnormal behavior with 2 unsaturated synthetic triglycerides and 2 natural fats was encountered. Latent heats of vaporizations for each material are calculated, and constants for Dühring's rule are also computed.

(12) Roehl, *Ind. Eng. Chem.*, **30**, 1320 (1938).

ROCHESTER 13, NEW YORK RECEIVED FEBRUARY 24, 1949

[CONTRIBUTION FROM THE LABORATORIES OF DISTILLATION PRODUCTS, INC.]

Vapor Pressures of Phlegmatic Liquids. II. High Molecular Weight Esters and Silicone Oils[1]

BY E. S. PERRY AND W. H. WEBER

The vapor pressures of a number of simple and mixed triglycerides have been reported in a previous paper.[2] At the time of these measurements there was available in this Laboratory a number of molecularly distilled phthalate and sebacate esters whose pressure–temperature relationships could be determined by the pendulum–tensimeter method.[3] A knowledge of the vapor pressures of this class of materials is of importance in certain aspects of their use as plasticizers and vacuum pump fluids. Therefore, the determination of their vapor pressures seemed advisable and worthy of publication.

The pressure–temperature curves for a few of these esters, particularly dibutyl phthalate, di-2-ethylhexyl phthalate, and di-2-ethylhexyl sebacate, have been obtained by others[3,4,5,5a] using both

(1) Communication No. 152 from Laboratories of Distillation Products, Inc.

(2) Perry, Weber and Daubert, THIS JOURNAL, **71**, 3720 (1949).

(3) Hickman, Hecker and Embree, *Ind. Eng. Chem.*, **9**, 264 (1937).

(4) Verhoek and Marshall, THIS JOURNAL, **61**, 2737 (1939).

(5) Kapff and Jacobs, *Rev. Sci. Instruments*, **18**, 581 (1947).

(5a) A recent publication on this subject by Small, Small and Cowley, *Trans. Faraday Soc.* (London), **44**, 810 (1948), has come to the authors' attention since the original manuscript of this paper was submitted for publication. Their dynamic method gave results which are in closer agreement than previously published results (from dynamic methods) to those of the present paper.

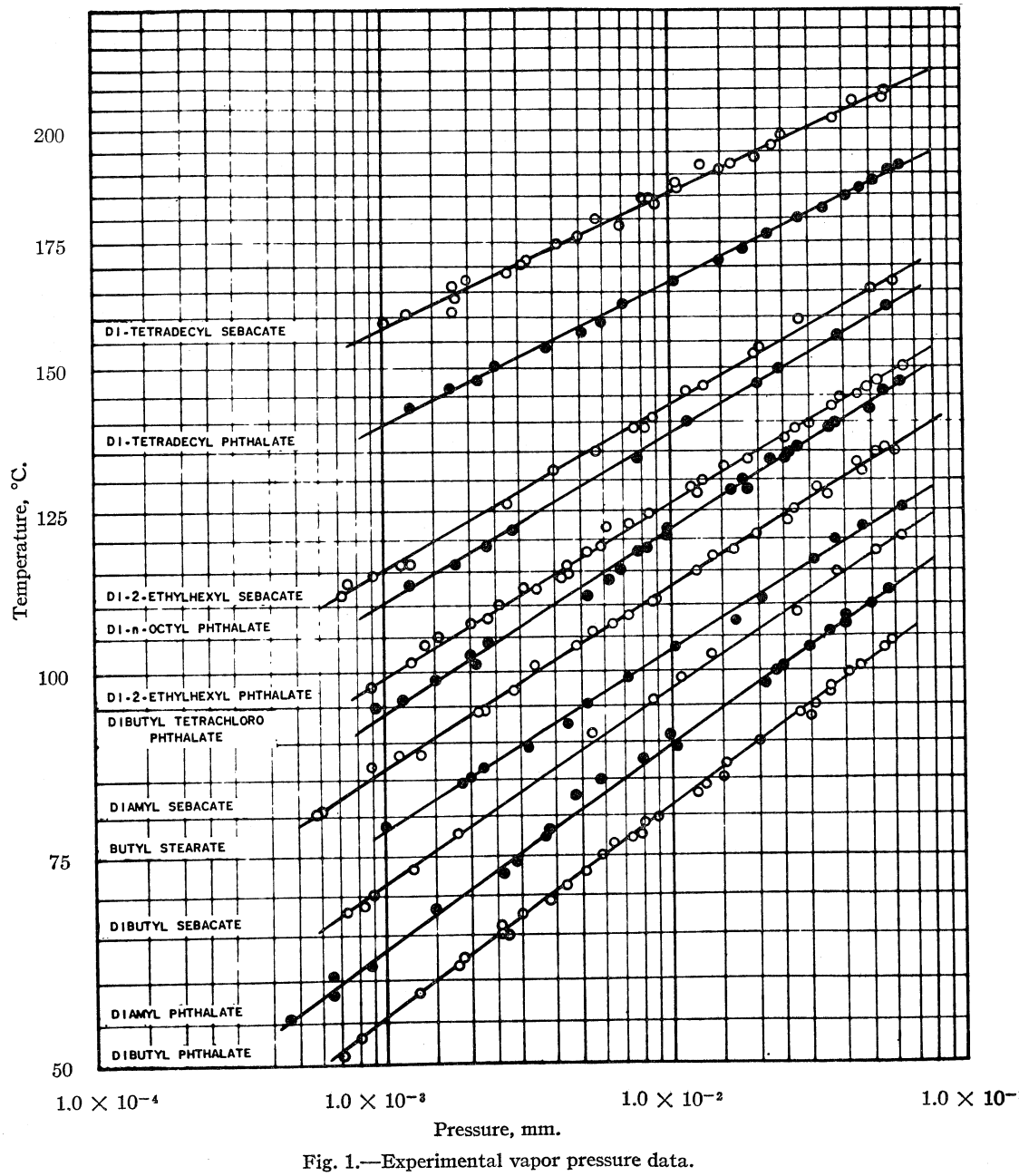


Fig. 1.—Experimental vapor pressure data.

the static pendulum-tensimeter method and dynamic methods. The agreement, however, between the methods of Verhoek and Marshall[4] and the pendulum tensimeter has been much better than that between the pendulum tensimeter and the dew-point method of Kapff and Jacobs.[5] The present results substantiate this point and definitely indicate that the dew-point method yields higher values.

In the present paper are reported the vapor pressure curves for fourteen esters, including new data for the three esters mentioned above, and for two commercial silicone fluids.

Experimental

The apparatus and procedure were identical to that described in the first paper.[2] One variation in the procedure was made in an attempt to increase the accuracy of the readings. Since these esters are fluids at room temperature, the return of the condensate to the boiler causes no difficulties. Consequently, a longer time for the establishment of equilibrium at each temperature was permissible. In spite of the additional time, the readings showed no better consistency over the methods used with the triglycerides.

The phthalates and sebacates of di-*n*-butyl, di-*n*-amyl and di-2-ethylhexyl alcohols were obtained from vacuum pump fluid stocks of Distillation Products, Inc. Di-*n*-octyl phthalate, di-*n*-tetradecyl phthalate and di-*n*-tetradecyl sebacate were synthesized in this Laboratory.

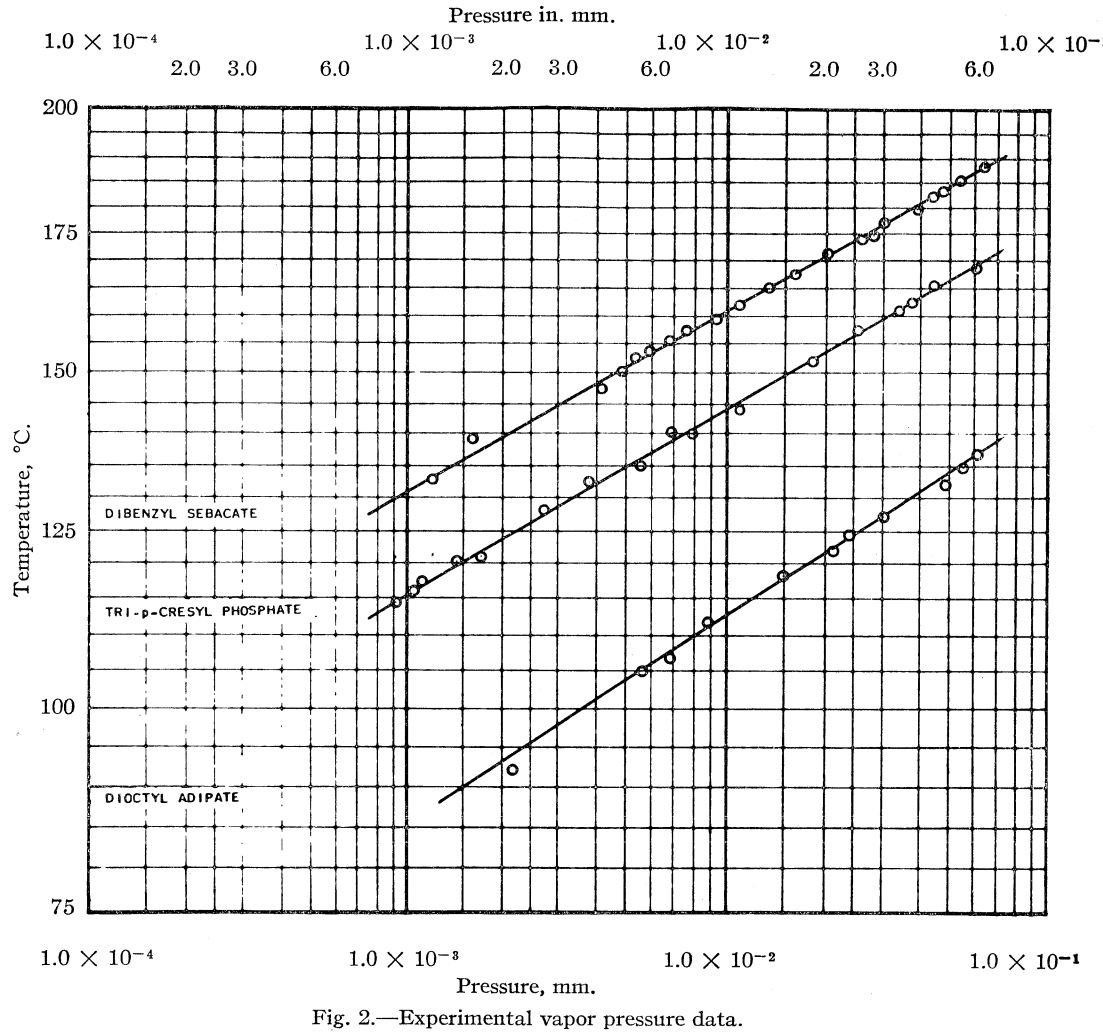


Fig. 2.—Experimental vapor pressure data.

The esterification was carried out in xylene using *p*-toluenesulfonic acid as catalyst. The tri-*p*-cresyl phosphate was a white-label quality product purchased from Eastman Kodak Company. The dibenzyl sebacate was obtained from Resinous Products and Chemical Company. The butyl stearate was a commercial-grade plasticizer sold by Commercial Solvents Corporation. The dibutyl tetrachlorophthalate was an experimental ester furnished by Commercial Solvents Corporation to whom we are grateful for the sample and permission to publish the results. The authors are indebted to the Pigments Department of E. I. du Pont de Nemours and Company, Inc., for supplying the samples of dioctyl adipate used in the measurements.

Regardless of the source or purity of these materials, each one was distilled in the cyclic molecular still before being used for the vapor pressure determinations. This consisted of removing 3 strip cuts which totaled 25% of the original charge. The 2 succeeding 25% fractions were used for the measurements. Dibenzyl sebacate, however, was first fractionated in a laboratory column equivalent to 6 theoretical plates. The distillate was then redistilled in the molecular still, as described above, to ensure complete removal of volatile constituents, if any, which could have been formed during the fractionation at the higher pressures. All of the esters were water-white with the exception of the dibutyl tetrachlorophthalate. Its amber color persisted even after treatment with a contact bleaching agent.

The silicone oils are commercial vacuum pump fluids made by the Dow Corning Corporation. These were used *per se* without the additional purification because distillation would alter their vapor pressure characteristics by removing the lower-boiling constituents. The exact nature of these fluids is not known, of course, but they are perhaps methyl and phenyl substituted polysiloxanes.

Results and Discussion

The experimental results of pressures and temperatures are plotted in Figs. 1, 2 and 3. The derived constants A and B for the Clausius–Clapeyron equation, $\log P = -A/T + B$, where $A = L/2.3R$, and the latent heats of vaporization L have been computed for each ester and are given in Table I. In all cases the experimental pressure–temperature values fall on a straight line with good regularity over the temperature range studied. There appears to be a rough linear relationship between decreasing vapor pressure and increasing molecular weights for all aliphatic esters with the exception of the chlorinated dibutyl phthalate. A plot of latent heats of vaporization as a function of the total number of carbon atoms in the alcohol side-chains for each

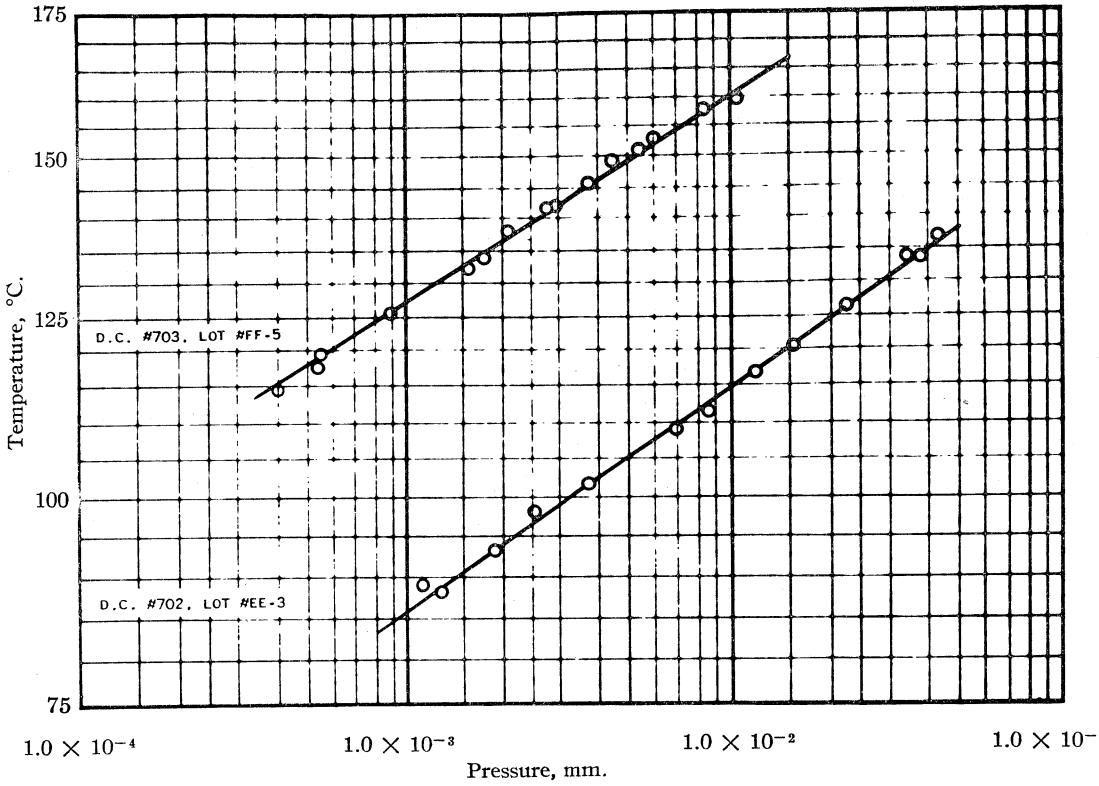


Fig. 3.—Experimental vapor pressure data.

of the phthalate and sebacate series also follows a nearly linear course, as shown in Fig. 4. The hollow circles are the points for the phthalate ester series and the solid dots represent the values for the sebacate esters. The number at each point is the order of listing of the esters in Table I. The depression of the vapor pressure by the aromatic nucleus in dibenzyl sebacate is clearly indicated in the figure. Likewise, the effect of the heavy chlorine atoms in lowering the vapor pressure of dibutyl tetrachlorophthalate over that of the parent dibutyl phthalate is evident. The lower vapor pressure of the normal octyl phthalate as compared to that for the isoöctyl phthalate is manifested in the disparity of the computed latent heats for these two isomeric esters. This is in agreement with the general behavior of aliphatic compounds in that the boiling point decreases with increased branching.

The constants for Dühring's rule, calculated as described in the previous paper,[2] are listed in Table II for each pair of adjacent members for both the phthalate and sebacate esters, excluding dibenzyl sebacate and dibutyl tetrachlorophthalate. The values of Table II are in good agreement with the theory for Dühring's rule.

The values of latent heats previously published for some of the esters are listed in Table I for comparison purposes. In every case the present values are lower than those published. Agreement is best between the values of this work and those of Hickman, Hecker and Embree[3] also using the pendulum tensimeter. Although somewhat higher, the values reported by Verhoek and Marshall[4,5a] are in consistent agreement with those of this report. The results of the dew-point method,[5] however, are considerably higher than those obtained by either of the other two methods. The results are not consistent over the range of esters studied and the values obtained for repeated determinations on the same material are at variance. For example, 2 values reported for

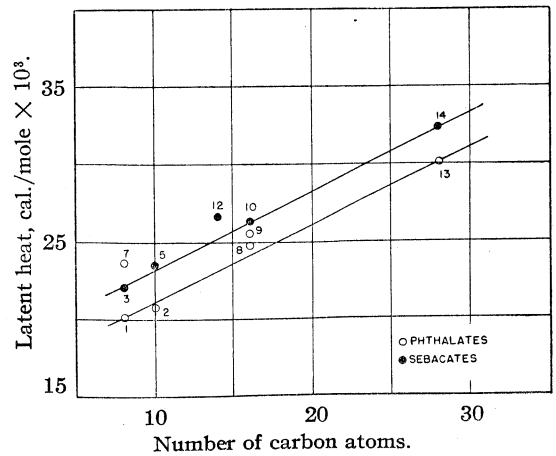


Fig. 4.—Relationship between molecular weights and latent heats.

TABLE I

EXPERIMENTAL DATA AND CALCULATED CONSTANTS OF THE ESTERS

	Material	Temp. (P_1 = 50μ) °C.	°K.	Temp. (P_2 = 1μ) °C.	°K.	A	B	L	L published	No. carbons in alcohol chains
				Esters						
1	Di-*n*-butyl phthalate	102	375	55	328	4450	13.58	20,300	21,400[3] 23,440[4] 25,500[5]	8
2	Di-*n*-amyl phthalate (Amoil)	111	384	63	336	4560	13.57	20,900	29,300[5]	10
3	Di-*n*-butyl sebacate	118	391	71	344	4850	14.10	22,200	....	8
4	*n*-Butyl stearate	123	396	78	351	5220	14.88	23,900	....	..
5	Di-*n*-amyl sebacate (Amoil-S)	134	407	86	359	5180	14.42	23,700	29,300[5]	10
6	Di-isoöctyl adipate	135	408	85	358	4960	13.85	22,700	....	..
7	Di-*n*-butyl tetrachlorophthalate	144	417	94	367	5210	14.20	23,800	....	8
8	Di-2-ethylhexyl phthalate (Octoil)	148	421	99	372	5440	14.62	24,900	25,600[3] 28,500[5]	16
9	Di-*n*-octyl phthalate	160	433	110	383	5620	14.68	25,700	....	16
10	Di-2-ethylhexyl sebacate (Octoil-S)	165	438	115	388	5780	14.90	26,400	29,800[5]	16
11	Tri-*p*-cresyl phosphate	168	441	115	388	5480	14.12	25,100	27,110[4]	..
12	Dibenzyl sebacate	185	458	131	404	5860	14.50	26,800	28,910[4]	14
13	Di-*n*-tetradecyl phthalate	188	461	139	412	6580	15.97	30,100	....	28
14	Di-*n*-tetradecyl sebacate	208	481	158	431	7080	16.42	32,400	....	28
				Silicones						
15	DC-702, Lot EE-3	138	411	86	359	4820	13.42	22,000	14,200[6]	..
16	DC-703, Lot FF-5	187	460	127	400	5210	13.02	23,800	14,780[6]	..

TABLE II

DÜHRING'S RULE CONSTANTS

	Material	Dühring's rule constant
	Phthalates	
1	Di-*n*-butyl phthalate	0.979
2	Di-*n*-amyl phthalate	.980
8	Di-2-ethylhexyl phthalate	.980
9	Di-*n*-octyl phthalate	1.040
12	Di-*n*-tetradecyl phthalate	
	Sebacates	
3	Di-*n*-butyl sebacate	0.979
5	Di-*n*-amyl sebacate	0.962
10	Di-2-ethylhexyl sebacate	1.000
14	Di-*n*-tetradecyl sebacate	

Amoil are 29,300 and 31,700, while 2 determinations on Amoil-S gave 29,300 and 28,700.

The latent heats of vaporization for the silicone fluids DC-702 and DC-703 are found to be much higher when calculated from present data than those reported in the commercial literature[6] of the manufacturer. Both sets of values are given in Table I. Boiling points at 10^{-2} mm. mercury for the 2 fluids taken from Fig. 3 are 115° for DC-702 and 160° for DC-703 as compared to 160 and 200°, respectively, reported in reference 6. A complete study of the vapor pressures of pure cyclic and linear methylpolysiloxanes has been made by Wilcock[7] but a comparison of his results with the present ones was not feasible because of the uncertainty of the structure of the commercial oils used in the present investigation.

(6) Dow Corning Silicone Notebook Fluid Series No. 2 issued July, 1946.

Summary

The vapor pressure–temperature relationships for five phthalate, five sebacate, 1 stearate, 1 adipate and 1 phosphate esters have been determined. Also 2 commercial silicone fluids have been examined. The latent heats of vaporization for each of these materials are computed and compared with previously published values. Constants for Dühring's rule are computed for each of the phthalate and sebacate series.

ROCHESTER 13, NEW YORK RECEIVED FEBRUARY 24, 1949

(7) Wilcock, THIS JOURNAL, **68**, 691 (1946).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

Polarographic Urea–Formaldehyde Kinetic Studies

BY GEORGE A. CROWE, JR.,[1] AND CECIL C. LYNCH

In a previous paper[2] we have shown polarographically the reaction between formaldehyde and urea to be reversible at 25° in 0.05 *N* lithium hydroxide. It seemed desirable to study the effects of change in temperature and *p*H on this reaction. Such a study is presented here.

Smythe[3] measured the urea–formaldehyde reaction rate in neutral solution between 30 and 60° and found that the reaction was bimolecular. (Crowe and Lynch[2] showed that the reaction was reversible in 0.05 *N* lithium hydroxide at 25°, and found that the reverse reaction was monomolecular.) Jahoda,[4,5] Bieber and Trümpler[6,7] and Vesely and Brdicka[7,8] observed that the electroreduction of formaldehyde at the dropping mercury electrode was very low at 25° in neutral solution. As the *p*H or temperature was increased, the rate of reduction was greatly increased. It was postulated[6,7,8] that formaldehyde was normally hydrated, and that the amount of electroreduction of formaldehyde was a measure of its dehydration rate; maximum dehydration was found to occur above 80°, or at *p*H 13.14 at 25°.[4,8]

The kinetic study described in this paper indicates that both dehydration of formaldehyde and the assumption of the formation of an anion of urea are necessary to account for the increase of urea–formaldehyde reaction rate with increase of *p*H. Increase of temperature probably affects the rate of dehydration of formaldehyde without markedly changing the rate of formation of this anion form of urea.

Experimental

The apparatus, chemicals and general technique were as described previously.[2] The supporting electrolytes consisted of 0.05 *N* lithium hydroxide (*p*H 12.7), 0.1 *M* sodium carbonate (*p*H 11.2), 0.1 *M* sodium bicarbonate (*p*H 8.7) and a buffer mixture of 0.05 *M* boric acid, 0.05 *M* lithium chloride and 0.045 *M* lithium hydroxide (*p*H 10.1). All reagents were C. P. Baker Analyzed except the lithium hydroxide which was Merck and Company lithium hydrate. The solutions were made up to twice the concentrations given above, and diluted with an equal volume of urea, formaldehyde or monomethylolurea solution to be tested.

Reaction rates for the reversible reaction of urea and formaldehyde to form monomethylolurea are given in Table I. The equilibrium constant appears to be constant within experimental error (±5% of the value determined) for changes of temperature and *p*H over the ranges tested.

TABLE I

RATES FOR THE REACTION $NH_2CONH_2 + HCHO \rightleftarrows NH_2CONHCH_2OH$, AND AVERAGE POLAROGRAPHIC CURRENT OF FORMALDEHYDE AT VARIOUS *p*H VALUES AND FOR VARIOUS TEMPERATURES

Temp., °C.	*p*H	k_f (sec.$^{-1}$)	k_r (sec.$^{-1}$)	*K* From reaction rates	*K* From equilibrium data	Av. pol. current of 0.00354 *M* formaldehyde, mma.
25	12.7	2.97×10^{-2}	1.45×10^{-3}	20	26	12.0
25	11.2	3.56×10^{-3}	6.04×10^{-5}	59	35	4.8
25	10.1	6.10×10^{-4}	1.75×10^{-5}	35	55	1.20
25	8.7	2.14×10^{-4}	1.38×10^{-5}	16	60	0.34
15	12.7	1.71×10^{-2}			18	5.97
20	12.7	2.67×10^{-2}			14	8.75
25	12.7	3.36×10^{-2}			30	12.0
25	12.7	2.97×10^{-2}	1.45×10^{-3}	20	26	12.0
30	12.7	9.80×10^{-2}			21	17.8
38	12.7	0.129			20	24.9
40	12.7	0.158			21	26.2

The average polarographic reduction current for formaldehyde with varying temperature and *p*H is also given in Table I. As can be seen from the table, for a given decrease in polarographic current, lowering the *p*H from 12.7 slows down the urea–formaldehyde reaction rate more than lowering the temperature. The amount of electroreduction of formaldehyde to methanol occurring at the dropping mercury electrode was about 0.2% of the formaldehyde in solution per hour, and occurred only when −1.65 volts or more was applied to the electrodes. Therefore the amount of reduction of formaldehyde was negligible in comparison to the amount involved in reaction with urea.

The change of the polarographic wave height of formaldehyde with temperature is shown for *p*H 8.7 and *p*H 12.7 in Fig. 1. The log of formaldehyde wave height is plotted *vs.* the reciprocal of the absolute temperature, as in an equation derived from the Arrhenius equation

$$\text{Log}\,\frac{i_2}{i_1} = \frac{\Delta E_{aa}}{2.303 \times 1.987}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \qquad (1)$$

where i_1 and i_2 are the formaldehyde wave heights for absolute temperatures T_1 and T_2, and ΔE_{aa} is the apparent energy of activation for the reduction of formaldehyde at the dropping mercury electrode. The lower, steeper slopes are limited by the rate of dehydration of formaldehyde; the upper, less steep slope is dependent only on the change of viscosity of the solution and the change of mercury mass and drop time with temperature.

(1) Present address: Hercules Powder Company, Hercules Experiment Station, Wilmington, Delaware.

(2) Crowe and Lynch, THIS JOURNAL, **70**, 3795 (1948).

(3) Smythe, *J. Phys. Colloid Chem.*, **51**, 369 (1947).

(4) Jahoda, *Coll. Czechoslov. Chem. Commun.*, **7**, 415 (1935).

(5) Kolthoff and Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941, p. 353.

(6) Bieber and Trümpler, *Helv. Chim. Acta*, **30**, 706 (1947).

(7) Wawzonek, *Anal. Chem.*, **21**, 61 (1949).

(8) Vesely and Brdicka, *Coll. Czechoslov. Chem. Commun.*, **12**, 313 (1947).

The sum of the effects of change of viscosity, mercury mass and drop time would give an apparent activation energy of about 4000 cal. per mole, as compared to the upper slope of 3560 cal. per mole. This indicates that only free formaldehyde is present above 55° at *p*H 12.7, and above 81° at *p*H 8.7. This latter value is in agreement with the value of 80° found by Yahoda.[4]

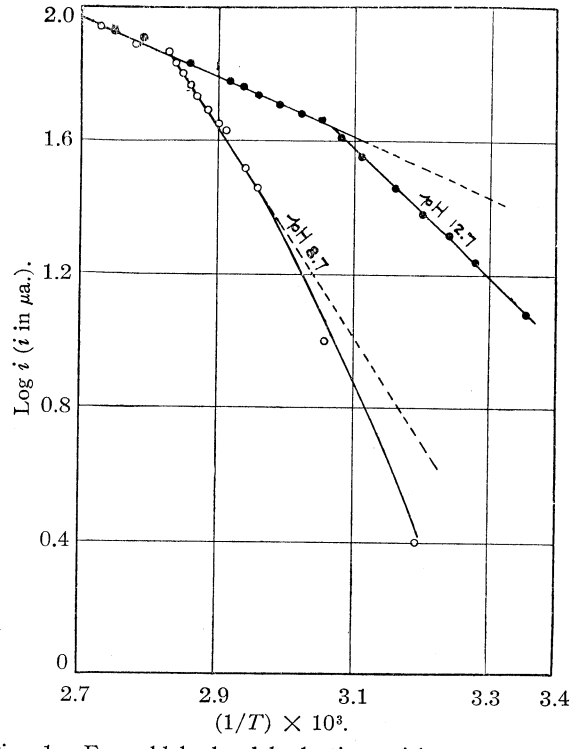


Fig. 1.—Formaldehyde dehydration with temperature.

The extent of dehydration of formaldehyde was estimated as the ratio of the actual formaldehyde wave height to the total dehydrated wave height from Fig. 1. At 25° the formaldehyde was found to be about 41% dehydrated at *p*H 12.7, and about 1.2% dehydrated at *p*H 8.7.

The forward urea–formaldehyde reaction rates were calculated with corrected formaldehyde values, and the same reaction rates were obtained as before, within experimental error. Since the extent of the reaction was small in evaluation of initial slopes, the values of the reaction rate constants obtained and the equilibrium constant should not differ significantly from the values given previously.[2] The results showed this to be true. It appeared impossible to calculate the observed effect of change in reaction rate with *p*H from the data included here, since not only does the concentration of formaldehyde in the reaction vary with *p*H, but also the concentration of the anion of urea appears to vary with *p*H.

For the change of urea–formaldehyde reaction rate with temperature in neutral solution, Smythe[3] found the energy of activation to be 14,700 cal./mole. Calculated by the Arrhenius equation from Table I, the effective energy of activation (ΔE_a) at *p*H 12.7 was 15,900 cal./mole, which is in agreement with Smythe within the limits of experimental error.

Equations were developed to relate the urea–formaldehyde reaction rate and the polarographic wave height of formaldehyde for changes of *p*H and temperature.

From the Arrhenius equation and equation (1), a relationship was found between urea–formaldehyde forward reaction rates (k_1 and k_2) at two temperatures and polarographic wave heights of formaldehyde (i_1 and i_2) at the same two temperatures, and at a constant *p*H.

$$\log \frac{k_2}{k_1} = \frac{\Delta E_a}{\Delta E_{aa}} \log \frac{i_2}{i_1} \qquad (2)$$

where ΔE_a was 15,900 cal./mole and ΔE_{aa} was 10,000 cal./mole for *p*H 12.7 over the range of 15 to 40°. Using these values, k_f was calculated from formaldehyde wave height, and at *p*H 12.7.

t, °C.	k_f (*p*H 12.7) Calcd.	Found
15	0.015	0.017
20	.028	.027
25	.045	.034
30	.085	.098
38	.14	.13
40	.16	.16

For changes of *p*H at a given temperature, the urea–formaldehyde forward reaction rate was calculated from the polarographic wave height of formaldehyde by the equation

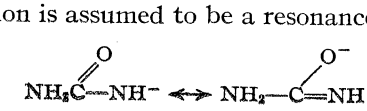
$$k_f = iB/A(A - i) \qquad (3)$$

where k_f was the forward reaction rate, i the formaldehyde wave height, and A and B constants. Equation (3) was deduced from analogy to the second-order equation $kt = x/a(a - x)$ and consideration of the relative amount of formaldehyde available for either electroreduction or reaction with urea. From the values in Table I, at 25° with $A = 15$ and $B = 0.12$

*p*H	k_f Calcd.	Found
12.7	0.032	0.030
11.2	.0038	.0036
10.1	.00070	.00061
8.7	.00019	.00021

Reverse reaction rates k_r can be calculated from the forward reaction rate k_f and the equilibrium constant K, where $K = k_f/k_r$.

The mechanism and reaction rate of the urea–formaldehyde reaction to form monomethylolurea appears to involve the dehydration of formaldehyde (the hydrated form, $H_2C(OH)_2$, does not react) and also the formation of an anion of urea. This anion is assumed to be a resonance structure



With changing pH, both urea and formaldehyde activation equilibria are shifted; whereas with changing temperature, the main change appears to be in the rate of dehydration of the formaldehyde. Thus for a given decrease of formaldehyde reduction current, the urea–formaldehyde reaction rate is affected more by changing the pH than changing the temperature, indicating that the amount of the anion of urea is affected by pH change more than by temperature change.

Summary

The effects of varying pH and temperature on the reversible reaction $HCHO + NH_2CONH_2 \rightleftarrows NH_2CONHCH_2OH$ have been studied, using the polarograph to measure formaldehyde concentration. Equations are presented to relate the urea–formaldehyde reaction rate to the polarographic current of formaldehyde for changes of pH or temperature.

The urea–formaldehyde reaction rate appears to be dependent both upon the rate of dehydration of formaldehyde and rate of anion formation of urea.

A method is given for estimating the fraction of dehydrated formaldehyde at various temperatures and pH values, based on polarographic wave heights of formaldehyde.

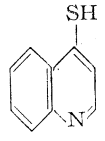
NEWARK, DELAWARE RECEIVED MARCH 18, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN CHEMICAL PHYSICS AND THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY OF MELLON INSTITUTE]

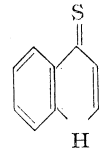
Ultraviolet and Infrared Spectra of Quinoline Derivatives: 2- and 4-Thiols

BY R. B. HANNAN, JR., J. H. LIEBLICH AND ALICE G. RENFREW

This investigation was undertaken in an attempt to determine the type of linkage between the sulfur atom and the quinoline nucleus in the substituted 2- and 4-quinolinethiols. Two structures are possible for these compounds: a thiol structure (A) and a thione structure (B).



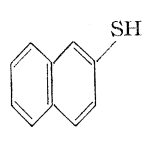
A



B

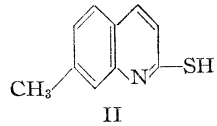
(These may be in tautomeric equilibrium.) Ewing and Steck[1] have attacked the same problem in the hydroxyquinolines by the use of ultraviolet spectra, and it was hoped that their method would be successful with the sulfur analogs. The infrared spectra of these sulfur compounds have also been studied. Unfortunately neither approach has provided an answer to the problem. Since the data may be of some utility, the results will be described briefly.

Ultraviolet and infrared absorption spectra of the following compounds are presented.



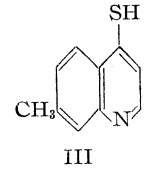
I

2-Naphthalenethiol



II

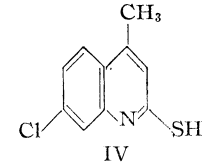
7-Methyl-2-quinolinethiol



III

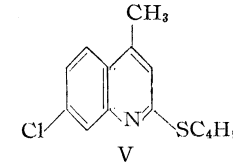
7-Methyl-4-quinolinethiol

(1) Ewing and Steck, THIS JOURNAL, **68**, 2181 (1946); Steck, Ewing and Nachod, Abstracts, Washington Meeting, A. C. S., Sept. 1948, page 12L.



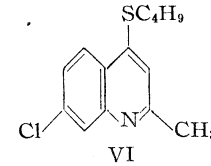
IV

7-Chloro-4-methyl-2-quinolinethiol



V

7-Chloro-4-methyl-2-*n*-butylthioquinoline



VI

7-Chloro-4-*n*-butylthio-2-methylquinoline

Few data for comparison are available in the literature. Morton and Stubbs[2] have reported the ultraviolet absorption spectra of 4-methyl-2-quinolinethiol and its ethers in neutral alcoholic solution only. Clinton and Suter[3] give spectrophotometric measurements for two 4-dialkylaminoalkyl sulfides of 7-chloroquinoline. The curve for 7-chloro-4-quinolylmercaptoacetic acid is given by Surrey.[4]

Experimental

The preparation and properties of the quinolinethiols (II, III and IV) have been reported by Renfrew.[5] The preparation of the two thioethers is described below.

7-Chloro-4-methyl-2-*n*-butylthioquinoline[6](V).—This sulfide was synthesized by the procedure described by

(2) Morton and Stubbs, *J. Chem. Soc.*, 1321 (1939).
(3) Clinton and Suter, THIS JOURNAL, **70**, 491 (1948).
(4) Surrey, *ibid.*, **70**, 2190 (1948).
(5) Renfrew, *ibid.*, **68**, 1433 (1946).
(6) Mrs. Pauline C. Piatt of the Department of Research in Pure Chemistry carried out much of the synthetic work.

Clinton and Suter.[3] *n*-Butylthiol (Eastman Kodak Co.) was dissolved in absolute alcohol containing an equivalent of sodium. The calculated amount of 2,7-dichloro-4-methylquinoline (0.07 mole) was added in portions during ten minutes, and the reaction mixture was refluxed four hours. After removal of alcohol, an ether solution of the sulfide was washed with dilute alkali until no further mercaptan was removed. The crude product was an oil, which crystallized first when supercooled to −30°. Samples were crystallized from methyl alcohol or ligroin (90–100°), using solvent equal to one-half the weight of the sample, and the supernatant liquid was removed by centrifuging in a cold room. Cooling curves indicated a melting point of 22.9°. The sulfide is soluble in ether, acetone, pentane and ligroin, insoluble in water, and tends to form a two-phase system with methanol and ethanol.

Anal. Calcd. for $C_{14}H_{16}NSCl$: N, 5.27; S, 12.06. Found: N, 5.22; S, 11.93.

7-Chloro-4-*n*-butylthio-2-methylquinoline (VI).—Synthesis was carried out as indicated above. Crystallization occurred during concentration of the dry ether solution and was repeated from one-half volume of pentane. Three recrystallizations from two volumes of ligroin (90–100°) gave a white solid, m. p., 53.8–54.5°. It was readily soluble in methyl alcohol and in ether but had a low solubility in hexane.

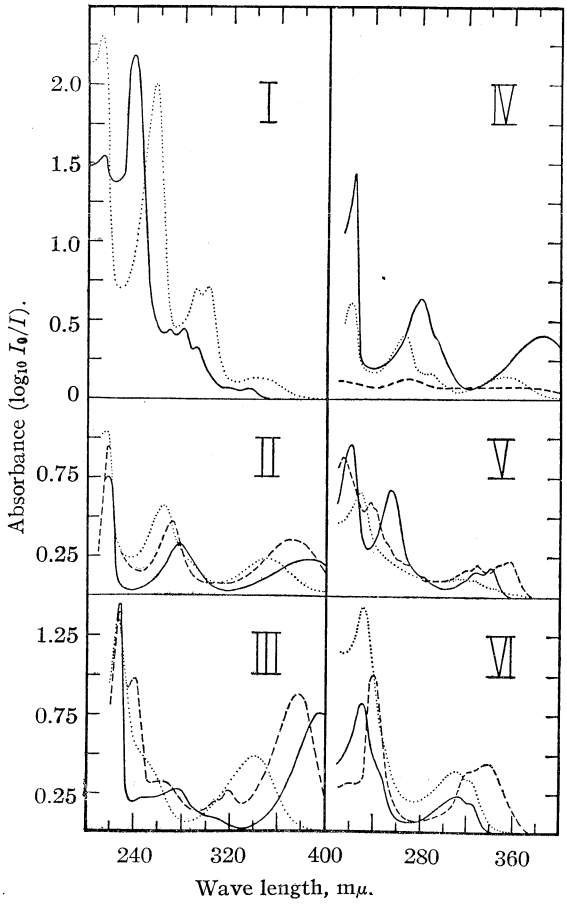


Fig. 1.—Ultraviolet spectra: — 95% ethanol; . . . . . 0.01 *N* sodium hydroxide; - - - - 0.01 *N* hydrochloric acid; I, 2-naphthalenethiol; II, 7-methyl-2-quinolinethiol; III, 7-methyl-4-quinolinethiol; IV, 7-chloro-4-methyl-2-quinolinethiol; V, 7-chloro-4-methyl-2-*n*-butylthioquinoline; VI, 7-chloro-4-*n*-butylthio-2-methylquinoline.

Anal. Calcd. for $C_{14}H_{16}NSCl$: N, 5.27; S, 12.06; Cl, 13.40. Found: N, 5.45; S, 12.13; Cl, 13.45.

The ultraviolet absorption spectra were obtained with a Cary recording spectrophotometer. The maximum error in the wave length calibration of the instrument was ±5 Å.

The spectrum of each compound has been obtained in acidic, basic and neutral (alcoholic) solution. These spectra are shown in Fig. 1. Intensities have been presented in terms of absorbance ($\log_{10} I_0/I$) rather than extinction coefficients because the solubilities were so low that concentrations could not be determined. For the aqueous acidic and basic solutions the solubilities were less than 5 mg./l. The solubility in 95% ethanol was higher, and the concentrations of the alcoholic solutions were: (I) 10.3 mg./l.; (II) 6.47 mg./l.; (III) 6.29 mg./l.; (IV) 6.02 mg./l.; (V) 5.36 mg./l.; (VI) 5.19 mg./l.

The infrared absorption spectra were recorded on a Baird spectrophotometer. The wave length accuracy of this instrument is better than ±0.1 micron. All of the spectra shown in Fig. 2 with

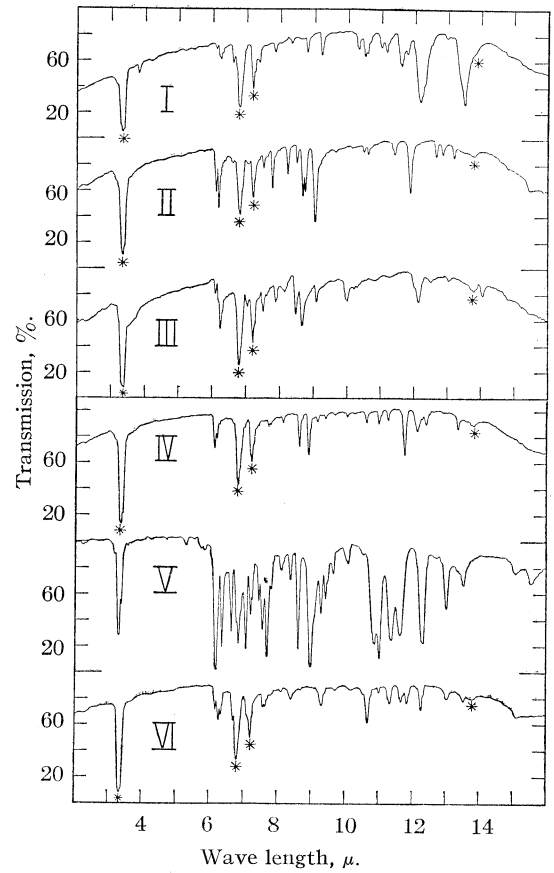


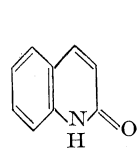
Fig. 2.—Infrared spectra, asterisks denote bands of Nujol: I, 2-naphthalenethiol; II, 7-methyl-2-quinolinethiol; III, 7-methyl-4-quinolinethiol; IV, 7-chloro-4-methyl-2-quinolinethiol; V, 7-chloro-4-methyl-2-*n*-butylthioquinoline; VI, 7-chloro-4-*n*-butylthio-2-methylquinoline.

the exception of V were obtained from suspensions of the solid samples in Nujol. The spectrum of the liquid thioether (V) was obtained from a sample of capillary thickness. The spectra of several of these samples were also obtained as fluorocarbon suspensions and in carbon tetrachloride solution in an attempt to find characteristic absorption bands for S–H or N–H linkages. The spectra of the Nujol suspensions are presented as being most informative.

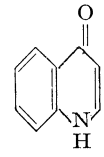
Discussion of Results

A. Ultraviolet Spectra.—Briefly, the conclusions of Ewing and Steck[1] on the hydroxyquinolines were based on the following observations and reasoning. The ultraviolet spectrum of quinoline undergoes a bathochromic shift (displacement of absorption maxima to longer wave lengths) in changing from a neutral to an acidic solvent. Similarly, the spectra of the naphthols undergo a bathochromic shift as the solvent is changed from neutral to basic in character. In either acidic or basic solvents, the spectra of the 3-, 5-, 6-, 7- and 8-quinolinols undergo bathochromic shifts, thus indicating that the oxygen retains its phenolic character and the heterocyclic ring retains its aromatic character in these particular quinolinols.

Conversely, the spectra of the 2- and 4-quinolinols do not undergo a shift in either acidic or basic media. This is explained by postulating the existence of these compounds in their respective keto forms.



2-Quinolone



4-Quinolone

In these compounds, the oxygen has lost its phenolic character and the spectrum does not undergo the bathochromic shift exhibited by the naphthols. Similarly, the heterocyclic ring has lost its aromatic character and the spectrum does not undergo the shift exhibited by quinoline.

It was hoped that the same reasoning could be applied to the sulfur analogs. The ultraviolet spectrum of 2-naphthalenethiol (I) was obtained and was found to undergo a bathochromic shift on going from neutral to basic medium (see Fig. 1). It would then be anticipated from the reasoning cited above that the spectra of the quinolinethiols would exhibit bathochromic shifts in acidic or basic media while the spectra of the quinolinethiones would remain unchanged in neutral, acid and basic media.

The spectra of 7-methyl-2-quinolinethiol (II), 7-methyl-4-quinolinethiol (III) and 7-chloro-4-methyl-2-quinolinethiol (IV) were obtained in neutral, acidic and basic media (see Fig. 1). Contrary to the anticipated results, the spectra of these three quinolinethiols exhibited hypsochromic shifts (displacements of absorption maxima to shorter wave lengths). These results cannot be explained by the reasoning applied to the bathochromic shifts observed for the quinolinols. A similar hypsochromic shift was encountered by Specker[7] and confirmed by Ewing and Steck[1] with solutions of 4-pyridone.

The spectrum of 7-chloro-4-*n*-butylthio-2-methylquinoline (VI) undergoes a bathochromic shift in an acidic medium but is not shifted in a basic medium. This is consistent with the sulfide structure in which the sulfur has lost its thiol character while the heterocyclic ring has retained its aromatic character.

7-Chloro-4-methyl-2-*n*-butylthioquinoline (V) dissolved very slowly in the aqueous solvents and it appears probable that the anomalous changes in the spectra are due to decomposition of the sulfide.

B. Infrared Spectra.—In a further attempt to confirm the structure of the mercaptoquinolines as thiols or thiones, their infrared spectra were recorded (see Fig. 2). It was hoped that the thiols would exhibit the characteristic absorption band associated with the S–H stretching vibration at 2400–2600 cm.$^{-1}$ (3.85–4.17μ). However, only the 2-naphthalenethiol spectrum showed this absorption band. The thiones would be expected to show an absorption band at about 3400 cm.$^{-1}$ (2.94μ), characteristic of the N–H stretching vibration. None of these compounds showed any absorption bands in this region. The thiones would also be expected to show a band characteristic of the C=S group in the 1400–1500 cm.$^{-1}$ region (6.67–7.13μ). However, the inherent weakness of this band and the complexity of the thioether spectra in this region indicate that this criterion will not provide any help. Therefore the infrared spectra do not offer a solution to the problem.

Summary

The ultraviolet absorption spectra of 2-naphthalenethiol, 7-methyl-2-quinolinethiol, 7-methyl-4-quinolinethiol, 7-chloro-4-methyl-2-quinolinethiol, 7-chloro-4-methyl-2-*n*-butylthioquinoline and 7-chloro-4-*n*-butylthio-2-methylquinoline were obtained in neutral, acidic and basic solvents. The observed wave length shifts are anomalous with respect to the reasoning used in establishing the structure of quinolinols and quinolones.

The infrared absorption spectra of these compounds have also been obtained but do not provide any further indication of their structure.

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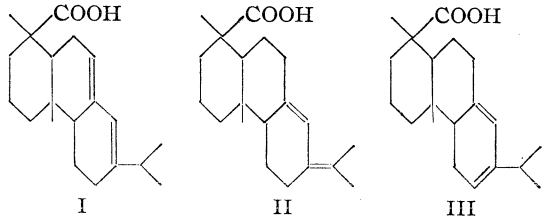
(7) Specker and Gawrosch, *Ber.*, **75**, 1338 (1942).

[CONTRIBUTION FROM THE HERCULES EXPERIMENT STATION, HERCULES POWDER COMPANY]

Kinetics of the Acid-catalyzed Isomerization of Levopimaric Acid in Anhydrous Ethanol

BY PAUL F. RITCHIE AND LANE F. MCBURNEY

For many years it has been known that certain constituents of wood rosin and oleoresin isomerize in the presence of strong acids or heat[1,2] and that the result of the preponderant reaction is an increase in the abietic acid content of the initial material.[3] The inadequacy of early techniques by which resin acids were isolated proved to be a serious handicap to investigators who attempted study of this isomerization reaction[4,5,6] and consequently the data acquired were incomplete or, in many cases, vitiated by the impurity of the resin acid specimens employed. Recent work established procedures by which resin acids were made available for study.[7] It is known now that the three isomeric, abietic-type acids—abietic (I), neoabietic (II), and levopimaric (III)—are the



I II III

resin acids participating in the isomerization and that the remaining components of oleoresin or rosin are relatively insensitive to strong acids or heat. The present communication is the result of an investigation, by a polarimetric method, of the kinetics of the acid-catalyzed isomerization of levopimaric acid in the solvent anhydrous ethanol.

Experimental

Preparation of Materials.—Anhydrous ethanol (Commercial Solvents Corp.) was purified from traces of aldehydes by the method of Dunlap.[8] The aldehyde-free alcohol was dried by the method of Lund and Bjerrum.[9] Levopimaric acid was isolated and purified by the method of Harris and Sanderson[7] $[\alpha]^{24}D$ −276° (C = 1%, ethanol), m. p. 150–152°. Hydrogen chloride was prepared by the method of Fieser.[10] Alcoholic hydrogen chloride was prepared by the absorption of dry hydrogen chloride in absolute ethanol until the concentration of the solution, as determined by weight, was approximately that desired. *p*-Toluenesulfonic acid was prepared from the monohydrate (Eastman Kodak Company, Eastman quality) by the methods of Gattermann[11] and Meyer,[12] melting point 105–105.5°. Methanesulfonic acid was prepared from "Indoil Methanesulfonic Acid," (Indoil Chemical Company) by the method of Smith and Hammett,[13] boiling point 136–138° at 0.4–0.6-mm. pressure. Trichloroacetic Acid (Eastman Kodak Company, Eastman quality, sulfate-free) was purified by the method of Jaeger.[14] The concentration of all ethanolic acid solutions was determined by titration of weighed samples with standard sodium hydroxide solution using methyl red as the indicator. Lithium ethylate solutions were prepared by the method of Elliott and Kilpatrick.[15] Lithium chloride (J. T. Baker Chemical Co., C.P. quality) was purified by the method of Elliott and Kilpatrick.[15]

Adequate precautions against acquisition of moisture by ethanolic solutions were taken at all stages in their preparation. In order to permit the withdrawal of a portion of a solution without exposing the bulk to the atmosphere, an all-glass apparatus—a modification of the automatic buret—was constructed and employed for the storage of solutions.

Apparatus.—A Pellin polarimeter sensitive to 0.02° was used in conjunction with a sodium-vapor lamp and a 5-dm. tube for all measurements. During experiments the temperature of the tube and contents was maintained constant within ±0.05° by water circulated from a thermostatically controlled bath through a jacket enclosing the tube.

Experimental Procedure.—Reaction mixtures were prepared by dispensing the desired volume of an ethanolic solution of levopimaric acid from an automatic buret into a 50-ml. volumetric flask, adding solutions of any other components, with the exception of the acid catalyst, from a weight buret and diluting with ethanol leaving only slightly more space than necessary to accommodate the catalyst solution. After placing the flask and contents in the water-bath at the temperature at which the experiment was to be conducted and allowing sufficient time for the attainment of thermal equilibrium, the proper amount of a solution of the acid catalyst was added from a weight

TABLE I

DATA FOR A TYPICAL REACTION, LOG $(\alpha - \alpha') = 0.785 - 0.00677t$

Concentration of reactants in moles per liter: levopimaric acid, 3.32×10^{-2}; hydrogen chloride, 4.20×10^{-3}.

t, min.	α	$t + \Delta t$, min.	α'	$(\alpha - \alpha')$ Obs.	$(\alpha - \alpha')$ Calcd.	$\Delta(\alpha - \alpha')$
4	(−)11.53°	64	(−)5.89°	(−)5.64°	(−)5.73°	+0.11°
9	10.91	69	5.61	5.30	5.30	.00
14	10.29	74	5.42	4.87	4.90	+ .03
19	9.75	79	5.17	4.58	4.53	− .05
24	9.20	84	4.98	4.22	4.20	− .02
29	8.69	89	4.76	3.93	3.88	− .05
34	8.23	94	4.57	3.66	3.59	− .07
39	7.76	99	4.44	3.32	3.32	.00
44	7.34	104	4.28	3.06	3.07	+ .01
49	7.00	109	4.18	2.82	2.84	+ .02
54	6.67	114	4.04	2.63	2.62	− .01
59	6.33	119	3.91	2.42	2.43	+ .01

Mean deviation ± .04°

(1) L. Ruzicka and H. Schinz, *Helv. Chim. Acta*, **6**, 662 (1923).
(2) S. Palkin and T. H. Harris, THIS JOURNAL, **55**, 3677 (1933).
(3) G. Dupont, *Bull. soc. chim.*, [4] **29**, 718 (1921).
(4) E. E. Fleck and S. Palkin, THIS JOURNAL, **59**, 1593 (1937).
(5) R. Lombard, *Bull. soc. chim.*, [5] **12**, 395 (1945).
(6) R. Lombard, *ibid.*, **745**, 1186 (1948).
(7) G. C. Harris and T. F. Sanderson, THIS JOURNAL, **70**, 334 (1948).
(8) F. L. Dunlap, *ibid.*, **28**, 395 (1906).
(9) H. Lund and J. Bjerrum, *Ber.*, **64B**, 210 (1931).
(10) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, New York, N. Y., 1941, p. 393.
(11) L. Gattermann, "Laboratory Methods of Organic Chemistry," Macmillan and Co., Ltd., London, 1941, p. 194.
(12) H. Meyer, *Ann.*, **433**, 327 (1923).
(13) L. C. Smith and L. P. Hammett, THIS JOURNAL, **67**, 23 (1945).
(14) F. M. Jaeger, *Z. anorg. allgem. Chem.*, **101**, 65 (1917).
(15) J. H. Elliott and M. Kilpatrick, *J. Phys. Chem.*, **45**, 454 (1941).

buret and the volume of the solution adjusted by the addition of ethanol. The flask was rotated to ensure thorough mixing of the contents, a portion of the solution transferred to the polarimeter tube, which had been brought to the desired temperature, and a stopper tightly fitted into the side tubulation.

Readings were taken in accordance with the directions of Guggenheim[16] and the constants of the general first order rate expression, $\log (\alpha - \alpha') = a - kt \log e$, calculated from the data by the method of averages. In Table I these methods have been applied to the data of a typical experiment for the purpose of deriving the rate constant, the calculated values of $(\alpha - \alpha')$ and the differences, $\Delta(\alpha - \alpha')$, between the observed and calculated values of $(\alpha - \alpha')$. The calculated mean deviation amounts to about 2% of the smallest observed value. Probable errors in the velocity constants were calculated and are represented by the radii of the circles in the graphs that follow. Unless otherwise noted, all measurements refer to 25°.

Results and Discussion

Preliminary investigations demonstrated that ethanolic solutions of levopimaric acid are perfectly stable for prolonged periods of time, but that in the presence of a strong acid catalyst the specific rotations of the solutions change rapidly from the initial value of −276°[7] to about −73° and, thereafter, very slowly to a final value of about −90°. The course of the rapid change was in strict accord with first order kinetics and examination of ultraviolet absorption spectra of reaction solutions of specific rotation −73° (Fig. 1) revealed that over 90% of the original levopimaric acid had been converted to abietic acid. It is not possible to determine levopimaric or neoabietic acid by absorption spectra in the presence of such large amounts of abietic acid. However, the fact that the same adduct, that of levopimaric acid, is formed when maleic anhydride reacts with either abietic or levopimaric acid in acidic media[17] is proof that levopimaric acid is present in the reaction solutions. The nature of the slow reaction is unknown although development of color in the solutions on standing for several hours may be an indication that the products of the isomerization are slowly oxidized by air under the experimental conditions. No detectable differences in the composition of the solutions of specific rotation −73° and −90° were exhibited by the ultraviolet absorption spectra. In the following discussion all measurements refer only to the rapid, relatively uncomplicated isomerization reaction.

A study of the effect of varying the initial concentration of levopimaric acid on the rate of isomerization was made using hydrogen chloride as catalyst. The results (Table II) show that the velocity of the reaction is independent of the initial concentration of levopimaric acid. Table III contains data obtained by measurement of the reaction velocity in solutions containing 1:1 trichloroacetic acid:lithium trichloroacetate buffers at 35.1°. The ionic strength of the medium was maintained constant at 7.02×10^{-2} by the addition of the proper amounts of lithium chloride.

(16) E. A. Guggenheim, *Phil. Mag.*, **I**, 538 (1926).

(17) L. Ruzicka and R. G. R. Bacon, *Helv. Chim. Acta*, **20**, 1542 (1937).

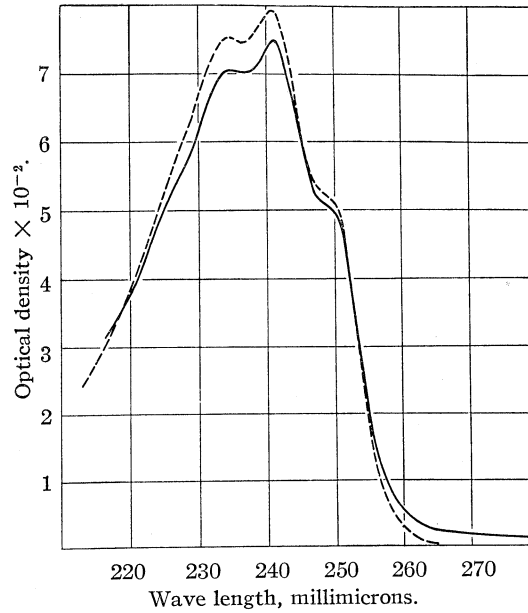


Fig. 1.—Ultraviolet absorption spectra of ethanolic solutions of resin acids: dotted curve, pure abietic acid, 10 g./liter; solid curve, acid-isomerized levopimaric acid, 10 g./liter.

Although the total buffer concentration was varied throughout a twelve-fold range, the rate of isomerization remained unaltered. Hence the reaction is catalyzed only by the solvated proton and not by undissociated acids or anions.

TABLE II

VELOCITY OF ISOMERIZATION AT VARIOUS INITIAL CONCENTRATIONS OF LEVOPIMARIC ACID

Concentration of hydrogen chloride: 4.48×10^{-3} mole/liter

Levopimaric acid, moles/liter × 10^2	Reaction velocity, $k \times 10^2$ (min.$^{-1}$)
1.11	1.53
1.88	2.02
2.33	1.88
2.77	2.07
4.01	1.60

TABLE III

ISOMERIZATION OF LEVOPIMARIC ACID IN 1:1 TRICHLOROACETIC ACID:TRICHLOROACETATE BUFFERS AT 35.1°

Concentration of levopimaric acid: 3.33×10^{-2} mole/liter.

Trichloroacetic acid, moles/liter × 10^3	Lithium trichloroacetate, moles/liter × 10^3	Lithium chloride, moles/liter × 10^2	Ionic strength, 1×10^2	Reaction velocity, $k \times 10^4$ (min.$^{-1}$)
2.66	2.66	6.75	7.02	6.78
12.6	12.6	5.76	7.02	6.93
19.2	19.2	5.10	7.02	7.05
31.6	31.6	3.86	7.02	6.82

The results of experiments in which three strong acids—hydrogen chloride, *p*-toluenesulfonic acid and methane sulfonic acid—were employed as catalysts are collected in Table IV. In Figs. 2 and 3 the values of k/c, where k is the reaction velocity

TABLE IV

ISOMERIZATION OF LEVOPIMARIC ACID CATALYZED BY STRONG ACIDS

Concentration of levopimaric acid: 3.32×10^{-2} mole/liter.

	Catalyst concentration, moles/liter $\times 10^4$	Reaction velocity, $k \times 10^3$ (min.$^{-1}$)
Hydrogen chloride	5.05	0.72
	10.2	1.50
	14.1	3.01
	21.8	5.96
	41.9	15.5
	68.3	34.2
	70.8	35.7
p-Toluenesulfonic acid	64.1	4.92
	140	12.0
	367	38.2
	599	70.1
Methanesulfonic acid	108	6.79
	288	17.0
	597	36.3
	928	57.0

and c the catalyst concentration, are plotted against c. Inspection of the plots reveals that, in the case of hydrogen chloride, a large primary electrolyte effect was found. Further evidence of the existence of a primary salt effect was obtained from experiments in which varying amounts of the uni-univalent salt lithium chloride were added to solutions containing constant amounts of levopimaric acid and hydrogen chloride. The plot of the ratio of the velocities at salt concentrations c and zero, k/k_0' *versus* c is linear (Fig. 4) in agreement with the Debye–Hückel theory.[18] A primary electrolyte effect was observed in connection with *p*-toluenesulfonic acid, but the values of

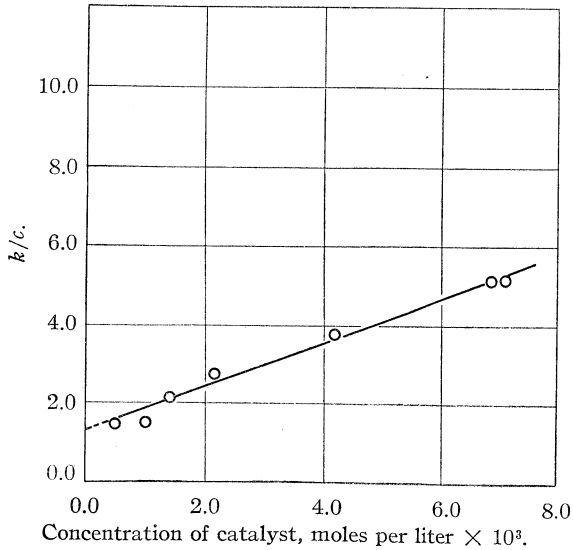


Fig. 2.—Hydrogen chloride-catalyzed isomerization of levopimaric acid: k is the reaction velocity and c the catalyst concentration in moles/liter.

(18) P. Debye and E. Hückel, *Physik. Z.*, **24**, 185 (1923).

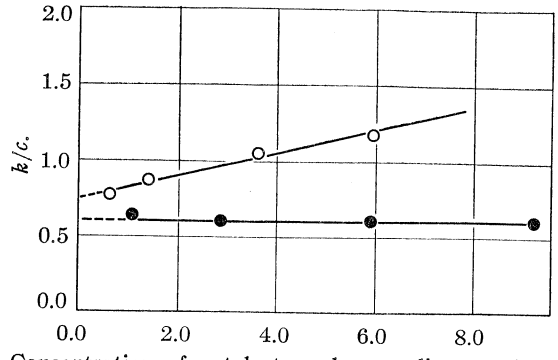


Fig. 3.—Isomerization of levopimaric acid catalyzed by (⊙) *p*-toluenesulfonic and (●) methanesulfonic acids. k is the reaction velocity and c the catalyst concentration in moles/liter.

k/c obtained with methanesulfonic acid were independent of the catalyst concentration.

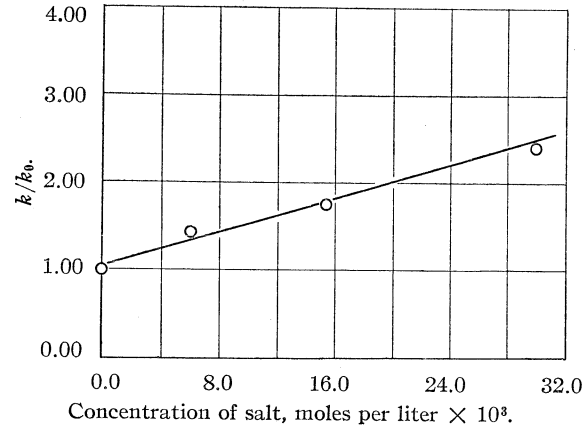


Fig. 4.—Neutral salt effect in the hydrogen chloride catalyzed isomerization of levopimaric acid: concentrations in moles/liter; hydrogen chloride, 4.62×10^{-3}; levopimaric acid, 3.33×10^{-2}; k/k_0 is the ratio of reaction velocities at salt concentrations c and zero.

Extrapolation of the curves of Figs. 2 and 3 leads to values of k/c at zero concentration with respect to each of the acid catalysts. The values thus obtained for *p*-toluenesulfonic acid (0.73) and methanesulfonic acid (0.61) are significantly lower than that corresponding to hydrogen chloride (1.23) and indicate that, at the concentrations employed, these two sulfonic acids are dissociated in ethanol to an extent less than hydrogen chloride. If it is assumed, in agreement, with the observations of Murray-Rust, and Hartley,[19] and Deyrup,[20] but contrary to the conclusions of Bezman and Verhoek[21] that hydrogen chloride is completely dissociated in ethanol, the value obtained for k/c at infinite dilution of hydrogen

(19) D. M. Murray-Rust and H. Hartley, *Proc. Roy. Soc.* (*London*), **A126**, 86 (1929).

(20) A. J. Deyrup, THIS JOURNAL, **56**, 60 (1934).

(21) I. I. Bezman and F. H. Verhoek, *ibid.*, **67**, 1330 (1945).

chloride is the catalytic coefficient $k_{C_2H_5OH_2^+}$ (in liters mole^{-1} min.$^{-1}$) of the reaction. From the catalytic coefficient and the data obtained in the experiments with trichloroacetic acid–trichloroacetate buffers (calculated to 25°) the dissociation constant of trichloroacetic acid was calculated. For purposes of comparison the dissociation constant at zero ionic strength was calculated from the Debye–Hückel limiting law, $\log_{10} K_0 = \log_{10} K_C - 5.6\sqrt{\mu}$, and found to be 6.9×10^{-6} in moderately good agreement with Deyrup's value of 3.5×10^{-6}.[20]

Both hydrogen chloride and *p*-toluenesulfonic acid were employed as catalysts in measuring the temperature coefficient of the reaction over the range 16 to 41°. The value obtained for the activation energy was 21.4 ± 0.5 kcal./mole and, as anticipated for a reaction catalyzed exclusively by solvated protons, independent of the nature of the strong acid catalyst (Fig. 5).

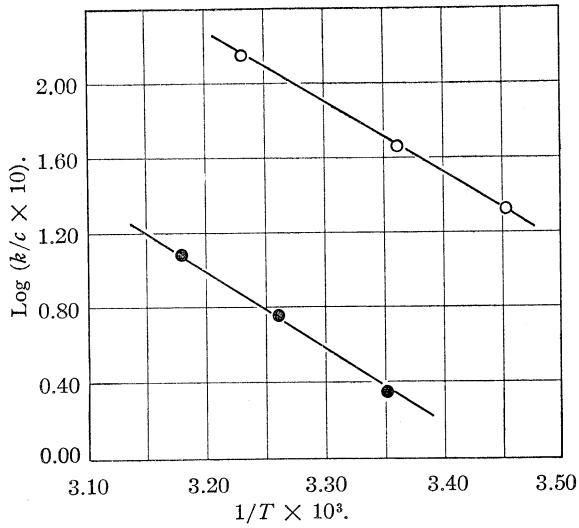


Fig. 5.—Temperature coefficient of the isomerization of levopimaric acid: concentrations in moles/liter; hydrogen chloride, ⊙, 6.01×10^{-3}; *p*-toluenesulfonic acid, ●, 2.05×10^{-2}; levopimaric acid, 3.32×10^{-2}; k is the reaction velocity; c, the catalyst concentration in moles/liter, and T the temperature (Å.).

Preliminary experiments indicated that the isomerization of levopimaric acid is retarded by the presence of even trace amounts of water in the medium. The reaction velocity was measured using solutions containing constant amounts of hydrogen chloride and levopimaric acid but varying amounts of water. Results of these experiments, collected in graphical form in Fig. 6, are very similar to those obtained by study of the inhibitive action of water in the acid-catalyzed formation of acetal,[20] in certain anionotropic rearrangements[22] and in many other reactions in anhydrous media as well as of the depressive effect of small amounts of water upon the activity coefficients of hydro-

(22) E. A. Braude, *J. Chem. Soc.*, 443 (1944).

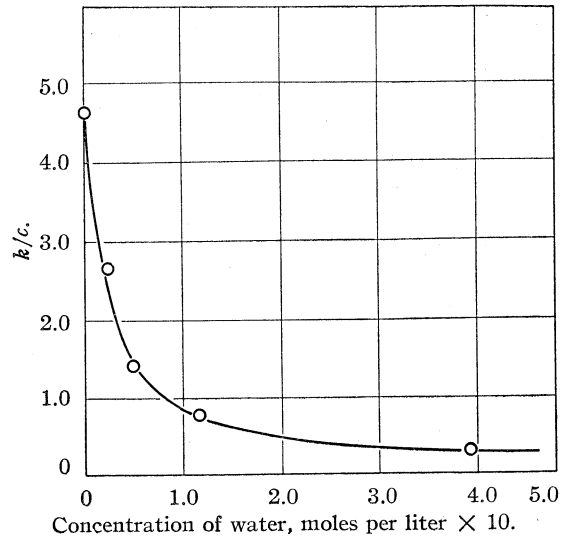


Fig. 6.—Inhibition by water of the hydrogen chloride-catalyzed isomerization of levopimaric acid: concentrations in moles/liter; levopimaric acid, 2.77×10^{-2}; hydrogen chloride, 4.46×10^{-3}; k is the reaction velocity, and c the catalyst concentration in moles/liter.

gen chloride in ethanol.[23] Since water is considerably more basic than alcohols, the equilibrium

$$C_nH_{2n+1}OH_2^+ + H_2O \rightleftharpoons C_nH_{2n+1}OH + H_3O^+$$

very much favors the formation of the hydronium ion[24] which would be expected to function less efficiently as a proton donor than alkoxonium ions. A plausible explanation of the inhibitive effect of low concentrations of water upon acid-catalyzed reactions in alcoholic solution is thus afforded.

Acknowledgment.—The authors take this opportunity to thank Dr. George C. Harris of these laboratories who supplied the levopimaric acid used in this research.

Summary

Isomerization of levopimaric acid in the presence of an acid catalyst leads to reaction mixtures which contain over 90% of abietic acid and small amounts of the starting material. No evidence of the presence of the third isomer, neoabietic acid, in the reaction mixtures can be obtained from ultraviolet spectra.

The isomerization of levopimaric acid in ethanol is catalyzed exclusively by solvated protons and is first order with respect to both levopimaric acid and the catalyst. Assuming complete dissociation of hydrogen chloride in ethanol at the concentrations used, the catalytic coefficient of the reaction (in liters mole^{-1} min.$^{-1}$) is given by $k_{C_2H_5OH_2^+} = 6.3 \times 10^{15}\, e^{-21,450/RT}$. The reaction is inhibited by the presence of water in the medium.

The dependence of reaction velocity upon con-

(23) H. S. Harned and M. H. Fleysher, THIS JOURNAL, **47**, 82 (1925).

(24) H. Goldschmidt and O. Udby, *Z. physik. Chem.*, **60**, 728 (1907).

centration of the catalysts hydrogen chloride and *p*-toluenesulfonic acid is in accord with the predictions of the Debye–Hückel theory, but the behavior of methanesulfonic acid is anomalous. It appears that *p*-toluenesulfonic acid and methanesulfonic acids are incompletely dissociated in ethanol at concentrations of 1×10^{-2} to 1×10^{-1} mole/liter. The value calculated for the dissociation constant of trichloroacetic acid in ethanol is 6.9×10^{-6} and in reasonable agreement with previously published values.

WILMINGTON 99, DELAWARE RECEIVED MAY 12, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, THE UNIVERSITY OF WISCONSIN]

Alkali-sensitive Glycosides of 3-Phenyl-4-hydroxycoumarin[1]

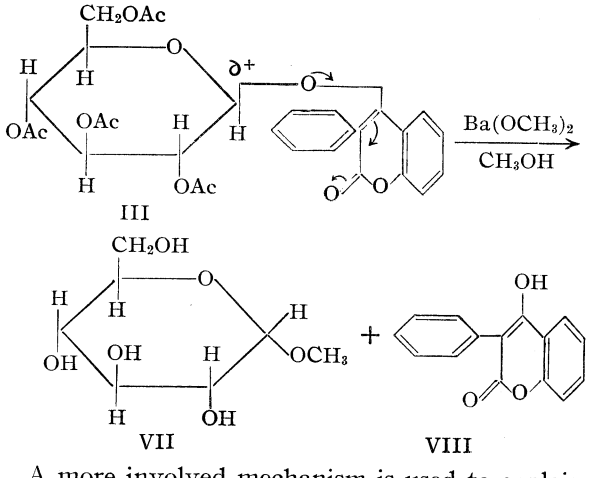
BY LEONARD SPERO,[2] CLINTON E. BALLOU AND KARL PAUL LINK

The synthesis and properties of some β-D-glucosides of 4-hydroxycoumarins were first reported from this Laboratory in 1944.[3] These compounds were made in connection with the biological studies on the hypoprothrombinemic effect of 3,3′-methylene-bis-(4-hydroxycoumarin) [Dicumarol] and related 4-hydroxycoumarins.[4] 4-Hydroxycoumarin D-glucoside tetraacetate (I), 4-hydroxy-6-methylcoumarin D-glucoside tetraacetate (II), 3-phenyl-4-hydroxycoumarin D-glucoside tetraacetate (III), and 3,3′-methylene-bis-(4-hydroxycoumarin) mono-D-glucoside tetraacetate (IV) were prepared by condensing the silver salt of the aglycon with tetraacetyl-D-glucosyl bromide. A modified Robertson method[5] was used in the preparation of 3,3′-methylene-bis-(4-hydroxycoumarin) diglucoside octaacetate (V), and 3-[6-oxo(1)-benzopyrano(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin D-glucoside tetraacetate (VI). Because of the method of preparation and the optical rotation of these glucosides the β-configuration was assigned.

As shown by Huebner, *et al.*,[3] these glucosides are extremely labile to alkali. Compounds I and II were deacetylated by the catalytic barium methoxide procedure. Attempts to deacetylate the glucosides in which there were substituents on position three of the coumarin residue resulted in cleavage of the glucoside linkage. This reaction is unique in that the starting compound is converted to the aglycon and methyl α-D-glucoside (VII). During attempted deacetylation of III, 80% of the starting material was converted to 3-phenyl-4-hydroxycoumarin (VIII) and VII.

Isbell's[6] interpretation of glycoside cleavage rationalizes the fact that the splitting may occur on either side of the glycosidic oxygen. An electrophilic aglycon promotes cleavage of the sugar–oxygen bond, while cleavage of the aglycon–oxygen bond occurs when the sugar residue is able to take electrons from the aglycon.

Cleavage of glycosides under anhydrous methanolic conditions could result in methanolysis, cyclization or unsaturation. This reaction demonstrates the methanolysis type. The formation of methyl α-D-glucoside (VII) indicates that a Walden inversion accompanies the cleavage of the glucosidic linkage, and this would be possible only if the sugar–oxygen bond were the one split. The following scheme, involving the indicated electronic shifts, may be used to rationalize this reaction.



A more involved mechanism is used to explain the products obtained during the alkaline cleavage of V [glucose, VII, and 3,3′-methylene-bis-(4-hydroxycoumarin) monomethyl ether]. For a detailed discussion see ref. 3.

It is conceivable that this reaction would be generally applicable to glycosides of this type.[7] One of the purposes of this study was to ascertain if the nature of the sugar residue played a role in determining the mechanism of the glycosidic cleavage. In order to study the reaction further,

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(2) Present address: Camp Detrick, Frederick, Maryland.

(3) Huebner, Karjala, Sullivan and Link, THIS JOURNAL, **66**, 906 (1944).

(4) Stahmann, Huebner and Link, *J. Biol. Chem.*, **138**, 513 (1941).

(5) Robertson and Waters, *J. Chem. Soc.*, 2729 (1930).

(6) Isbell, *Ann. Rev. Biochem.*, **XII**, 215 (1943).

(7) Dr. C. S. Hudson had originally suggested to one of us (K. P. L.) that this reaction might serve as the route through which certain inaccessible α-glycosides could be realized.

a series of glycosides of 3-phenyl-4-hydroxycoumarin (VIII) was prepared, and the methanolysis was carried out in a similar manner on each.

The silver salt of the aglycon is quite stable, and when treated with the acetylglycosyl bromide, forms the acetylated glycoside in yields of from 56–76%. The products were difficult to crystallize and purify.

The glucoside,[3] galactoside, mannoside and xyloside (all in the D series), which were assigned β-configurations because of the mode of synthesis, were cleaved to form methyl α-D-glycosides. The D-arabinoside, assigned an α-configuration by the same precedence, produced methyl β-D-arabinoside. These results corroborate the generalization of configurational assignment from mode of synthesis if a Walden inversion is assumed.

A study of the rotational changes[8] accompanying the cleavage showed a simple mutarotation curve (Figs. 1 and 2), and varying amounts of the catalytic agent increased the rate at which the reaction occurred (Fig. 3). The reactions were generally quite slow as determined by the length of time required for the rotation to stop changing. Cleavage of the glucoside required about two weeks, while cleavage of the arabinoside was not complete after six months. The concentration of the catalyst was the same in both reactions.

If concentrations of barium methoxide above 0.02 *N* were used, side reactions resulted and uncrystallizable sirups were obtained. In these cases the reaction went with extreme rapidity, the barium salt of the aglycon precipitated from the solution, and the final rotation indicated the formation of the free sugar residue. This may have been due to the presence of a small amount of barium hydroxide in the barium methoxide stock solution, and at higher concentrations of the latter, the former might have become critical.

Experimental

Preparation of the Silver Salt of 3-Phenyl-4-hydroxycoumarin[3] (IX).—Precautions were taken to work in a feeble light. VIII was dissolved in one equivalent of 1.5 *N* aqueous sodium hydroxide and one equivalent of silver nitrate plus 2% excess dissolved in a little water, was added while the solution was being vigorously stirred. The gelatinous, white silver salt which precipitated immediately, was filtered off. It was resuspended in water, collected on a funnel, pressed dry, and washed once with absolute ethanol. The salt was dried over calcium chloride *in vacuo*, finely pulverized, and dried again at 45° and 3 mm. pressure over phosphorus pentoxide. The product varied from a colorless to a light-gray powder; yield 96%.

Preparation of 3-Phenyl-4-hydroxycoumarin β-D-Galactoside Tetraacetate (X).—Pentaacetyl-β-D-galactose prepared according to Erwig and Koenigs[9] was converted to tetraacetyl-D-galactosyl bromide according to Ohle.[10] A mixture of 6.7 g. of IX, 7.2 g. of tetraacetyl-D-galactosyl bromide, 1.3 g. of Drierite and 65 ml. of dry benzene, was shaken in a dark bottle on a mechanical shaker. Upon completion of the reaction, as indicated by a negative free bromide test (no precipitate in a centrifuged sample when it was mixed with a drop of alcoholic silver nitrate and 3 volumes of absolute ethanol), the silver salts were centrifuged off and washed with hot benzene. The combined benzene solutions were concentrated *in vacuo* to a thick sirup. The sirup was taken up in hot methanol and the solution allowed to stand until crystallization was complete. Yield of the crude material was 6.9 g. Yield after one recrystallization was 76%, m. p. 91–

(8) The polarimetric studies were done with the use of a Franz Schmidt and Haensch polarimeter No. 52B with a monochromator attachment.

(9) Erwig and Koenigs, *Ber.*, **22**, 2207 (1889).

(10) Ohle, Marecek and Borjau, *ibid.*, **62**, 849 (1929).

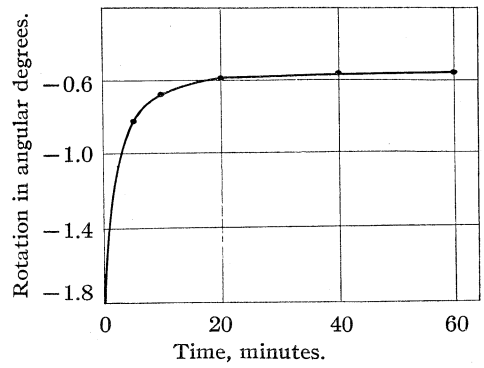


Fig. 1.—Mutarotation of 3-phenyl-4-hydroxycoumarin β-D-glucoside tetraacetate, 0.053 *M* in absolute methanol containing barium methoxide, 0.006 *M*.

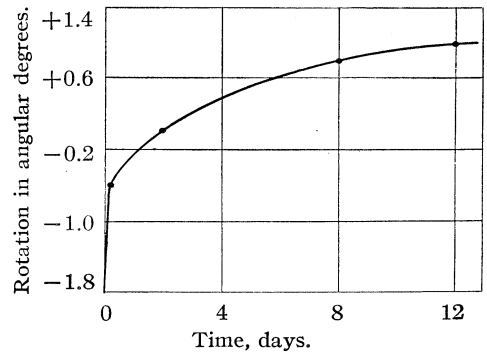


Fig. 2.—Mutarotation of 3-phenyl-4-hydroxycoumarin β-D-glucoside tetraacetate, 0.053 *M* in absolute methanol containing barium methoxide, 0.006 *M*.

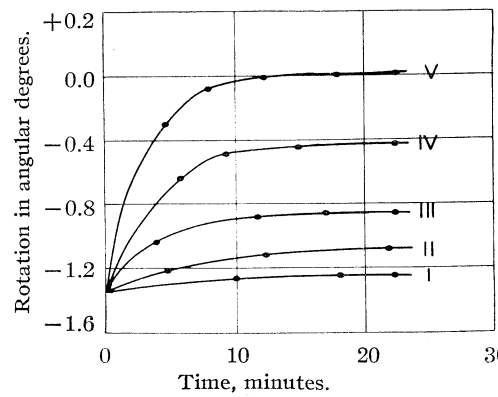


Fig. 3.—The effect of varying concentrations of barium methoxide (milliequivalents/liter of solution) on the methanolysis of 3-phenyl-4-hydroxycoumarin β-D-glucoside tetraacetate (0.058 *M*): I (1.14), II (2.28), III (4.56), IV(9.14), V(18.28).

93°; $[\alpha]^{25}D$ −39.6° (*c*, 1.2, benzene). *Anal.* Calcd. for $C_{29}H_{28}O_{12}$: C, 61.36; H, 4.94. Calcd. for $C_{29}H_{28}O_{12}\cdot{}^1/_2H_2O$: C, 60.31; H, 5.07. Found: C, 60.19; H, 5.27.

When dried over phosphorus pentoxide at 56.5° and 2 mm. pressure for fifteen hours, 96.12 mg. of substance lost 1.52 mg. of water. Calcd. for $C_{29}H_{28}O_{12}\cdot{}^1/_2H_2O$: H_2O, 1.57. Found: H_2O, 1.58.

Preparation of 3-Phenyl-4-hydroxycoumarin β-D-Xyloside Triacetate (XI).—D-Xylose was acetylated to tetraacetyl-β-D-xylose according to Stone.[11] The bromosugar was made by the method of Hudson and Johnson.[12] To 150 ml. of dry benzene in a dark bottle were added 18.7 g. of IX, 16.5 g. of triacetyl-D-xylosyl bromide and 3.0 g. of Drierite. The mixture was shaken for three days or until a centrifuged portion gave the negative test for free bromide as described above.

The silver salts were centrifuged off, washed with hot benzene, and the benzene solution concentrated *in vacuo* to a thick sirup which crystallized from a mixture of ethanol and water. The crude material amounted to 17.0 g. It was recrystallized from methanol; yield 60%, m. p. 120–122°; $[\alpha]^{25}D$ −98.9° (*c*, 0.95, benzene). *Anal.* Calcd. for $C_{26}H_{24}O_{10}$: C, 62.90; H, 4.87. Found: C, 62.79; H, 4.98.

Preparation of 3-Phenyl-4-hydroxycoumarin α-D-Arabinoside Triacetate (XII).—D-Arabinose prepared by the method of Hockett and Hudson[13] was converted directly to the triacetyl-D-arabinosyl bromide according to Chavanne.[14] A mixture of 11.1 g. of the triacetyl-D-arabinosyl bromide, 12.6 g. of IX, 2.0 g. of Drierite and 110 ml. of dry benzene was shaken in a dark bottle for three days. The benzene solution obtained after centrifuging the silver salts off was concentrated to a thick sirup *in vacuo*. The product could not be obtained in a well-crystallized form. It was obtained as a white amorphous powder by pouring a methanolic solution of the sirup into a large volume of water; yield 56%, m. p. 76–96 (gradually softening); $[\alpha]^{25}D$ +43.3° (*c*, 0.9, benzene). *Anal.* Calcd. for $C_{26}H_{24}O_{10}$: C, 62.90; H, 4.87. Calcd. for $C_{26}H_{24}O_{10}\cdot{}^1/_2H_2O$: C, 61.8; H, 4.95. Found: C, 62.1; H, 5.07.

Preparation of 3-Phenyl-4-hydroxycoumarin β-D-Mannoside Tetraacetate (XIII).—Pentaacetyl-β-D-mannose was converted to the acetyl-D-mannosyl bromide according to Micheel.[15] The product was not crystallized, but was used as a sirup. To 100 ml. of dry benzene in a dark bottle were added 9.9 g. of the sirupy tetraacetyl-D-mannosyl bromide, 9.3 g. of IX and 2.0 g. of Drierite. After shaking for three and one-half days the reaction mixture gave a negative test with alcoholic silver nitrate. The silver salts were removed as above, and the benzene solution was concentrated *in vacuo*. The product could not be crystallized but turned to a white amorphous powder on standing. The same powder could be obtained by pouring a methanolic solution of the sirup into water; yield 72%, m. p. 68–72°; $[\alpha]^{25}D$ +29.6° (*c*, 1.4, benzene). *Anal.* Calcd. for $C_{29}H_{28}O_{12}$: C, 61.35; H, 4.94. Calcd. for $C_{29}H_{28}O_{12}\cdot{}^1/_2H_2O$: C, 60.3; H, 5.39. Found: C, 60.39; H, 5.39.

When dried over phosphorus pentoxide at 56.5° and 2 mm. pressure for four days, 78.46 mg. of substance lost 1.10 mg. of water. Calcd. for $C_{29}H_{28}O_{12}\cdot{}^1/_2H_2O$: H_2O, 1.57. Found: H_2O, 1.40.

Methanolysis of 3-Phenyl-4-hydroxycoumarin β-D-Galactoside Tetraacetate (X).—To 7.5 g. of the galactoside dissolved in 600 ml. of absolute methanol[16] was added 3.0 ml. of 0.573 *N* barium methoxide. An aliquot was taken to find the rotation at zero time, −0.98°, and the rotation was followed polarimetrically. Mutarotation ceased after ten days. The final value was +1.24°. Complete conversion to methyl α-D-galactoside would give a rotation of +1.68°.

The reaction mixture was treated with enough 0.1 *N* sulfuric acid to remove the barium. The barium sulfate was removed by filtration through an asbestos mat, and the filtrate concentrated to 50 ml. *in vacuo*. The aglycon that crystallized out during the concentration was filtered off. An equal volume of water was added and the concentration was repeated. A second crop of VIII was obtained. A total of 2.83 g. (90%) was isolated, m. p. 235°.

The filtrate was concentrated to a sirup and a small volume of ethanol added. On scratching, 1.2 g. (47%) of methyl α-D-galactoside crystallized; m. p. 109°, with no depression when mixed with an authentic sample, $[\alpha]^{25}D$ +175.3° (*c*, 1.05, water). Reported for methyl α-D-galactoside, m. p. 110°, $[\alpha]^{20}D$ +179.3° (*c*, 9.1, water). The product was acetylated to the tetraacetate with acetic anhydride and pyridine; m. p. 87°; $[\alpha]^{27}D$ +135.0° (*c*, 0.95, chloroform). Reported for methyl α-D-galactoside tetraacetate, m. p. 87°; $[\alpha]^{20}D$ +132.5° (*c*, 2.9, chloroform).

Methanolysis of 3-Phenyl-4-hydroxycoumarin β-D-Xyloside Triacetate (XI).—To 7.2 g. of the xyloside dissolved in 380 ml. of absolute methanol was added 3.0 ml. of 0.573 *N* barium methoxide. An aliquot was taken to find the rotation at zero time, −3.72°, and the reaction was followed polarimetrically. Mutarotation stopped after seven weeks. The final value was +1.21°. Some of the aglycon that crystallized in the reaction flask was filtered off. Enough 0.1 *N* sulfuric acid was added to remove the barium. The salt was removed by filtration through an asbestos mat, and the filtrate concentrated to 50 ml. *in vacuo*. The aglycon that crystallized out was collected on a funnel. An equal volume of water was added and the solution again concentrated. A third crop of the aglycon was removed to make a total of 2.2 g. (94%), m. p. 235°. The filtrate was concentrated to a sirup which did not crystallize. A small portion of the sirup was acetylated with acetic anhydride and sodium acetate. The product was crystallized from 95% ethanol; m. p. 84°, reported for methyl α-D-xyloside triacetate, m. p. 86°.

Methanolysis of 3-Phenyl-4-hydroxycoumarin α-D-Arabinoside Triacetate (XII).—One gram of the arabinoside was dissolved in 100 ml. of absolute methanol. To the solution was added 0.75 ml. of 0.387 *N* barium methoxide. The rotation at the start was +0.21°. It changed slowly over a period of six months. When it reached +0.92° the rate of mutarotation was about 0.03° per week.

To the solution was added 3.03 ml. of 0.096 *N* sulfuric acid and the barium sulfate removed as above. The filtrate was concentrated to dryness, and the white residue suspended in 5 ml. of water. The aglycon was filtered off; yield 0.5 g., after one recrystallization m. p. 235°.

The filtrate was concentrated to dryness, and the sirup taken up in absolute methanol. After three weeks in the cold, the crystals were collected by filtration; yield 30 mg., m. p. 165–169°. After one recrystallization from methanol, m. p. 167–169°; no depression with an authentic sample of methyl β-D-arabinoside; $[\alpha]^{26}D$ −239.0° (*c*, 1, water); reported for methyl β-D-arabinoside, m. p. 168°, $[\alpha]^{16}D$ −241.1° (*c*, 1, water).

Methanolysis of 3-Phenyl-4-hydroxycoumarin β-D-Mannoside Tetraacetate (XIII).—One gram of XIII was dissolved in 100 ml. of absolute methanol. The polarimetric reading at zero time was +0.36°. To this solution was added 0.75 ml. of 0.387 *N* barium methoxide. The rotation changed to +0.46° in twenty minutes. The rotation did not change for the next five days. Another milliliter of 0.387 *N* barium methoxide was added but the rotation remained constant for the next five days.

An amount of 0.1 *N* sulfuric acid equivalent to the barium was added. The barium sulfate was removed as above, and the filtrate concentrated to dryness. The white powder obtained was suspended in a few milliliters

(11) Stone, *Am. Chem. J.*, **15**, 653 (1893).

(12) Hudson and Johnson, THIS JOURNAL, **37**, 2748 (1915).

(13) Hockett and Hudson, *ibid.*, **56**, 1632 (1934).

(14) Chavanne, *Compt. rend.*, **134**, 661 (1902).

(15) Micheel and Micheel, *Ber.*, **63**, 386 (1930).

(16) The absolute methanol was obtained by refluxing commercial (99.9%) methanol with magnesium turnings (10 g./l.) until the magnesium had reacted completely. The methanol was then distilled and the center fraction was collected in small bottles and stored for use.

of water and the aglycon filtered off; yield 0.2 g., 50%; m. p. 235° after one recrystallization from ethanol and water.

The aqueous filtrate was concentrated to dryness. The sirup was taken up in 1 ml. of methanol. Upon standing in the cold for a week, crystals formed; yield 64 mg., m. p. 184–188°, after one recrystallization from methanol m. p. 188°; no depression when mixed with an authentic sample of methyl α-D-mannoside; $[\alpha]^{28}D$ +86.7° (*c*, 1, methanol). Reported for methyl α-D-mannoside, m. p. 193–194°; $[\alpha]^{20}D$ +87.5° (*c*, 1, methanol).

Effect of Varying Concentrations of Barium Methoxide on the Methanolysis.—A solution of glucoside tetraacetate of VIII was made up to contain 3.33 g. per 100 ml. of methanol. To 10-ml. aliquots, 0.02, 0.04, 0.08, 0.16 and 0.32 ml. of 0.573 *N* barium methoxide was added. The rotation was followed until the change in ten minutes was less than 0.02°. The results are plotted in Fig. 3.

Summary

1. A series of glycosides of 3-phenyl-4-hydroxycoumarin (VIII) has been prepared by condensing the enol silver salt of the aglycon with the respective acetylglycosyl bromides.

2. The glycosides all undergo methanolysis when treated with catalytic amounts of barium methoxide in dry methanol. The mechanism appears to be the same in each case. A Walden inversion accompanies the cleavage. From the β-D-glycosides of VIII are formed methyl α-D-glycosides, and from the α-D-arabinoside of VIII methyl β-D-arabinoside is obtained.

3. An electronic mechanism, in which the electrophilic nature of VIII promotes electronic shifts which labilize the sugar–oxygen bond, is offered as a rationalization of the products of the alkaline cleavage.

MADISON, WISCONSIN RECEIVED JUNE 2, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

Alkaline Methanolysis of Theobromine β-D-Glucoside Tetraacetate[1]

BY CLINTON E. BALLOU AND KARL PAUL LINK

The observations of Huebner, *et al.*,[2] and Spero, *et al.*,[3] concerning the cleavage products formed during the attempted deacetylation of 3-phenyl-4-hydroxycoumarin D-glycoside tetraacetates, have stimulated an investigation of various other alkali labile glycosides. This paper is on the alkaline methanolysis of theobromine D-glucoside tetraacetate (I).

Fischer[4] first described the difficulty of deacetylating certain purine glucoside tetraacetates without cleaving the glucosidic linkage. From theobromine D-glucoside tetraacetate (I) in aqueous alkali, Fischer obtained theobromine and glucose (II). Due to the sensitivity of this glucoside to aqueous acid and alkali, he postulated the glucosidic linkage as being to position 2 or 6 of the enol form of the purine residue.

In our studies of the cleavage of alkali sensitive glycosides the reactions are run in dry methanol[5] in the presence of catalytic amounts of barium methoxide. Under these conditions cleavage involves a methanolysis of the glycosidic linkage, and in those cases reported[2,3] a methyl glycoside and the free aglycon are formed. The cleavage is accompanied by a Walden inversion, and the products formed suggest a mechanism for the cleavage.

According to the mechanism advanced by Isbell,[6] the cleavage anion may add to either the sugar residue or the aglycon, depending upon the shift of electrons between these two parts of the molecule. During the cleavage of the glycosidic linkage under the influence of basic catalysts, a cationoid center is derived from either the sugar residue or the aglycon. If the cation comes from the sugar residue it may be attacked by an anion such as hydroxyl or methoxyl, to give the free sugar or a methyl glycoside. This sugar cation may also be attacked by an anion present within the sugar molecule with the formation of an inner anhydride. If the cationoid center derives from the aglycon it likewise may be attacked by an anion present, again hydroxyl or methoxyl, to give the free aglycon or a methoxyl derivative, or it may coördinate with an adjacent carbon atom to form a carbon–carbon double bond, a proton being expelled during the reaction.

The cleavage of 3-phenyl-4-hydroxycoumarin β-D-glucoside tetraacetate[2] with the formation of methyl α-D-glucoside represents a case in which the oxygen–sugar bond is split. This is indicated because the anion, in this reaction the methoxyl group, becomes attached to the sugar residue, and the configuration of the anomeric carbon atom changes from the β to the α form. Peat[7] has thoroughly reviewed this type of inversion as encountered in alkaline scission of anhydro sugar rings.

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation. This paper was presented before the Division of Sugar Chemistry and Technology at the 116th Meeting of the American Chemical Society, Atlantic City, September, 1949.

(2) Huebner, Karjala, Sullivan and Link, THIS JOURNAL, **66**, 906 (1944).

(3) Spero, Ballou and Link, *ibid.*, **71**, 3740 (1949).

(4) Fischer and Helferich, *Ber.*, **47**, 210 (1914).

(5) The dry methanol was obtained by refluxing commercial (99.9%) methanol with magnesium turnings (10 g./liter) until the magnesium had completely reacted. The methanol was then distilled and the center fraction was collected in small bottles and stored for use.

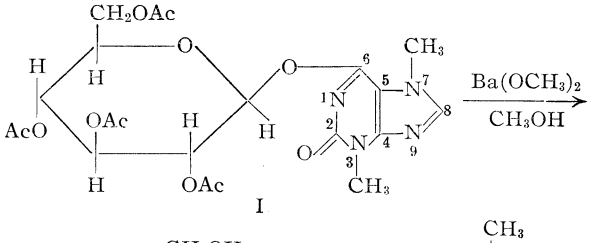
(6) Isbell, *Ann. Rev. Biochem.*, **XII**, 215 (1943).

(7) Peat, *Adv. in Carbohydrate Chem.*, Vol. 2, 45 (1946).

He states, "If the carbonium cation derives from an asymmetric atom then the configuration change becomes manifest in an inversion of optical rotation (Walden inversion)." In the cleavage of the glycosides of 3-phenyl-4-hydroxycoumarin, the cationoid center derives from the anomeric carbon atom, and is attacked by the methoxyl anion. The Walden inversion is manifested by the formation of a methyl α-D-glycoside from the original β-D-glycoside.

Possibly representative of the cleavage of the oxygen–aglycon linkage is the reaction reported by Kuhn and Löw[8] for the alkaline hydrolysis of picrocrocin. In this reaction an unsaturated carbon–carbon linkage arises in the aglucon, indicating cleavage of the oxygen–aglucon bond with a simultaneous expulsion of a proton from an adjacent carbon atom. Evidence was offered to indicate that the mechanism does not follow hydrolysis of the glucoside linkage, with subsequent dehydration of the aglucon to form the unsaturated product.

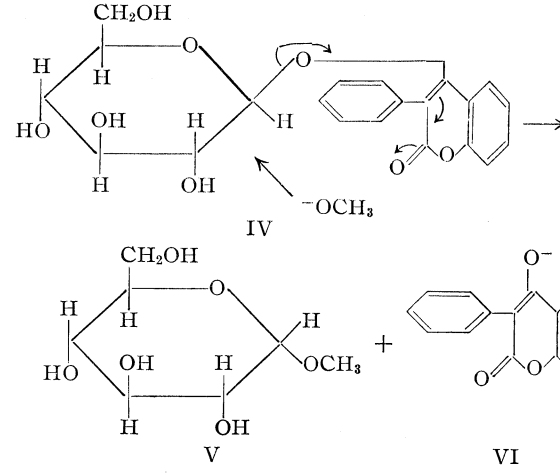
A clear-cut illustration of this second type of glycosidic cleavage is reported herewith. Theobromine D-glucoside tetraacetate (I) was cleaved in absolute methanol containing catalytic amounts of barium methoxide to form glucose (II) and a methoxy-oxy-3,7-dimethyl purine (III) in a yield of 95%. This reaction may be formulated as



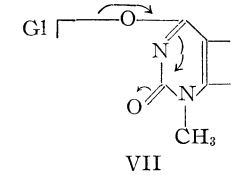
The fact that the aglucon was recovered as a methoxyl derivative indicates that the point of attack of the methoxyl anion was between the glucosidic oxygen and the aglucon. Thus the cationoid center must derive from the aglucon. This is in contrast to the cleavage of the glycosides of 3-phenyl-4-hydroxycoumarin in which the methoxyl anion attacks the anomeric carbon atom of the sugar residue.

An electronic rationalization of this reaction is not embraced by the concepts outlined by Isbell.[6] The expected electron shifts in the aglucon would tend to labilize the sugar–oxygen bond, not the aglucon–oxygen bond. It is possible that the inherent pyridinium nature of the pyrimidine portion of the purine nucleus may be involved.[9]

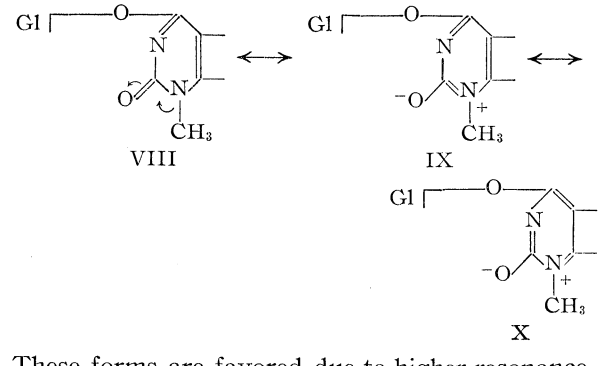
In the structure IV, the indicated "discontinuous" polarizations permit the methoxyl anion to attack the glucose portion to give V and VI.



Representing the glucoside of theobromine (I) as shown in VII, the effect of the carbonyl group would be to permit the same type of attack (weaken the glucosyl oxygen bond).



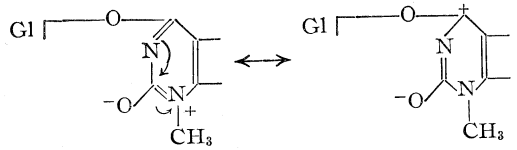
However, the products of methanolysis indicate that this is not so. As shown in VIII, the polarization of the nitrogen in position 3 could establish the continuous system IX, of which X is a resonance hybrid.



These forms are favored due to higher resonance, and would be further stabilized by the barium ions in solution. IX and X may give rise to XI as indicated

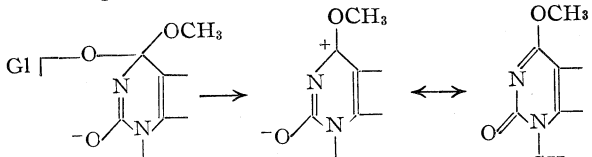
(8) Kuhn and Löw, *Ber.*, **74**, 219 (1941).

(9) We are deeply indebted to Prof. S. M. McElvain of the Chemistry Department of the University of Wisconsin for his generous suggestions concerning the electronic interpretations presented in this paper, and to Dr. H. S. Isbell of the National Bureau of Standards for reading the manuscript prior to submission for publication, and for the helpful ideas he gave.



IX XI

and upon attack by a methoxyl anion, there would be formed the intermediate XII. In methanol solution the decomposition of XII to give XIV and the glucose anion would be favored.



XII XIII XIV

This interpretation implies a fundamental difference in the activating effect upon the glycosidic linkage between the discontinuous system as represented by IV, and the continuous system formulated in IX and X. The latter permit the consideration of an aromatic type structure in which a positive center could become located on the carbon atom of the aglucon involved in the glucosidic linkage, and make this atom susceptible to attack by the methoxyl anion. Obviously the corresponding aromatic oxonium form of the 3-phenyl-4-hydroxycoumarin glycosides is not as effective a contributing structure in the alkaline cleavage of those compounds as is the ammonium cation of IX.

Whether the imidazole ring of the purine nucleus contributes to the labilizing effect of the aglucon is not known. The xyloside of 1-methyluracil is labile to alkali,[10] and it is possible that this same type of methanolysis could be duplicated with this compound.

The exact position of the methoxyl group in the theobromine residue (III) was not established. It could be either on position 2 or 6 as shown, since enolization would be possible at either carbon atom. It seems quite likely that the methoxyl group will occupy the position at which the sugar molecule was attached. The data on the ultraviolet absorption spectra indicate this (Table I).

TABLE I

ULTRAVIOLET ABSORPTION DATA OF PURINES IN METHANOL

Compound	Wave length of maxima, mμ	Mol. ext. coeff. of maxima	Wave length of minima, mμ
Methoxy-oxy-3,7-dimethylpurine (III)	245	0.36×10^4	235
	295	$.85 \times 10^4$	260
Theobromine β-D-glucoside tetraacetate (I)	245	$.33 \times 10^4$	235
	295	$.67 \times 10^4$	260
Theobromine	275	$.91 \times 10^4$	245
Caffeine	275	$.87 \times 10^4$	245

(10) Levene and Sobotka, *J. Biol. Chem.*, **65**, 469 (1925).

It is seen that the maxima and minima of I and III are identical. These are significantly different from the characteristics shown by theobromine and caffeine. By a similar study of the appropriate purine bases it should be possible to determine whether the correct linkage in the glucoside (I) is to position 2 or 6. This method has been most successfully employed by Gulland and Holiday[11] in establishing linkages in the ribosylpurines.

The methoxy-oxy-3,7-dimethylpurine (III) formed in this reaction was characterized by carbon and hydrogen analysis, by a methoxyl determination, by conversion to caffeine via the well known imidoester rearrangement,[12] and by hydrolysis to theobromine. The formation of glucose is indicated by the final rotation of the methanolysis reaction mixture, and by its reducing power.

Hydroxycaffeine D-glucoside tetraacetate, also prepared according to Fischer,[4] was treated in the same manner with dry methanol and barium methoxide. The expected 8-methoxycaffeine was not isolated, and the only substance found was the aglucon hydroxycaffeine. The structure of this glucoside is not strictly comparable to that of the theobromine glucoside, since the glycosidic linkage is to position 8 in the imidazole ring of the purine nucleus. However, it is still labile to alkali, and the methanolysis should produce definitive products. It is possible that these conditions simply effect deacetylation of the glucoside, and the process of working up the reaction, which introduces moisture, hydrolyzes the deacetylated glucoside.

Experimental

Preparation of Theobromine D-Glucoside Tetraacetate (I).—I was made from the silver salt of theobromine and tetraacetyl-D-glucosyl bromide as described by Fischer,[4] but extreme care was necessary in the preparation of the silver salt of theobromine before the reaction could be completed successfully. Thirty grams of theobromine was dissolved in 2 liters of boiling water containing an excess of ammonia, and an ammoniacal solution of silver nitrate (1 equivalent plus 2% excess) was added with stirring. The salt precipitated immediately.

To remove the last traces of ammonia, the precipitated salt was washed several times with water, and then resuspended in about a liter of water. This suspension was concentrated by boiling at atmospheric pressure until the volume was about 200 ml. This step was repeated. The salt was filtered off, washed with absolute ethanol, and dried in an oven at 130°. If this purification of the theobromine salt was not carried out, the glucoside formed in the coupling reaction was cleaved during the subsequent recrystallizations. An acetone–Skelly "B" mixture was found to be a more desirable solvent for recrystallization of the glucoside than ethyl acetate as directed by Fischer.

Methanolysis of Theobromine D-Glucoside Tetraacetate (I).—Three grams of I was dissolved in 240.4 g. of dry methanol.[5] The optical rotation of this solution was −0.37° (25°, 1 dcm.). To this solution was added 1.0 ml. of 0.387 *N* barium methoxide, and the rotation was observed until it stopped changing twelve hours later at the value +0.23° (25°, 1 dcm.). Complete conversion of the glucoside to free glucose would give a value of +0.23 (25°, 1 dcm.). To this solution was

(11) Gulland and Holiday, *Nature*, **132**, 782 (1933).

(12) Hibbert and Johnson, THIS JOURNAL, **52**, 2001 (1930).

added 4.0 ml. of 0.096 *N* sulfuric acid to precipitate the barium ions. The barium sulfate was removed by filtration through an asbestos mat. The filtrate was concentrated to dryness *in vacuo* at 50°. The white crystalline product obtained was dissolved in the minimum amount of hot absolute ethanol. The solution was filtered, and upon cooling, fine white needles separated. They were filtered off and dried in a desiccator over phosphorus pentoxide, yield 1.0 g., m. p. 244–245° when heated rapidly. Otherwise, it begins to sinter at 230° and undergoes rearrangement to caffeine. The substance is very soluble in cold water and hot alcohol. Theobromine is quite insoluble in both.

Anal. Calcd. for $C_7H_3ON_4(OCH_3)$: C, 49.5; H, 5.15; OCH_3, 15.95. Found: C, 49.7; H, 5.38; OCH_3, 15.83.

The ethanolic filtrate was diluted with water to a known volume and an aliquot was taken for the determination of the reducing power by the method of Shaffer and Somogyi.[13] Ninety per cent. of the glucose of the original glucoside was accounted for. The reducing value, the rotation of the reaction given above, and a 95% recovery of the aglucon as the methoxy derivative III establishes the formation of glucose.

Rearrangement of the Methoxy-oxy-3,7-dimethylpurine (III) to Theobromine.—Lactim ethers readily undergo rearrangement to the isomeric lactam ($N{=}C{-}OCH_3 \rightarrow CH_3{-}N{-}C{=}O$) upon heating.[12] This rearrangement was employed to establish the structure of the purine residue III. About 0.2 g. of III was heated in a sealed tube at 290–300° in a lead-bath for one hour. After cooling, the tube was opened and the contents ground up in a mortar. The mixture was heated in a crucible, and the substance that sublimed was collected on the under surface of a watch glass over the crucible. The sublimate was recrystallized from absolute ethanol. It formed fine white needles, m. p. 227–231°, yield 0.15 g. One more recrystallization from the same solvent gave m. p. 230–232°. The substance showed no depression of the melting point when mixed with an authentic sample of caffeine which melted at 232–233°. A methoxyl determination was negative.

(13) Shaffer and Somogyi, *J. Biol. Chem.* **100**, 695 (1933).

The substance formed a mercuric chloride salt, m. p. 246°; reported for caffeine–mercuric chloride salt, m. p. 246°.

Conversion of III to Theobromine.—Ethers of the enolic forms of purines and pyrimidines (lactim ethers) are easily hydrolyzed by dilute acid. A small amount of III was dissolved in water and 0.1 volume of concentrated hydrochloric acid was added. The solution was boiled for five minutes. Upon cooling, it was neutralized with dilute sodium hydroxide and a white crystalline powder separated. This was filtered off and dried. The substance begins to sublime at 300° and melts at 350–355° with decomposition. An authentic sample of theobromine showed this same behavior. The material showed the characteristic solubility of theobromine, and formed an insoluble silver salt when ammoniacal silver nitrate was added to a solution of the substance in dilute ammonia water.

Anal. Calcd. for $C_7H_8O_2N_4$: C, 46.6; H, 4.45. Found: C, 46.8; H, 4.74.

Summary

1. Two purine glucosides, theobromine D-glucoside tetraacetate and hydroxycaffeine D-glucoside tetraacetate were treated with barium methoxide in dry methanol in an attempt to cleave the glucosidic linkage by methanolysis.

2. Methanolysis of theobromine D-glucoside tetraacetate occurred and the products of the cleavage were glucose and a methoxyl derivative of the aglucon. This indicates that the cleavage occurs between the glucosidic oxygen and the aglucon. The cleavage of the glucoside of hydroxycaffeine did not result in products which were indicative of the mechanism of the splitting.

3. An electronic interpretation of this reaction is offered in an attempt to rationalize the results with respect to the present concepts of the various mechanisms involved in the alkaline cleavage of the glycosidic linkage.

MADISON, WISCONSIN RECEIVED JUNE 2, 1949

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORY]

The Reaction of Amides with Isocyanates. II. N-Substituted Amides

BY PAUL F. WILEY

In previous studies[1,2,3] of the reaction of isocyanates with amides in which the amide nitrogen was not substituted the reaction has been shown to occur according to the equation (R′ = H).

$$RCONHR' + R''NCO \longrightarrow RCONCONHR''$$
$$\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\quad R'$$

R = alkyl or aryl
R″ = alkyl or aryl

Recent investigators[4,5,6,7] who have had occasion to use the reaction of nitrogen-substituted amides with isocyanates have generally made no mention of any divergence from the above equation. However, Kühn[1,2] has reported unknown products from formanilide, acetanilide, acetnaphthalide and benznaphthalide and phenyl isocyanate as well as the formation of N,N′-diphenylbenzamidine from benzanilide. A further investigation along the lines of Kühn's[1,2] earlier work has been made in the present study.

In these experiments phenyl isocyanate was the only isocyanate used, and in addition to the amides shown in Table I, N-*n*-butylacetamide, N-isobutylundecylenamide and N-ethylbenzamide were used. The reactions were run using either boiling toluene or xylene as reaction media or no solvent at temperatures varying from 120 to 220°. Table I lists identified products obtained and

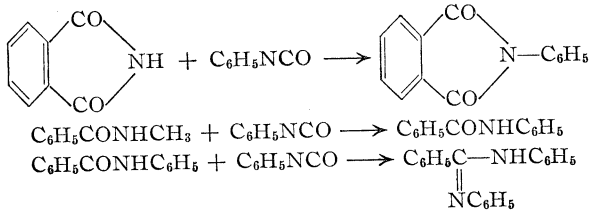
(1) Kühn, *Ber.*, **17**, 2880 (1884).
(2) Kühn, *ibid.*, **18**, 1476 (1885).
(3) Wiley, THIS JOURNAL, **71**, 1310 (1949).
(4) French and Wirtel, *ibid.*, **48**, 1736 (1926).
(5) Lüdke, *Z. physiol. Chem.*, **150**, 215 (1925).
(6) Berchet, U. S. Patent 2,333,914 (November 9, 1943).
(7) Foster, U. S. Patent 2,333,922 (November 9, 1943).

TABLE I

Amide	Solvent or temperature	Time in hours	Yield, %	Product
N-Ethylacetamide	Toluene	24	19.4	1-Acetyl-1-ethyl-3-phenylurea
ϵ-Caprolactam	Toluene	24	92	N-(Phenylcarbamyl)-ϵ-caprolactam
Succinimide	165–180°	7	1.3	1-Succinoyl-3-phenylurea
Acetanilide	Xylene	24	17.3	1-Acetyl-1,3-diphenylurea
N-Methylbenzamide	190°	2	13.2	Benzanilide
Benzanilide	200–220°	4	44	N,N′-Diphenylbenzamidine
Phthalimide	165–180°	4	14	N-Phenylphthalimide

reaction conditions. Of the products reported in Table I, the first three are new. Analyses and method of preparation were felt to be sufficient proof of structure for the first two of these compounds. However, the product obtained from succinimide and phenyl isocyanate did not give an analysis completely consistent with the proposed structure, the yield was very low, and the reaction conditions were severe. It is quite probable that the proposed structure is incorrect, but numerous attempts directed toward an independent synthesis were unsuccessful. The amides used but not listed in Table I could not be caused to react with phenyl isocyanate.

The most generally occurring reaction between substituted amides and isocyanates was the one in accord with the above equation where R′ was alkyl, aryl or acyl. This reaction occurred in all cases where reaction could be made to proceed to any detectable degree in boiling toluene or xylene. Other reactions that occurred were



$$C_6H_5CONHCH_3 + C_6H_5NCO \longrightarrow C_6H_5CONHC_6H_5$$

$$C_6H_5CONHC_6H_5 + C_6H_5NCO \longrightarrow C_6H_5C(=NC_6H_5)-NHC_6H_5$$

These three reactions appear to be quite unlike, but it is probable that the first step in each is an attachment of the isocyanate nitrogen atom to the carbon in the carbonyl group of the amide. Other products were formed in small amounts when ϵ-caprolactam and acetanilide were used at 200°, but these compounds were not identified. The product from acetanilide was a yellow solid melting above 340°. The analysis indicated a molecular formula of $C_{36}H_{28}N_5O_4$, but, due to insolubility of the compound, a molecular weight determination could not be made. The product was undoubtedly the same as that reported by Kühn[2] from the same reaction. From ϵ-caprolactam and phenyl isocyanate at 200° there was obtained a white solid for which the molecular formula $C_{13}H_{14}N_2$ seemed most likely. No satisfactory formula could be postulated for either of these compounds on a basis of the reaction of phenyl isocyanate with the amides. It is probable that they are derived from reaction of phenyl isocyanate with itself.

Reaction of substituted amides with isocyanates is much slower and more difficult to bring about than is the case with unsubstituted amides. In general the completely aliphatic amides in which the nitrogen was relatively basic and little steric hindrance was present, *i. e.*, ϵ-caprolactam, reacted best under mild conditions. Under severe conditions no clear cut pattern of reaction appeared.

Acknowledgment.—I am indebted to Messrs. W. L. Brown, H. L. Hunter and W. J. Schenck for microanalyses.

Experimental[8]

1-Acetyl-1-ethyl-3-phenylurea.—A solution of 11.9 g. (0.1 mole) of phenyl isocyanate and 8.7 g. (0.1 mole) of N-ethylacetamide in 200 cc. of dry toluene was refluxed for twenty-four hours. The solvent was removed by evaporation under reduced pressure. The residue was separated further by distillation *in vacuo* removing material boiling at 55–60° at 0.5 mm. pressure. The semi-solid substance remaining was crystallized twice from alcohol. The yield of 1-acetyl-1-ethyl-3-phenylurea, m. p. 54–58°, was 4.0 g. (19%). Three recrystallizations from alcohol changed the melting point to 55–58°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.80; N, 13.59. Found: C, 63.86; H, 6.80; N, 13.57.

N-Phenylcarbamyl-ϵ-caprolactam.—A solution of 11.3 g. (0.1 mole) of ϵ-caprolactam and 11.9 g. (0.1 mole) of phenyl isocyanate in 200 cc. of dry toluene was refluxed for twenty-four hours. Removal of the solvent by reduced pressure evaporation left a colorless liquid residue which crystallized on cooling. The solid melted at 62–67° and weighed 22.7 g. Recrystallization of the product from alcohol gave a yield of 21.6 g. (92%) of white crystalline material, m. p. 67–69°. A small portion was recrystallized three times from alcohol, m. p. 67–69°.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.24; H, 6.95; N, 12.06. Found: C, 67.00; H, 6.67; N, 12.03.

1,1-Succinoyl-3-phenylurea.—A mixture of 11.1 g. (0.1 mole) of succinimide and 11.9 g. (0.1 mole) of phenyl isocyanate was refluxed for seven hours. The temperature of the reaction mixture ranged from 166 to 178°. The cooled reaction mixture was dissolved in absolute alcohol, and the resulting solution was diluted with dry ether. The supernatant liquid was decanted, and the residue was dissolved in boiling alcohol, treated with charcoal, and recrystallized five times. The product crystallized in shiny white crystals, m. p. 118–120°. The yield was 0.3 g. (1.3%).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.58; N, 12.84. Found: C, 60.17; H, 4.43; N, 13.28.

1-Acetyl-1,3-diphenylurea.—A solution of 6.7 g. (0.05 mole) of acetanilide and 5.95 g. (0.05 mole) of phenyl isocyanate in 100 cc. of dry xylene was refluxed for twenty-four hours. Cooling the reaction mixture caused deposition of 4.4 g. of acetanilide, m. p. 100–105°. After the mixture was filtered, the solvent was removed from the

(8) Melting points are uncorrected.

filtrate by reduced pressure evaporation. The residue was shaken thoroughly with water, and the mixture was allowed to stand overnight. The water was poured off, and the remaining solid was crystallized from alcohol. There was obtained 2.2 g. (17%) of 1-acetyl-1,3-diphenylurea, m. p. 103–105° (lit. 105°).

N-Methylbenzamide and Phenyl Isocyanate.—A mixture of 13.5 g. (0.1 mole) of N-methylbenzamide and 11.9 g. (0.1 mole) of phenyl isocyanate was heated slowly to about 190° and maintained at that temperature for about two hours. The cooled reaction mixture solidified. Five recrystallizations from alcohol gave 2.6 g. (13%) of benzanilide, m. p. 160–162°, and no depression in melting point upon admixture with benzanilide.

N-Phenylphthalimide.—A mixture of 29.4 g. (0.2 mole) of phthalimide and 23.8 g. (0.2 mole) of phenyl isocyanate was refluxed for four hours. The cooled reaction mixture was broken up and boiled in alcohol. The alcohol was removed by filtration. The residue was dissolved in boiling acetic acid and treated with charcoal. This was followed by three recrystallizations from acetic acid. The product was a white solid, m. p. 204–206°, crystallizing in long white needles (lit. m. p. 204°). A yield of 6.2 g. (14%) was obtained.

Anal. Calcd. for $C_{14}H_9NO_2$: N, 6.28. Found: N, 6.25.

N,N'-Diphenylbenzamidine.—A mixture of 11.9 g. (0.1 mole) of phenyl isocyanate and 19.7 g. (0.1 mole) of benzanilide was heated at 200–220° for four hours. The solid obtained on cooling was recrystallized three times from absolute alcohol. The yield of white solid, m. p. 130–132°, was 12.1 g. (44%). A product melting at 140–144° was obtained after five more recrystallizations from alcohol. Kühn[2] reported a melting point of 145°.

Anal. Calcd. for $C_{19}H_{16}N_2$: N, 10.29. Found: N, 10.46.

Phenyl Isocyanate and Acetanilide at 200°.—A mixture of 13.5 g. (0.1 mole) of acetanilide and 11.9 g. (0.1 mole) of phenyl isocyanate was heated at 200–210° for four hours. The product was broken up and boiled with 150 cc. of alcohol. This mixture was cooled and filtered. There was obtained 5.3 g. of a yellow solid which melted at about 350°. This product was recrystallized four times from boiling nitrobenzene. The final compound melted at 340–375° with decomposition.

Anal. Calcd. for $C_{36}H_{28}N_5O_4$: C, 72.72; H, 4.74; N, 11.77. Found: C, 72.79; H, 4.66; N, 11.85.

Phenyl Isocyanate and ε-Caprolactam at 200°.—A mixture of 11.3 g. (0.1 mole) of ε-caprolactam and 11.9 g. (0.1 mole) of phenyl isocyanate was heated at 190–210° for four hours. The cooled reaction mixture was dissolved in boiling alcohol and filtered. The cooled filtrate deposited 1.7 g. of white crystals melting at 202–205°. Charcoaling and concentrating the filtrate gave only a black non-crystallizable oil. Five recrystallizations of the solid product from alcohol gave a sample, m. p. 209–210°.

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.79; H, 7.07; N, 14.12; mol. wt., 198. Found: C, 78.28, 78.65, 79.21; H, 7.30, 6.48, 7.24; N, 14.53, 14.74; mol. wt., 232.

Summary

1. Under mild conditions some nitrogen substituted amides react with phenyl isocyanate to form 1,1-disubstituted-3-phenylureas, and some do not react.

2. The products obtained under severe conditions are varied and not predictable.

INDIANAPOLIS, INDIANA RECEIVED APRIL 16, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF GEORGIA SCHOOL OF MEDICINE]

Chemotherapeutic Agents from Heterocyclic Amines. I. Amine Arsenicals[1]

BY DAVID FIELDING MARSH[2] AND ROBERT A. WOODBURY

The replacement of the amide NH_2 group of sulfanilamide by an NHR radical in which R represents a heterocyclic nucleus has led to compounds which are more potent and are useful for a greater variety of infections.[3] It seemed advisable to utilize these heterocyclic nuclei as substituents in other series of compounds characterized by chemotherapeutic activity.

Gough and King[4] showed the trypanocidal activity of *p*-arsenosobenzamide, and Eagle, Doak, Steinman and Hogan[5] have exhaustively investigated simple derivatives and homologs of this compound and have indicated their favorable treponemicidal activity.

The present communication reports the preparation of *p*-arsenosobenzamidoheterocycles by the reaction of *p*-dichloroarsylbenzoyl chloride with the required amine in benzene followed by hydrolysis of the *p*-arsenosobenzamidoheterocycles.

Experimental Part

Preparation of Amides.—The amine (0.2 mole), recrystallized from benzene before use, was dissolved in 250–600 ml. of warm benzene in an erlenmeyer flask and 12 ml. of freshly distilled *p*-dichloroarsylbenzoyl chloride[6] was added with shaking. The mixture was refluxed for twenty minutes to an hour and the supernatant liquid decanted into a beaker. The material which adhered to the flask was dissolved in warm 95% ethanol. On cooling, the desired *p*-arsenosobenzamide separated and was removed by filtration. Partial evaporation of the filtrate yielded some *p*-arsenosobenzoic acid. The by-product amine hydrochloride can be obtained by complete evaporation of the filtrate. The yields of amide were 35–45%, based on the amount of amine used. By recrystallizing the residual material from absolute methanol instead of 95% ethanol it was possible to prepare the dichloroarsylbenzamides. The decanted benzene contained some of the corresponding dichloroarsylbenzamide along with some unreacted amine. The products are white amorphous powders that are tinged slightly yellow or pink if

(1) Presented on the program of the Medicinal Division at the American Chemical Society meeting, New York, September 11, 1944.

(2) Present address: Department of Pharmacology, West Virginia University School of Medicine, Morgantown, West Virginia.

(3) Fosbinder and Walton, THIS JOURNAL, **61**, 2032 (1939); and Roblin, Williams, Winnek and English, *ibid.*, **62**, 2002 (1940).

(4) Gough and King, *J. Chem. Soc.*, 669 (1930).

(5) (a) Doak, Eagle and Steinman, THIS JOURNAL, **62**, 3012 (1940); (b) Steinman, Doak and Eagle, *ibid.*, **66**, 192 (1944); and (c) Eagle, Hogan, Doak and Steinman, *J. Pharmacol.*, **81**, 142 (1944).

(6) Prepared by the method of Lewis and Cheetham, THIS JOURNAL, **43**, 2117 (1921), from *p*-carboxyphenylarsonic acid which was synthesized either by their method or from *p*-cyanophenylarsonic acid prepared by the method of Linsker and Bogert, *ibid.*, **65**, 932 (1943).

not absolutely pure. The compounds are not water soluble to any appreciable extent but are readily soluble in methanol, ethanol and chloroform. None of these compounds has a definite melting point, but they begin to decompose above 220° and decomposition is complete at 300°.

TABLE I

ARSENOSO COMPOUNDS DERIVED FROM HETEROCYCLIC AMINES

R-*p*-Arsenosobenzamido-Compound	As analysis, % Calcd.	Found	N analysis, % Calcd.	Found	MTD[a] mouse
2-R-Thiazole[b]	25.45	25.2	9.55	9.4	7.5
2-R-4-Methylthiazole	24.3	24.1	9.11	9.1	3.5
2-R-Thiazoline[c]	25.3	25.0	9.48	9.3	30.0
2-R-Pyridine[d]	26.0	26.1	9.74	9.8	2.0
2-R-Pyrimidine[e]	25.9	25.8	14.56	14.4[f]	30.0
2-R-4-Methylpyrimidine[e]	24.7	24.9	13.9	13.7[f]	3.5
2-R-4,6-Dimethylpyrimidine[e]	23.6	23.6	13.3	13.0[f]	3.5
R-*p*-Dichloroarsylbenzamido-					
2-R-Thiazole	21.45	21.4	8.0	7.9	..
2-R-Thiazoline[g]	21.3	21.3	7.8	7.8	..

[a] Maximal tolerated dose for intraperitoneal injection in twenty gram mice, expressed as the number of milligrams/kilogram, and determined by Dr. H. J. Robinson, Merck Institute for Therapeutic Research, Rahway, N. J. [b] 2-Aminothiazole was generously supplied by Dr. D. F. Robertson, Merck & Co., Rahway, N. J. [c] 2-Aminothiazoline was generously supplied by Dr. George W. Raiziss, Dermatological Research Laboratories, Philadelphia, Pa. [d] Previously synthesized by Doak, *et al.*, ref. 5a. [e] 2-Aminopyrimidine, 2-amino-4-methylpyrimidine and 2-amino-4,6-dimethylpyrimidine were generously supplied by Dr. Jackson P. English, American Cyanamid Co., Stamford, Conn., and Dr. E. H. Northey, Calco Chemical Division of the American Cyanamid Co., Bound Brook, N. J. [f] The customary difficulties in determining the nitrogen content of pyrimidines was experienced. The values represent the average of the two highest determinations. The other nitrogen determinations and the arsenic determinations are the average of three or more determinations. [g] The dichloroarsylbenzamide compounds of pyridine, 4-methylthiazole and the pyrimidines were not isolated.

Pharmacological Activity.—We are grateful to Dr. H. J. Robinson of the Merck Institute for Therapeutic Research for carrying out preliminary tests on these compounds. Our own preliminary studies against *T. equiperdum* infections in mice have not proved encouraging. Dr. Robinson found that although the compounds are highly active *in vitro* against *T. equiperdum* and *Dirofilaria immitis*, their high toxicity *in vivo* for the host makes their use undesirable. The results with the 2-*p*-arsenosobenzamidopyridine agree with those of Eagle, *et al.*,[5c] who reported the MTD for mice as 2.3 mg./kg. and although the compound possessed a high treponemicidal activity it had a low chemotherapeutic index.

Summary

The *p*-arsenosobenzoyl derivatives of 2-aminothiazole, 2-aminothiazoline, 2-aminopyridine, 2-amino-4-methylthiazole, 2-aminopyrimidine, 2-amino-4-methylpyrimidine and 2-amino-4,6-dimethylpyrimidine were synthesized. The *p*-dichloroarsylbenzoyl derivatives of 2-aminothiazol- and 2-aminothiazoline have been prepared.

Preliminary pharmacological tests with these compounds have not indicated favorable chemotherapeutic activity.

AUGUSTA, GA. RECEIVED JUNE 16, 1949

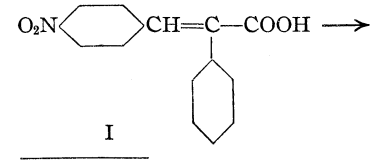
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of Three Aminodiiodophenyl-phenylpropionic Acids

BY T. R. LEWIS, MARGARET G. PRATT, E. D. HOMILLER, B. F. TULLAR AND S. ARCHER

Several years ago a program was initiated in this Laboratory the goal of which was the discovery of a superior radiopaque to be used in clinical cholecystography. As a part of this study, three isomeric aminodiiodophenylphenylpropionic acids were prepared for pharmacological evaluation. The synthesis of these acids is the subject of the present report.

A common structural feature which is shared by the cholecystographic agents examined clinically up to now is the diiodohydroxyphenyl group. It has been suggested that the presence of the hydroxyl in a gall-bladder contrast medium is necessary for visualization of this organ.[1] The utility of our compounds has been determined by Hoppe[2] who has found that the amino may replace the hydroxyl group without impairing the usefulness of the drug.[3] It is our belief that the sole function of these radicals is to facilitate the introduction of the iodine atoms into the benzene ring. The diiodo acid, III, was prepared according to the equations

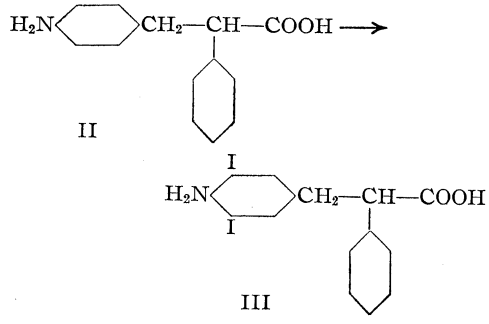


I

(1) Epstein, Natelson and Kramer, *J. Am. Roentgenol.*, **56**, 202 (1946).

(2) Hoppe and Archer, *Federation Proc.*, **8**, 303 (1949).

(3) Other work in this Laboratory has demonstrated that neither the amino nor hydroxyl group is essential for good visualization.



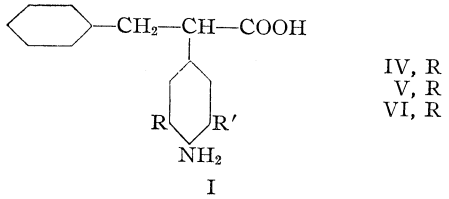
II

III

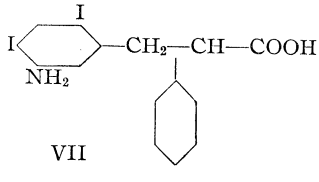
The *p*-nitrobenzaldiacetate was prepared by a slight modification of the standard method.[4] A readily separable mixture of *cis* and *trans* isomers was obtained by modification of known methods.[5,6] Under optimum conditions the combined yield of isomers was 80–85%.[7]

Reduction of the pure higher melting form of I in the presence of Raney nickel catalyst afforded the amino acid, II, in 97% yield. The crude mixed isomers yielded the same substance of comparable purity in 90% of the theoretical amount. The iodination was carried out in dilute acetic acid with iodine monochloride. Analytically pure III was obtained as tan needles after recrystallization from methanol in 64% yield. After our work had been completed the acid, III, was reported by Barnett and coworkers.[8]

The isomeric diiodo acid, V, was synthesized by a similar series of reactions. A mixture of



IV, R = R′ = H
V, R = R′ = I
VI, R = H, R′ = I



VII

isomeric α-*p*-nitrophenylcinnamic acids was obtained in about 80% yield. Buckles[7] obtained only one isomer in 13% yield with the aid of triethylamine. Catalytic reduction of the nitro acid resulted in a quantitative yield of the saturated amino acid, IV.

When the iodination of this compound was performed under conditions which were satisfactory for the formation of the isomeric acid, III, the product, V, was obtained in very small amounts (15–25% yield). The material was contaminated with tarry by-products which were difficult to remove. When iodinated in hydrochloric acid solution, IV gave two products which were separated by chloroform extraction. The soluble product proved to be the desired diiodo acid, V. The insoluble material, which could not be recrystallized and melted at 182°, contained ionic chlorine. When dissolved in sodium hydroxide and the solution carefully acidified a new substance separated. The analytical data indicated that this was the monoiodo acid, VI, and the substance from which it was obtained was the corresponding hydrochloride salt.

It appeared that in acetic acid solution the desired product, V, was being attacked further by the iodine monochloride thereby lowering the yield. It was hoped that removal of the diiodo acid from the reaction zone as soon as it was formed would result in improvement in both quantity and quality of the final product. Actually this proved to be the case, for when chloroform or tetrachloroethane was added to the reaction mixture iodination proceeded smoothly. The over-all yield of analytically pure material, based on α-nitrophenylcinnamic acid, was 64%.

It was of some pharmacological interest to obtain the optical antipodes of V. These were secured by iodination of the active forms of IV. *d*-Desoxyephedrine served as a satisfactory resolving agent for α-phenyl-β-aminophenylpropionic acid since there was a wide difference in solubility of the diastereomeric salts in ethyl acetate. The iodination of the optically active forms of IV was carried out as in the case of the *dl*-form.

The isomer VII was prepared by the same sequence that was used for III and V. The α-phenyl-*m*-nitrocinnamic acid was prepared by Koelsch's method.[6] No attempt was made to find optimum conditions for the iodination step. The position of the iodine atoms in the benzene ring was not determined but it is believed that the expression, VII, is the most probable structure for the compound.

Experimental[9]

α-Phenyl-*p*-nitrocinnamic Acid.—A mixture of 560 g. of *p*-nitrobenzaldiacetate, 340 g. of phenylacetic acid, 228 g. of fused sodium acetate and 560 ml. of acetic acid was refluxed for ten hours. At the end of this time the dark reaction mixture was cooled to 40° and slowly poured with stirring into three liters of water. After cooling to 5° the crystalline product was collected and the filtrate (A) reserved.

The filter cake was broken up and added to a solution of 80 g. of sodium hydroxide in four liters of water. The solution was clarified (Filtercel) and acidified with glacial acetic acid. The acid which separated was collected on a filter, washed with water and dried; yield, 387 g., m. p. 190–205°. The filtrate was combined with filtrate (A) above and acidified strongly with hydrochloric acid. In this way 40 g. of crude low melting isomer (m. p. 100–

(4) "Organic Syntheses," Coll. Vol. II, p. 441 (1941).
(5) Bakunin, *Gazz. chim. ital.*, **27**, II, 36 (1897); **31**, II, 83 (1901).
(6) Koelsch and Johnson, THIS JOURNAL, **65**, 565 (1943).
(7) Buckles and Housman, *ibid.*, **70**, 414 (1948), prepared the acid, I, in 66% yield using triethylamine instead of sodium acetate. They did not report the presence of the low melting isomer.
(8) Barnett, Robinson and Wilson, *J. Chem. Soc.*, 203 (1947).
(9) All melting points unless otherwise specified are uncorrected. Analyses were carried out under the supervision of Mr. M. E. Auerbach.

110°) was obtained; total yield, 427 g. or 70% of the theoretical. When the reflux period was doubled the combined yield of the desired product was increased to 80–85%. When recrystallized from ethanol, the higher melting form melted at 208–210°. The lower melting form was crystallized from dilute ethanol, m. p. 143–145°. Bakunin[5] reported 213–214° and 147°, respectively, as the melting points of these isomers.

β-*p*-Aminophenyl-α-phenylpropionic Acid.—A water solution of 427 g. of the crude mixed acids and 66 g. of sodium hydroxide was reduced at 70° and 1,000 p.s.i. in the presence of Raney nickel catalyst. After six hours the theoretical amount of hydrogen was absorbed. The catalyst was filtered off and the filtrate made acid to congo red with 400 ml. of hydrochloric acid. The solution was cooled in ice and filtered. The crystalline hydrochloride was washed with 20% hydrochloric acid and dried *in vacuo* at 50°; yield, 400 g. (90%), m. p. >270°. Neutralization of the filtrate afforded 20 g. of the amino acid, m. p. 204–205°.

Anal. Calcd. for $C_{15}H_{15}NO_2 \cdot HCl$: Cl, 13.07. Found: Cl, 12.95.

When the pure α-phenyl-*p*-nitrocinnamic acid, m. p. 208–210°, was reduced and the filtrate from the reduction mixture made slightly acidic the free amino acid was secured in 97% of the theoretical yield, m. p. 200–203°.

β-(4-Amino-3,5-diiodophenyl)-2-phenylpropionic Acid.—A solution of 85 g. of the amino acid hydrochloride, II, in 750 ml. of acetic acid and 650 ml. of water was heated to 80°. Then a solution of 36 ml. of iodine monochloride in 120 ml. of acetic acid was added over a period of thirty minutes. After one hour more at this temperature the mixture was cooled to 60° and treated with 20 g. of sodium bisulfite. After cooling to zero degrees the whole was filtered. The product was washed with water and air-dried, wt. 110 g.

The crude acid was dissolved in 600 ml. of warm methanol, treated with 50 ml. of water previously saturated with sulfur dioxide and decolorized with Norite. Water was added to the filtrate to incipient turbidity and the solution cooled. The product was removed by filtration, washed with 70% methanol and dried; wt. 98 g. or 64% of the theoretical yield, m. p. 175–176.8° (cor.).

Anal. Calcd. for $C_{15}H_{13}I_2NO_2$: I, 51.48; N, 2.66. Found: I, 51.87; N, 2.70.

The compound obtained above was light tan. A white product was obtained in the following way. A 120-g. sample of the diiodo acid, m. p. 162–166°, was dissolved in acetone and treated with 25 g. of morpholine. The salt was collected and recrystallized from dilute ethanol. The first crop of needles was collected and dried, wt. 72 g. The melting point depended upon the rate of heating.

Anal. Calcd. for $C_{15}H_{13}I_2NO_2 \cdot C_4H_8NO$: $N_{A.P.}$, 2.44. Found: $N_{A.P.}$, 2.62.[10] The salt was dissolved in 1.5. liters of ethanol and to the solution there was added 200 ml. of 3% sodium hydrosulfite. The cloudy solution was filtered (Filtercel) and the filtrate further diluted with 750 ml. of water. It was saturated with sulfur dioxide and allowed to cool slowly. The next day the heavy white crystals of the pure acid were filtered and dried. The product, which weighed 65 g., melted at 175–176.2° (cor.).

***p*-Nitrophenylacetic Acid.**—The following is better suited for a large scale preparation than the one described in "Organic Syntheses."[11] In a 22-liter flask equipped with a stirrer and reflux condenser there was placed 7 liters of water. Then 7.5 liters of sulfuric acid was added carefully and, when the solution had cooled to 50°, 2500 g. of *p*-nitrobenzyl cyanide was added in one portion. The contents of the flask were heated (Glas-col mantle) until the inner temperature had reached 140–150° and the solution began to reflux. Heating was continued for another fifteen minutes. The total heating time was one and one-half hours. The clear solution was poured into 15 liters of water with vigorous stirring. The nitrophenylacetic acid was removed by filtration, washed with cold water and dried. The cream-colored solid weighed 2700 g. and melted at 151–153°. The yield was 97% of the theoretical.

α-*p*-Nitrophenylcinnamic Acid.—A mixture of 380 g. of *p*-nitrophenylacetic acid, 267 g. of benzaldehyde, 264 g. of fused sodium acetate and 1200 ml. of acetic anhydride was refluxed for twelve hours and poured into 3500 ml. of water. The cooled mixture was filtered and the solid (Fraction A) was saved. The filtrate was made strongly acid with hydrochloric acid and cooled. The pale yellow crystals (Fraction B) were collected.

Fraction A was heated in a sodium carbonate solution and the mixture filtered. The filtrate was extracted with benzene to remove some oily material and then acidified to give 410 g. of the higher melting acid (m. p. 210–213). After recrystallization from ethanol the product melted at 219–221°.[12]

Anal. Calcd. for $C_{15}H_{11}NO_4$: N, 5.20. Found: N, 4.92.

Fraction B, which weighed 44 g. and melted at 140–143° was crystallized from chloroform–ligroin until the melting point reached 150–152°.

Anal. Calcd. for $C_{15}H_{11}NO_4$: N, 5.20. Found: N, 5.25.

In another experiment, in which benzaldiacetate was generated *in situ* from benzaldehyde and acetic anhydride the yield of mixed *cis* and *trans* isomers was 80% after a sixteen-hour heating period. This product was reduced to the amino acid in 93% yield.

α-Aminophenyl-β-phenylpropionic Acid.—The reduction of 48.2 g. of the sodium salt of the higher melting acid was carried out at 350 p.s.i. Hydrogen was absorbed at room temperature and after the gas uptake had slackened the temperature was raised to 130° to complete the reaction. The operation required ninety minutes. The catalyst (Raney nickel) was removed and the filtrate then made faintly acidic. The solid that separated weighed 48.7 g. (98%) and melted at 200–203°. A small sample, after recrystallization from ethanol, melted at 202–204°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: N, 5.81. Found: N, 5.76.

The hydrochloride was prepared by cooling a hot solution of the amino acid in 6 *N* hydrochloric acid. The white needles thus obtained melted above 250°.

Anal. Calcd. for $C_{15}H_{15}NO_2 \cdot HCl$: C, 74.66; H, 6.27. Found: C, 74.47; H, 6.08.

α-(4-Amino-3,5-diiodophenyl)-β-phenylpropionic Acid.—The filtered reduction mixture which originally contained 50 g. of α-*p*-nitrophenylcinnamic acid was acidified with 40 ml. of hydrochloric acid and maintained at 80°.

A mixture of 300 ml. of *sym*-tetrachloroethane (or an equal volume of chloroform), 67.0 g. of iodine monochloride and 180 ml. of 6 *N* hydrochloric acid was warmed to 50°. The solution of amino acid hydrochloride was added over a period of fifteen minutes at 50–55°. The mixture was heated at 55° for ten more minutes and cooled. The layers were separated and the organic phase washed with 250 ml. of 5% sodium hydrosulfite. After washing with water, 5 g. of Darco was added and the mixture stirrred at room temperature for one hour. After the charcoal was removed, the solution was diluted with three volumes of petroleum ether. The solid that separated was collected and dried. It weighed 79.6 g. and melted at 142.6–143.8° (cor.). It was taken up in a mixture of 350 ml. of ethanol and 125 ml. of water and decolorized. The filtrate deposited 65 g. of the diiodo acid, m. p. 141–145.4° (cor.). After recrystallization from benzene–ligroin there was obtained 57.4 g. of cream-colored needles, m. p. 144–146.2° (cor.). The yield was 64% based on the cinnamic acid.

Anal. Calcd. for $C_{15}H_{13}I_2NO_2$: I, 51.48. Found: I, 51.24.

A typical experiment in which the organic solvent was omitted from the reaction mixture gave a product from which two substances were isolated.

(10) Perchloric acid titration of the morpholine nitrogen. This salt was first prepared by M. E. Auerbach of this Laboratory.

(11) "Organic Syntheses," Coll. Vol. I, p. 406.

(12) Walther and Wetzlich, *J. prakt. Chem.*, [2] **61**, 181 (1900), reported the m. p. as 224.5°.

Seventy grams of the amino acid hydrochloride was added to a solution of 900 ml. of 4 *N* hydrochloric acid and 32 ml. of iodine monochloride over a period of two hours. After one-half hour 200 ml. of hydrochloric acid was added and about one hour later 950 ml. of water. The mixture was heated to 80° for one hour and diluted with 500 ml. of water. It was cooled to 35° and saturated with sulfur dioxide. The solid was filtered off and dried, wt. 107 g. It was heated with chloroform and filtered. The insoluble residue weighed 53 g. The chloroform solution was diluted with petroleum ether and cooled. A total of 35 g. of crude diiodo acid was collected which, after recrystallization from ethanol, amounted to 16.0 g. of crystals, m. p. 139–141°. The recrystallization was not smooth since a dark oil tended to separate and contaminate the product. The chloroform-insoluble fraction which melted at 182° (dec.) was probably the hydrochloride of VI.

Anal. Calcd. for $C_{15}H_{14}INO_2 \cdot HCl$: Cl, 8.80. Found: Cl, 8.63. Twenty grams of this material was dissolved in 15% sodium hydroxide and carefully neutralized. The oil that separated soon solidified. It was recrystallized from dilute methanol several times and then melted at 116.8–117.7° (cor.).

Anal. Calcd. for $C_{15}H_{14}INO_2$: I, 34.55. Found: I, 34.60.

α-(4-Acetamido-3,5-diiodophenyl)-β-phenylpropionic Acid.—Thirty grams of α-(4-amino-3,5-diiodophenyl)-β-phenylpropionic acid and 250 ml. of acetic anhydride containing 0.5 ml. of sulfuric acid was refluxed for ninety minutes and poured into water. The semi-solid product was washed with water by decantation and then dissolved in 100 ml. of 10% sodium hydroxide solution. After filtration the solution was made acid with acetic acid. The crystals were filtered and recrystallized from ethanol. There was obtained 19 g. of acetyl body, m. p. 215–217°. After another recrystallization it melted at 221.2–223.5° (cor.).

Anal. Calcd. for $C_{17}H_{15}I_2NO_3$: C, 38.16; H, 2.83; I, 47.44. Found: C, 38.37; H, 3.04; I, 47.60.

Resolution of *dl*-α-(4-Aminophenyl)-β-phenylpropionic Acid.—A solution of 240 g. of the *dl*-amino acid and 160 g. of *d*-desoxyephedrine in 2500 ml. of ethyl acetate was allowed to stand at 25° for one hour. The crystals were filtered and recrystallized from ethyl acetate. In this way 129 g. of a pure diastereomeric salt, m. p. 148–150°, was secured. A 120-g. sample was dissolved in 2500 ml. of boiling water and slowly acidified with 50 ml. of acetic acid. On cooling, 70 g. of pure *d*-α-(4-aminophenyl)-β-phenylpropionic acid deposited. The acid melted at 186–188°; $[\alpha]^{25}D$ (5% in H_2O) +102°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: neutral equivalent, 241.1. Found: neutral equivalent, 240.2.

The ethyl acetate filtrate from the original crystallization was concentrated to dryness *in vacuo*. The residue was dissolved in water and made strongly basic. The desoxyephedrine was gathered with ether. In this way 100 g. of the resolving agent was recovered. The aqueous solution was acidified and the crude *l*-amino acid was filtered off.

The product was dissolved in 1600 ml. of boiling ethyl acetate and 104 g. of *l*-desoxyephedrine added. On cooling a salt separated which was recrystallized from the same solvent. It weighed 115 g. and melted at 148–150°. Thirty three grams of this salt was converted to 19 g. of the *l*-amino acid, which melted at 186–188°, $[\alpha]^{25}D$ (5% in water) −103°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: neutral equivalent, 241.1. Found: neutral equivalent, 239.5.

***d*-α-(4-Amino-3,5-diiodophenyl)-β-phenylpropionic Acid.**—The *d*-amino acid (70 g.) was iodinated according to the procedure described for the *dl* compound. However, the diiodo acid was separated from the chloroform solution by extraction with ammonium hydroxide in which the ammonium salt of the diiodo acid was insoluble. It was collected, washed with acetone and dried, wt. 125 g. It was dissolved in water containing a few ml. of ammonium hydroxide and slowly acidified with acetic acid. The product was collected, dried and recrystallized from chloroform–petroleum ether. There was recovered 87 g. (63%) of pure material, m. p. 118.4–119.8° (cor.), $[\alpha]^{25}D$ (1.5% in 95% ethanol) +88.5°.

Anal. Calcd. for $C_{15}H_{13}I_2NO_2$: C, 36.54; H, 2.66; I, 51.48. Found: C, 36.39; H, 2.79; I, 51.75.

***l*-α-(4-Amino-3,5-diiodophenyl)-β-phenylpropionic Acid.**—Seventeen grams of the *l*-amino acid gave 13.0 g. of the *l*-diiodo acid, m. p. 118–120° (cor.), $[\alpha]^{25}D$ (1.5% in 95% ethanol) −88.4°. The specimen of the iodinated product which was first obtained melted at 102.5–103.5° (cor.). The rotation and analytical data were the same as that obtained for the higher melting form. Apparently this was an unstable polymorph since on standing it changed to the higher melting form. Once the latter was obtained we were unable to secure the low-melting compound.

Anal. Calcd. for $C_{15}H_{13}I_2NO_2$: C, 36.54; H, 2.66; I, 51.48. Found: C, 36.68; H, 2.70; I, 51.60.

α-Phenyl-*m*-nitrocinnamic Acid.—A mixture of 16.0 g. of *m*-nitrobenzaldehyde, 13.6 g. of phenylacetic acid, 16.0 g. of fused sodium acetate and 51 ml. of acetic anhydride was refluxed for sixteen hours. The whole was poured into water, cooled and filtered. The solid (Fraction A) was dissolved in 200 ml. of 3% sodium hydroxide solution, extracted with benzene and acidified with 11 ml. of acetic acid. In this way 21.1 g. of a crystalline solid, m. p. 130–140°, was obtained. The filtrate was combined with the one obtained above and acidified strongly with hydrochloric acid. The solid that separated weighed 2.2 g. and melted at 160–170° (Fraction B). The combined yield, 23.3 g., was 87% of the theoretical. This material was suitable for use in the reduction step.

Fraction A was twice recrystallized from ethanol. Seven grams of pure isomer, m. p. 183.8–185.2° (cor.), was obtained. Fraction B was purified in the same way, m. p. 193–196°.[13]

β-*m*-Aminophenyl-α-phenylpropionic Acid.—A solution of 48.2 g. of the nitrocinnamic acid in 500 ml. of 0.4 *N* sodium hydroxide was reduced at 70° using Raney nickel catalyst. Slight acidification of the filtrate from the catalyst resulted in the deposition of a gummy solid. The *p*H was adjusted to 7 and the suspension warmed on the steam-bath. The gum gradually solidified. It was filtered and dried. It weighed 46.4 g. (96%) and melted at 129–132°. After recrystallization from water the product melted at 131–132°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27. Found: C, 74.62; H, 6.07.

β-(5-Amino-2,4-diiodophenyl)-α-phenylpropionic Acid.—The amino acid (49.0 g.) was dissolved in 800 ml. of acetic acid and heated to 80°. A solution of 23 ml. of iodine monochloride in 150 ml. of acetic acid was added over a period of forty minutes. The mixture was heated at 80–90° for an additional hour, cooled and filtered. The filter cake was washed with acetic acid and then ether. The crude material amounted to 90 g. After two recrystallizations from dilute ethanol (sulfur dioxide was used to decolorize the solution in the first crystallization) the pure diiodo acid melted at 205–205.4° (cor.) and weighed 26.5 g.

Anal. Calcd. for $C_{15}H_{13}I_2NO_2$: I, 51.48; N, 2.84. Found: I, 51.90; N, 2.76.

Summary

1. The preparation of β-(4-amino-3,5-diiodophenyl)-α-phenylpropionic acid, α-(4-amino-3,5-diiodophenyl)-β-phenylpropionic acid and β-(5-amino-2,4-diiodophenyl)-α-phenylpropionic acid has been described.

2. The resolution of α-(4-aminophenyl)-β-phenylpropionic acid has been achieved and the resulting optical antipodes converted to the corresponding diiodo derivatives.

RENSSELAER, NEW YORK RECEIVED MARCH 14, 1949

(13) Bakunin (ref. 5) reported 181–182° and 195–196° as the melting points of the isomers.

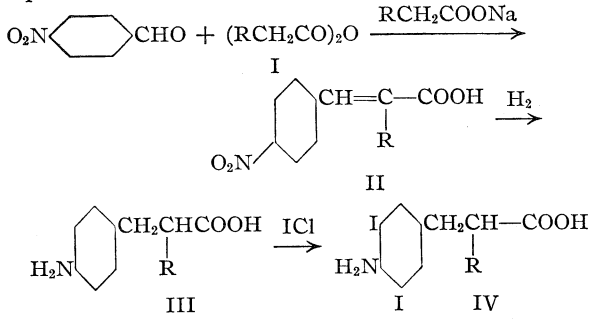
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of Some Iodinated Aminophenylalkanoic Acids

BY T. R. LEWIS AND S. ARCHER

In a previous communication the synthesis of three isomeric (amino-diiodophenyl)-phenylpropionic acids was reported.[1] It was found that two of these concentrated sufficiently in the gall-bladder so as to render this organ opaque to X-rays.[2] It seemed advisable to determine whether one of the phenyl radicals may be replaced by another hydrocarbon group without impairing the efficiency of the compounds as contrast media. While this work was in progress two papers appeared in which it was shown that certain (diiodo-hydroxyphenyl)-alkanoic acids did provide visualization of the gall-bladder for radiological examination.[3,4] The compounds reported below were fed orally to animals and after a suitable interval cholecystograms were obtained. The compounds represented by IV produced adequate visualization of the gall-bladder except in the cases where R contained a cyclohexyl group.

The (4-amino-3,5-diiodophenyl)-alkanoic acids were prepared according to the following general equations.

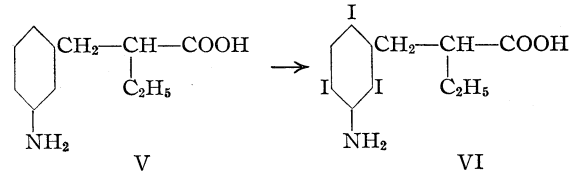


The anhydrides, I, were prepared according to the general procedure of Allen, *et al.*[5] These condensed with *p*-nitrobenzaldehyde in the presence of the sodium salt of the corresponding acid to give II in yields varying from 25–80%. In one preparation (R = *i*-amyl) we employed triethylamine in place of sodium isoheptanoate and secured the acid II (R = *i*-amyl) in 52% yield. In contrast to the aromatic series in no instance were we able to isolate more than one isomer corresponding to II.

Reduction of the unsaturated nitro acids was carried out with the aid of Raney nickel catalyst and the iodination of the resulting amino acids was carried out as described previously.[1]

Condensation of *m*-nitrobenzaldehyde with butyric anhydride in the presence of sodium butyrate resulted in the formation of α-ethyl-*m*-nitrocinnamic acid in 72% yield. When triethylamine was used as the condensing agent the yield fell off to 52% of the theoretical.

Reduction of the acid gave V, which, surprisingly, was quite low melting and difficult to obtain analytically pure. Both methods A and



B were tried but the latter did not seem to offer any advantages with respect to yield. The substance which was isolated from the reaction mixture proved to be the triiodoacid, VI. It may be recalled that when β-(*m*-aminophenyl)-α-phenylpropionic acid was iodinated only the diiodo acid was secured.[1] It is probable that the bulkier phenyl group prevented the third iodine atom from entering the remaining position ortho to the amino group.

Experimental[6]

Preparation of the Acid Anhydrides (I).—Without exception, the method described in "Organic Syntheses"[5] was used. Most of the anhydrides have been described previously.

β-Cyclohexylpropionic anhydride was obtained in 71% yield. It boiled at 154–158° at 0.5 mm., $n^{25}D$ 1.4720.

Anal. Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.74; H, 10.15.

γ-Cyclohexylbutyric anhydride was obtained in 68% yield. It boiled at 169–172° at 0.5 mm., $n^{25}D$ 1.4730.

Anal. Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.34; H, 10.45.

α-Ethyl-*m*-nitrocinnamic Acid.—A mixture of 100 g. of *m*-nitrobenzaldehyde, 210 g. of butyric anhydride and 73 g. of dry sodium butyrate was heated with stirring at 140° for seven hours. The red reaction mixture was cooled and then steam distilled for four hours, when crystals appeared in the flask. These were filtered and dried, wt., 130 g. The product was dissolved in 2 *N* sodium hydroxide and the solution filtered. After acidification with hydrochloric acid, the acid which separated was collected and recrystallized from dilute ethanol. In this way there was obtained 105 g. of the acid which melted at 140–142° (uncor.).

Anal. Calcd. for $C_{11}H_{11}NO_4$: N, 6.33. Found: N, 6.35.

The nitrocinnamic acids listed in Table I were prepared by essentially the same method. In the cases wherein the alkanoic acids were not volatile with steam, the hydrolyzed reaction mixture was dissolved in sodium hydroxide solution and then extracted with ether. The basic layer was acidified and the organic acids removed with ether. The solution was concentrated and the residue leached with a

(1) Lewis, Pratt, Homiller, Tullar and Archer, THIS JOURNAL, **71**, 3749 (1949).

(2) Hoppe and Archer, *Fed. Proc.*, **8**, 303 (1949).

(3) Epstein, Natelson and Kramer, *Am. J. Roentgenol.*, **56**, 202 (1946).

(4) Pratt, Hoppe and Archer, *J. Org. Chem.*, **13**, 576 (1948).

(5) Allen, Kibler, McLachlin and Wilson, *Org. Syntheses*, **26**, 1 (1946).

(6) Analyses were performed under the supervision of Mr. M. E. Auerbach of this Laboratory.

TABLE I

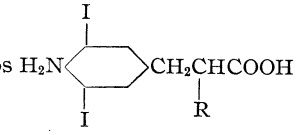
PROPERTIES OF THE α-ALKYL-*p*-NITROCINNAMIC ACIDS AND THE α-ALKYL-*p*-AMINOPHENYLPROPIONIC ACIDS

	α-Alkyl-*p*-nitrocinnamic acids					α-Alkyl-*p*-aminophenylpropionic acids					
R =	Yield, %[b]	M. p., °C.[c]	Formula	Nitrogen, % Calcd.	Found	Yield, %	Solvent	M. p., °C.[e]	Formula	Nitrogen, % Calcd.	Found
C_2H_5	80	168–169	$C_{11}H_{11}NO_4$	6.33	6.17	92	C_6H_6	129–130	$C_{11}H_{15}NO_2$	7.25	7.28
n-C_3H_7	39	132–134	$C_{12}H_{13}NO_4$	5.96	5.86	82	CH_3OH–H_2O	151–153	$C_{12}H_{17}NO_2$	6.76	6.73
n-C_4H_9	70	162–163	$C_{13}H_{15}NO_4$	5.62	5.55	79	C_2H_5OH–H_2O	151.5–152	$C_{13}H_{19}NO_2$	6.33	6.28
n-C_5H_{11}	37	167–169	$C_{14}H_{17}NO_4$	5.36	5.32	93	C_6H_5–Lig.[d]	140–142	$C_{14}H_{21}NO_2$	5.95	5.92
i-C_5H_{11}	52	163–164	$C_{14}H_{17}NO_4$	5.36	5.13	99	C_2H_5OH–H_2O	161–162.5	$C_{14}H_{21}NO_2$[f]		
C_6H_{11}[a]	25	181–183	$C_{15}H_{17}NO_4$	5.09	5.04	95	C_2H_5OH	215–216	$C_{15}H_{21}NO_2$	5.66	5.64
$C_6H_{11}CH_2$[a]	42	195–196.5	$C_{16}H_{19}NO_4$	4.84	4.60	97	C_6H_6	176–177	$C_{16}H_{23}NO_2$[g]		
$C_6H_{11}CH_2CH_2$[a]	45	170–172	$C_{17}H_{21}NO_4$	4.62	4.64	95	C_2H_5OH	176–177	$C_{17}H_{25}NO_2$	5.09	5.05

[a] C_6H_{11} = Cyclohexyl. [b] All the nitro acids were purified by recrystallization from either ethanol or dilute ethanol. The yields are calculated on the basis of purified compounds. [c] Uncorrected. [d] Lig. = Ligroin. [e] Corrected. [f] *Anal.* Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00. Found: C, 71.65; H, 8.40. [g] *Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.87. Found: C, 73.91; H, 8.80.

TABLE II

PROPERTIES OF THE α-ALKYL-β-(4-AMINO-3,5-DIIODOPHENYL)-PROPIONIC ACIDS



R =	Yield, %	M. p. (cor.), °C.	Method[a]	Solvent	Morpholine salt M. p. (uncor.), °C.	Formula	Iodine, % Calcd.	Found
C_2H_5	54	114.2–115.1	A	Dil. methanol	130–132	$C_{11}H_{13}I_2NO_2$	57.03	57.00
n-C_3H_7	54	121–121.8	A	Dil. methanol	131–133	$C_{12}H_{15}I_2NO_2$	55.29	55.68
n-C_4H_9	60	108–109.2	B	Dil. methanol		$C_{13}H_{17}I_2NO_2$	53.65	53.75
n-C_5H_{11}	40	104–105.7	A	Benzene–ligroin	117–119	$C_{14}H_{19}I_2NO_2$	52.11	51.90
i-C_5H_{11}	20	100–102	B	Dil. methanol	105–107	$C_{14}H_{19}I_2NO_2$	52.11	52.40
C_6H_{11}[b]	81	172–174.3	B	Dil. ethanol		$C_{15}H_{19}I_2NO_2$	50.87	50.32
$C_6H_{11}CH_2$[b]	83	142–144	B	Dil. ethanol		$C_{16}H_{21}I_2NO_2$	49.46	49.30
$C_6H_{11}CH_2CH_2$[b]	62	123–123.6	A	Dil. ethanol	129–133	$C_{17}H_{23}I_2NO_2$	48.14	47.95

[a] Details of Methods A and B are found in the Experimental Part. [b] C_6H_{11} = Cyclohexyl.

large volume of petroleum ether. The insoluble material was the desired α-alkyl-*p*-nitrocinnamic acid.

α-Ethyl-β-(*m*-aminophenyl)-propionic Acid.—Fifty grams of the nitro acid was dissolved in 500 ml. of ether containing 9.1 g. of sodium hydroxide and reduced at 70° with Raney nickel catalyst. After two hours reduction was complete. The filtered solution was made slightly acidic with acetic acid and concentrated to about 200 ml. A few ml. of acetic acid was added whereupon an oil separated which gradually solidified. It weighed 20 g. The supernatant liquid was decanted and concentrated to dryness *in vacuo*. The residue was leached with boiling ether. The leachings were concentrated to leave a viscous oil which crystallized on cooling and seeding (wt. 20 g.). The solids were combined and recrystallized from benzene–petroleum ether (Darco). The product, which melted at 67–70° weighed 34.5 g. and was suitable for use in the iodination. Further purification raised the m. p. to 78–80°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.21.

The amino acids listed in Table II were prepared by the same procedure. In all cases careful acidification of the filtered reduction mixture caused the compounds to separate in the yields indicated and in satisfactory condition for use in the next step. The analytical samples were obtained after one or two crystallizations from the solvents noted.

β-(Amino-2,4,6-triiodophenyl)-α-ethylpropionic Acid.—A solution of 34.0 g. of β-(*m*-aminophenyl)-α-ethylpropionic acid in 110 ml. of 6 *N* hydrochloric acid was warmed to 70°. Then a solution of 94.3 g. of iodine monochloride in 220 ml. of 6 *N* hydrochloric acid was added in one portion. A dark oil separated almost immediately. After one hour 500 ml. of water was added over a fifteen-minute period. The oil solidified. While the temperature was kept at 70°, 1000 ml. of water and 28.5 g. of iodine monochloride was added during the next five hours. The whole was cooled and filtered. The crude, dried solid which weighed 103 g. was crystallized from chloroform–ligroin. It then weighed 74 g. and melted at 147–150°. After three crystallizations from dilute methanol (Darco was used in the first two) there was obtained 42 g. of cream-colored needles melting at 155.2–157° (cor.) (42%).

Anal. Calcd. for $C_{11}H_{13}I_2NO_2$: I, 66.68. Found: I, 66.70.

β-(4-Amino-3,5-diiodophenyl)-α-propylpropionic Acid (Method A).—A solution of 26.2 g. of iodine monochloride in 200 ml. of 6 *N* hydrochloric acid was warmed to 70°. To the stirred solution there was added over a period of ninety minutes a solution of 16.0 g. of β-(*p*-aminophenyl)-α-propylpropionic acid in 440 ml. of 0.12 *N* hydrochloric acid. After one-half hour an oil separated. It gradually solidified. After one hour more at 70° the mixture was cooled, diluted with 500 ml. of water and saturated with sulfur dioxide. The product was filtered and dried. It melted at 111–113° and amounted to 32 g. It was recrystallized from dilute methanol with practically no change in melting point. The compound (29.5 g.) was dissolved in ether and treated with a slight excess of morpholine. The salt was filtered and recrystallized twice from benzene–ligroin. The pink plates melted at 130–132°. The crystals were dissolved in methanol and the solution diluted with water. It was then saturated with sulfur dioxide and further diluted to the point of incipient crystallization. On slow cooling 19.0 g. of the product separated which melted at 121–121.8° (cor.).

Anal. Calcd. for $C_{12}H_{15}I_2NO_2$: C, 31.39; H, 3.29. Found: C, 31.52; H, 3.18.

β-(4-Amino-3,5-diiodophenyl)-α-ethylpropionic Acid (Method B).—A solution of 87.4 g. of iodine monochloride in 150 ml. of 8 *N* hydrochloric acid and 300 ml. of chloroform was stirred and warmed to maintain a gentle reflux. A solution of β-(*p*-aminophenyl)-α-ethylpropionic acid in dilute hydrochloric acid prepared by acidifying the reduction mixture from 50 g. of α-ethyl-*p*-nitrocinnamic acid was added over a forty-minute period. After refluxing for forty minutes more the two-phase system was cooled and the layers separated. The aqueous portion was washed with chloroform. The combined organic layers were washed with two 150-ml. portions of water, two 120-ml. portions of 5% aqueous sodium hydrosulfite and again with water. The chloroform solution was dried over Drierite and diluted with petroleum ether. On standing 66.5 g. of the crude diiodo acid separated. After recrystallization from dilute methanol with the aid of Darco there was obtained 58.7 g. of pure product which melted at 114.2–115.1° (cor.).

Summary

1. The preparation of several β-(4-amino-3,5-diiodophenyl)-α-alkylpropionic acids has been described. These were obtained by iodination of the corresponding α-alkyl-β-(aminophenyl)-propionic acids which in turn were secured by catalytic reduction of the α-alkyl-*p*-nitrocinnamic acids.

2. α-Ethyl-β-(*m*-aminophenyl)-propionic acid gave a triiodo acid when treated with iodine monochloride.

RENSSELAER, NEW YORK RECEIVED MAY 10, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF LOUISVILLE, SCHOOL OF MEDICINE]

Reaction of Aliphatic Amines with 3-Nitro-4-chlorophenylarsonic Acid

BY ROBERT L. MCGEACHIN

In the study of the preparation of organic arsenicals of possible therapeutic use against protozoa and spirochetes, it has been found[1,2,3,4] that 3-nitro-4-chlorophenylarsonic and 3-nitro-4-bromophenylarsonic acids will react with certain amines and phenols to give 3-nitro-4-alkylaminophenylarsonic and 3-nitro-4-phenoxyphenylarsonic acids. There are a number of amines that have not been used in this type reaction, however, particularly the polyethylenepolyamines, so it was decided to investigate the preparation of these substituted 4-amino compounds.

In all cases the products of these condensation reactions were yellow solids, soluble in dilute alkali giving blood-red solutions. The product obtained from tetraethylenepentamine, however, precipitated from solution as a heavy oil and resisted all attempts to crystallize it. For this reason it was isolated as the dipicrate. The products obtained from aminoethylethanolamine and aminoethylmorpholine were very soluble in water, probably due to the character of the side-chains, so that the yields here were low and the products were isolated as hydrates. In the condensation with dipropylenetriamine the product obtained constantly contained more arsenic than the theoretical amount for the product from one mole of amine and one mole of arsonic acid. Though several runs with increasing amounts of amine were tried, the desired product was not obtained.

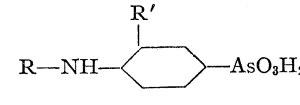
The condensation of 2-amino-2-methyl-1-propanol with 3-nitro-4-chlorophenylarsonic acid did not proceed satisfactorily under standard conditions but was successful when an excess of the amine was heated with the arsonic acid at 160–170° for six hours. Apparently the amino group in 2-amino-2-methyl-1-propanol, which is linked to a tertiary carbon atom, is not reactive enough to allow condensation in aqueous solution at the lower temperatures. An attempt at a similar condensation using 2-amino-2-methyl-1,3-propanediol was unsuccessful.

(1) Maclay and Hamilton, THIS JOURNAL, **54**, 3310 (1932).
(2) Fourneau and Funke, *Bull. soc. chim.*, **43**, 889 (1928).
(3) King, *J. Chem. Soc.*, 1094 (1927).
(4) Cragoe and Hamilton, THIS JOURNAL, **67**, 536 (1945).

Experimental

General Procedure for the Condensation of 3-Nitro-4-chlorophenylarsonic Acid with Amines in Aqueous Alkali.—Five grams of 3-nitro-4-chlorophenylarsonic acid, 15 ml. of 10% sodium hydroxide, 10 ml. of water and 3–5 ml. of the amine were heated, under reflux, at 135–140° for three to eight hours. The solution was cooled, made neutral to congo red with concd. hydrochloric acid. The product precipitated out as a yellow solid (except in the case of tetraethylenepentamine where the product was a thick brown oil). The product was redissolved in 5% sodium hydroxide, the solution charcoaled, filtered, and the yellow solid reprecipitated by addition of concd. hydrochloric acid to the congo red neutral point. The

TABLE I



R	R′	Formula	% Arsenic[a] Calcd.	Found
$-CH_2CH_2NHCH_2CH_2NH_2$	NO_2	$C_{10}H_{17}O_5N_4As$	21.53	21.64
$-CH_2CH_2NHCH_2CH_2NH_2$	NH_2	$C_{10}H_{19}O_3N_4As$	23.57	23.48
$-(CH_2CH_2NH)_2CH_2CH_2NH_2$	NO_2	$C_{12}H_{22}O_5N_5As$	19.15	18.94
$-(CH_2CH_2NH)_2CH_2CH_2NH_2$	NH_2	$C_{12}H_{24}O_3N_5As$	20.77	20.98
$-(CH_2CH_2NH)_3CH_2CH_2NH_2$	NO_2	$C_{26}H_{33}O_{19}N_{12}As$[b]	8.41	8.60
$-CH_2CH_2NHCH_2CH_2OH$	NO_2	$C_{10}H_{16}O_6N_3As$[d]	20.41	20.29
$-CH_2CHNH_2CH_3$	NO_2	$C_9H_{14}O_5N_3As$	23.49	23.17
$-CH_2CHNH_2CH_3$	NH_2	$C_9H_{16}O_3N_3As$	25.95	25.61
$-CH_2CHOHCH_3$	NO_2	$C_9H_{13}O_6N_2As$	23.41	23.30
$-CH_2CH_2NC_4H_8O$	NO_2	$C_{12}H_{18}O_6N_3As$[d]	19.08	18.75
$-CH_2CH_2NC_4H_8O$	NO_2	$C_{18}H_{21}O_{13}N_6As$[c]	12.40	11.93
$-CH_2CH=CH_2$	NO_2	$C_9H_{11}O_5N_2As$	24.81	24.56
$-CH_2CH=CH_2$	NH_2	$C_9H_{13}O_3N_2As$	27.54	27.36
$-CH_2CHOHCH_2NH_2$	NO_2	$C_9H_{14}O_6N_3As$	22.37	21.98
$-C(CH_3)_2CH_2OH$	NO_2	$C_{10}H_{15}O_6N_2As$	22.45	22.39
$-C(CH_3)_2CH_2OH$	NH_2	$C_{10}H_{17}O_4N_2As$	24.67	24.17

[a] Arsenic was determined by a modification of the method of Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930). [b] Isolated as the dipicrate. [c] Isolated as the monopicrate. [d] Plus one molecule of water.

product was dried overnight at 90° and then *in vacuo* over concd. sulfuric acid. Yield varied from 30–50%.

Condensation of 3-Nitro-4-chlorophenylarsonic Acid with 2-Amino-2-methyl-1-propanol.—Five grams of 3-nitro-4-chlorophenylarsonic acid and 10 cc. of 2-amino-2-methyl-1-propanol were heated, under reflux, on an oil-bath at 160–170° for six hours. During this time the mixture became almost black and was very viscous. The tarry residue was *dissolved* out in 50 ml. of hot water, the solution charcoaled, filtered and then made neutral to congo red with concd. hydrochloric acid. The yellow solid that separated was purified by reprecipitation from alkaline solution with concd. hydrochloric acid, dried at 90° in an oven overnight and then *in vacuo* over concd. sulfuric acid.

General Procedure for the Preparation of the 3-Amino Derivatives.—The nitro groups in the compounds described above were reduced to amino groups using the method of Jacobs, Heidelberger and Rolf.[5] The products obtained were light-red solids, which turned dark rapidly on exposure to air; yields, 10–30%.

Summary

The preparation of a number of 3-nitro-4-substituted aminophenylarsonic acids and the corresponding 3-amino compounds has been reported.

(5) Jacobs, Heidelberger and Rolf, THIS JOURNAL, **40**, 1581 (1918).

LOUISVILLE, KENTUCKY RECEIVED MAY 16, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGY AND VITAL ECONOMICS, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY]

The Synthesis of 4,5-Diethyl-*o*-phenylenediamine through the Nitration of *o*-Diethylbenzene

BY JOHN P. LAMBOOY

Until relatively recently *o*-diethylbenzene has been available in such limited quantities that it has been used for synthetic purposes by no one but its discoverer. A. Voswinkel[1] first synthesized *o*-diethylbenzene in 1888 and along with it he reported the syntheses of barium *o*-diethylbenzenesulfonate, *o* diethylbenzenesulfonamide and 1,2-diethyl-3,4,5,6-tetrabromobenzene. He was discouraged from more than preliminary efforts at nitration because of lack of starting material and the explosive nature of the product he obtained. The nature of this product as well as the position of the sulfonic acid group remain unknown.

Karabinos, Serijan and Gibbons[2] have introduced a method by which relatively large amounts of pure *o*-diethylbenzene are made available. Our need for compounds related to 4,5-diethyl-*o*-phenylenediamine made the prospect of obtaining it through successive nitrations of *o*-diethylbenzene attractive.

o-Diethylbenzene was nitrated and while it is probable that other products were produced, repeated vacuum fractional distillations yielded only one readily available product. This was shown by oxidation to the nitrophthalic acid to be exclusively 1,2-diethyl-4-nitrobenzene. The nitro compound was reduced catalytically to 3,4-diethylaniline. After carbethoxylation of the amino group the material was again subjected to nitration with the formation, for the most part, of 4,5-diethyl-2-nitrocarbethoxyaniline. Removal of the carbethoxy group to produce 4,5-diethyl-2-nitroaniline followed by deamination located the second nitro group by producing 1,2-diethyl-4-nitrobenzene. The 4,5-diethyl-2-nitroaniline was reduced catalytically to produce 4,5-diethyl-*o*-phenylenediamine.

(1) Voswinkel, *Ber.*, **21**, 3499 (1888).

(2) Karabinos, Serijan and Gibbons, THIS JOURNAL, **68**, 2107 (1946).

Experimental

1,2-Diethyl-4-nitrobenzene.—A mixture of 175 ml. of fuming nitric acid (sp. gr. 1.59–1.60) and 87.5 ml. of glacial acetic acid was cooled to 10°. While this solution was stirred vigorously, 50 g. of *o*-diethylbenzene[3] was added at a rate to maintain the temperature between 10–20°. After the last of the *o*-diethylbenzene had been added the stirring was continued for forty-five minutes at the same temperature. The reaction mixture was then poured into one liter of ice-water. The crude nitro compounds were extracted with four 125-ml. portions of ether and the ether extract washed with three 50-ml. portions of water, with six 50-ml. portions (until the reaction has become alkaline) of 10% sodium hydroxide solution and again with three 50-ml. portions of water. The ether extract was dried over anhydrous sodium sulfate and the solvent removed. After preliminary studies the following procedure was used for the separation of the desired product. The combined nitration products obtained from the nitration of 422 g. of *o*-diethylbenzene were distilled from a Claisen flask at 10 mm. pressure. Only that material collected over the temperature range 130–150°, which amounted to 380 g. or 74% yield, was fractionated. The column used was 60 cm. long, 1.5 cm. i. d., and filled with small, single-turn glass helices. The fractionating head was designed so that any desired portion of the condensate could be returned to the column. The material was fractionated three consecutive times into three degree ranges between 120–141°. The material collected in the boiling point range 139–141° at 10 mm. weighed 230.5 g., which is 41% of the theoretical amount, and was identified as 1,2-diethyl-4-nitrobenzene; yellow oil, b. p. 139–141° at 10 mm. mercury pressure, d^{22} 1.0852, $n^{25}D$ 1.5440.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.22; H, 7.24; N, 8.10.

The 1,2-diethyl-4-nitrobenzene was characterized by permanganate and also nitric acid oxidation to the 4-nitrophthalic acid which was identified by the melting points of the acid, anhydride, the acid aniline salt and the anil. No evidence could be found for the presence of any of the 3-nitrophthalic acid.

3,4-Diethylaniline.—The 1,2-diethyl-4-nitrobenzene was reduced catalytically in a Parr hydrogenator at initial pressures of 60 p.s.i., using platinum oxide, platinum on zirconium or palladium on zirconium oxide. Seventeen and nine-tenths grams (0.1 mole) of 1,2-diethyl-4-nitrobenzene was dissolved in 150 ml. of absolute alcohol and

(3) The *o*-diethylbenzene used in this study was generously furnished by the National Advisory Committee for Aeronautics.

0.2 g. of platinum oxide added. At 24° the reduction was 97% complete in twenty minutes and 100% in one hour. The catalyst and solvent were removed and the 3,4-diethylaniline distilled at 10 mm. pressure to obtain 13.9–14.7 g. (93–99% yield) of product; colorless or very pale yellow oil, b. p. 116–117° at 10 mm., d^{28} 0.952, $n^{29}D$ 1.5458.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.17; H, 10.10; N, 9.4.

The material becomes discolored rapidly on exposure to air.

The **acetanilide** recrystallized from 50% alcohol as white platelets, m. p. 119°.[4]

Anal. Calcd. for $C_{12}H_{17}NO$: N, 7.33. Found: N, 7.1.

The **benzanilide** recrystallized from 70–80% alcohol as white needles, m. p. 116–117°.

Anal. Calcd. for $C_{17}H_{19}NO$: N, 5.53. Found: N, 5.5.

The **aniline hydrochloride** was prepared by passing dry hydrogen chloride into an anhydrous ether solution of the aniline. When recrystallized from a mixture of chloroform and ligroin it was obtained as white needles, m. p. 196–197°.

Anal. Calcd. for $C_{10}H_{16}NCl$: Cl, 19.10. Found: Cl, 19.17.

4,5-Diethyl-2-nitrocarbethoxyanilide.—The procedure outlined by Karrer and Becker[5] was used for the synthesis of this compound. Twenty-eight and seven-tenths grams (0.193 mole) of 3,4-diethylaniline, 73 ml. of acetone, 43 ml. of water and 34 ml. of sodium hydroxide solution (24%) and 29 g. of ethylchlorocarbonate were used to prepare the urethan. The urethan was used directly in the nitration which was accomplished in a mixture of 118 ml. of concentrated nitric acid and 43 ml. of concentrated sulfuric acid. After the product was poured onto ice and had solidified, it was dissolved in ether. The ether solution was washed with water until neutral, dried over anhydrous sodium sulfate and the solvent removed on the steam-bath. The product was recrystallized from alcohol to produce 29.8 g. (57% yield) of fine yellow needles, m. p. 60°.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.74; H, 6.64; N, 10.2.

4,5-Diethyl-2-nitroaniline.—To a solution of 20 g. of sodium hydroxide, 50 ml. of water and 150 ml. of alcohol, 12.0 g. (0.062 mole) of 4,5-diethyl-2-nitrocarbethoxyanilide was added. While the solution was stirred the temperature was raised to 70° and held there for one hour. The alcohol was removed under diminished pressure and 100 ml. of water added. The suspension was extracted repeatedly with benzene. The benzene solution was dried over anhydrous sodium sulfate and the benzene removed under diminished pressure. The residue was recrystallized from dilute alcohol to produce 7.1 g. (81% yield) of orange prisms, m. p. 64–65°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.43. Found: C, 62.10; H, 7.33; N, 14.2.

The nitroaniline is steam distillable. The position of the nitro group was determined by deamination of 2.6 g. of the nitroaniline by the procedure outlined by Hodgson and Turner.[6] The nitro compound produced was isolated by steam distillation and the distillate extracted with ether. After the solution was dried and the ether removed the residue was distilled at reduced pressure to produce 1.4 g. (58% yield) of product. The boiling point could not be determined with certainty on this amount so it was reduced to the aniline and converted to the benzanilide, m. p. 114–115°. A mixture of this material and the benzanilide prepared from known 3,4-diethylaniline melted at 116°. This proves the nitro group to be in the 2-position.

4,5-Diethyl-*o*-phenylenediamine.—One and nine-tenths grams (0.01 mole) of 4,5-diethyl-2-nitroaniline was reduced in 75 ml. of absolute alcohol with 1.1 g. of platinum on zirconium with an initial pressure of 60 p.s.i. After removal of the catalyst and removal of the solvent the residue was recrystallized from benzene to produce 1.3 g. (81% yield) of white platelets, m. p. 114–115°.

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.07. Found: C, 73.16; H, 9.66; N, 17.6, 17.7.

o-Phenylenediamine sublimes.[7] 4,5-Diethyl-*o*-phenylenediamine was found to sublime slowly at 78° at 2 mm. mercury pressure and very slowly at 100° at atmospheric pressure. 4-Methyl-*o*-phenylenediamine was prepared in 90% yield by catalytic (platinum oxide at 60 p.s.i.) reduction of a tenth mole lot of 3-nitro-4-aminotoluene to produce material of m. p. 90–92°. This material was found to sublime under the same conditions as those described above.

Summary

1. The synthesis of 4,5-diethyl-*o*-phenylenediamine through the successive nitrations of *o*-diethylbenzene has been described.

2. Several new compounds involved as intermediates in the above synthesis have been reported including 1,2-diethyl-4-nitrobenzene, 3,4-diethylaniline, 4,5-diethyl-2-nitrocarbethoxyanilide and 4,5-diethyl-2-nitroaniline.

3. The nitration of *o*-diethylbenzene has been shown to result in approximately a 40% yield of 1,2-diethyl-4-nitrobenzene.

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(4) All melting points given were observed on thermometers calibrated against U. S. P. Melting Point Reference Standards and Anschütz thermometers.

(5) Karrer and Becker, *Helv. Chim. Acta*, **18**, 1435 (1935).

(6) Hodgson and Turner, *J. Chem. Soc.*, 748 (1942).

(7) Zincke and Sintenis, *Ber.*, **6**, 123 (1873).

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGY AND VITAL ECONOMICS, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY]

Synthesis of 2,5-Dihydroxyphenylalanine

BY JOHN P. LAMBOOY

Theoretical consideration of the pathway of phenylalanine and tyrosine metabolism in inborn or ascorbic acid deficiency induced alcaptonuria has frequently included 2,5-dihydroxyphenylalanine as an intermediate. Hirai[1] reported its synthesis in 1927 but the yield which he obtained was poor and it now appears that the identity of his product may be subject to question. Recently Neuberger[2] reported the synthesis of this amino acid by Hirai's procedure and by a procedure similar to one of those reported here. Our two products are clearly identical and very unlike that obtained by Hirai. While this article must, in view of Neuberger's recent article, be considered primarily as confirmatory in nature, it is felt that our superior yields and considerably more convenient procedure will be of interest to investigators in the field of metabolism.

Essentially, the synthetic procedures studied were the condensations of 2,5-dihydroxybenzaldehyde or 2,5-diacetoxybenzaldehyde with either acetylglycine or benzoylglycine in the presence of acetic anhydride and sodium acetate. The products thus formed were converted directly to the amino acid by one-step reduction and hydrolysis with hydriodic acid and red phosphorus.

In the condensation between 2,5-dihydroxybenzaldehyde or 2,5-diacetoxybenzaldehyde and acetylglycine Neuberger's results differ somewhat from ours. We both obtain two compounds, a high melting, and colorless compound shown by Neuberger to be 2-keto-3-acetamino-6-acetoxycoumarin and a lower melting compound which was the true azlactone. Neuberger's optimum reaction conditions for the formation of almost exclusively the azlactone differ very slightly from ours which led to the almost exclusive formation of the acetoxycoumarin. Both compounds are converted to the desired amino acid by reduction and hydrolysis.

Our primary concern was to outline a procedure by which relatively good yields of the amino acid could be obtained with a minimum of effort. Since purification procedures led to relatively large losses of material the use of crude intermediates was investigated. This led to a considerable increase in the yield of amino acid based on starting material 2,5-dihydroxybenzaldehyde.

The best procedure was found to be the conversion of 2,5-dihydroxybenzaldehyde to 2,5-diacetoxybenzaldehyde. This material in the crude form was converted to 2-phenyl-4-(2,5-diacetoxybenzal)-5-oxazolone which in turn, in its crude form was converted to 2,5-dihydroxyphenylalanine of a high degree of purity with an over-all yield of 26% based on starting material 2,5-dihydroxybenzaldehyde. The triacetyl derivative was prepared for purposes of identification through its sharp melting point.

(1) Hirai, *Biochem. Z.*, **189**, 88 (1927).

(2) Neuberger, *Biochem. J.*, **43**, 599 (1948).

Experimental

2,5-Diacetoxybenzaldehyde.—The method used was essentially that of Malkin and Nierenstein[3] except that the shaking time was increased to one hour and the product permitted to stand at room temperature for twenty-four hours before filtering and evaporation of the ether. From 13.8 g. (0.1 mole) of 2,5-dihydroxybenzaldehyde[4] one obtains 19.3 g. (87% yield) of crude product, m. p. 66–68°,[5] or 14.2 g. (64% yield) of material in the form of fine white needles, purified by recrystallization from 95% alcohol, m. p. 71–72°.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.28; H, 4.89.

The crude material can be used advantageously for the subsequent step of either route. Acetylation in pyridine produced lower yields of purified material.

2-Keto-3-acetamino-6-acetoxycoumarin. (a) **From 2,5-Diacetoxybenzaldehyde.**—An intimate mixture of 21.6 g. of 2,5-diacetoxybenzaldehyde and 18.4 g. of acetylglycine was dried in a vacuum desiccator over calcium chloride for twenty-four hours. After adding 12.8 g. of freshly fused and ground sodium acetate and 60 ml. of 99–100% acetic anhydride the mixture was heated on the steam-bath for forty-five minutes and then permitted to stand at room temperature for twelve hours. The crystalline mass was triturated with 200 ml. of water and permitted to stand for approximately six hours to completely hydrolyze the excess acetic anhydride. The material was filtered, washed with water on the filter and pressed with a dam. The precipitate was placed in a beaker, broken up and suspended in about 50 ml. of ether and again filtered. The product was washed on the filter with about 20 ml. of ether and air-dried. Recrystallization from benzene produced 7.0 g. (27% yield) of purified material as colorless prisms, m. p. 230–231°.

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.28; N, 5.36. Found: C, 59.79; H, 4.30; N, (Dumas) 5.4, 5.7, 5.5, (Kjeldahl) 5.1, 5.2, 4.9.

Before this method for the preparation of the amino acid was abandoned in favor of the more productive one which made use of benzoylglycine it was thought that this compound was the azlactone. Calcd. for $C_{15}H_{13}NO_6$: C, 59.40; H, 4.33; N, 4.62. Before the six-hour hydrolysis period was used the condensation reaction was treated with ice-water for short periods of time. The precipitate was always oily and difficult to purify but did yield small amounts of material which on purification was obtained as yellow crystals, m. p. 141–142°.[2] It seems probable that the long hydrolysis conducted at room temperature was responsible for the conversion of the true azlactone (m. p. 141–142°) to the acetoxycoumarin (m. p. 230–231°).

(b) **From 2,5-Dihydroxybenzaldehyde.**—The details are the same as those given in (a) above. Thus 13.8 g. (0.1 mole) of 2,5-dihydroxybenzaldehyde, 12.0 g. (0.102 mole)

(3) Malkin and Nierenstein, THIS JOURNAL, **53**, 239 (1931).

(4) Neubauer and Flatow, *Z. physiol. Chem.*, **52**, 380 (1907).

(5) Observed melting points from thermometers calibrated from U. S. P. Melting Point Reference Standards and Anschütz thermometers.

of acetylglycine, 11.2 g. (0.136 mole) of sodium acetate and 44 g. (0.43 mole) of 99–100% acetic anhydride produced 11 g. (38% yield) of the crude acetoxycoumarin, m. p. 180–201°, or 5.4 g. (21% yield) of the purified material, m. p. 230–231°.

2-Phenyl-4-(2,5-diacetoxybenzal)-5-oxazolone. (a) **From 2,5-Diacetoxybenzaldehyde.**—This material had previously been prepared by Neubauer and Flatow[4] from 2,5-dihydroxybenzaldehyde (method b). An intimate mixture of 25.9 g. (0.117 mole) of crude 2,5-diacetoxybenzaldehyde and 19.2 g. (0.216 mole) of benzoylglycine was dried in a vacuum desiccator over calcium chloride for twenty-four hours. One adds 12.0 g. of freshly fused, finely ground sodium acetate and 60 ml. of 99–100% acetic anhydride. The mixture was heated on the steam-bath for forty-five minutes and then during the process of cooling subjected to a partial vacuum which removed approximately 15 ml. of acetic anhydride. After standing at room temperature for a minimum of twelve hours 200 ml. of water was added, the mixture triturated and permitted to stand approximately six hours. The granular material was filtered, resuspended in 100 ml. of water and filtered again and pressed on the filter. The precipitate was suspended in about 50 ml. of ether and filtered, followed by washing on the filter with 25 ml. of ether, and air-dried. This material was light tan in color, weighed 24.1 g. (57% yield based on the crude diacetoxybenzaldehyde or 49% yield based on starting 2,5-dihydroxybenzaldehyde), m. p. 170–187°. When recrystallized from benzene the product melted 195–196°, which is somewhat higher than 190° reported before.[4]

(b) **From 2,5-Dihydroxybenzaldehyde.**—The details are the same as those used in (a) above. After the hydrolysis period the precipitate was of stiff gummy consistency, but after blotting between sheets of filter paper it could be triturated in 50 ml. of ether at which time it became sufficiently granular for successful filtration. Thus 13.8 g. of 2,5-dihydroxybenzaldehyde produced 21.8 g. (60% yield), m. p. 155–172°. When recrystallized from benzene the product weighed 10.4 g. (29% yield), m. p. 195–196°.

2,5-Dihydroxyphenylalanine.—The method used to convert any of the intermediate preparations to the amino acid was based on and made from a combination of methods found in the literature.[6,7,8] The amino acid was prepared by the use of all possible combinations of purified and crude intermediates to find the method which produced the largest amount of purified amino acid from the starting 2,5-dihydroxybenzaldehyde. Twenty-four grams (0.066 mole) of crude 2-phenyl-4-(2,5-diacetoxybenzal)-5-oxazolone (m. p. 170–187° from crude 2,5-diacetoxybenzaldehyde), 120 g. of glacial acetic acid, 120 g. of hydriodic acid (sp. gr. 1.7) and 3 g. of red phosphorus were gently refluxed for ninety minutes. While still hot the mixture was filtered through an asbestos mat and the phosphorus washed with a little hot glacial acetic acid. The filtrate was evaporated to dryness in an atmosphere of hydrogen under diminished pressure. One adds 100 ml. of water and evaporates to dryness as above. The residue was then dissolved as completely as possible in 100 ml. of water at 50° and filtered to remove undissolved benzoic acid. (When prepared from the acetoxycoumarin filtration is unnecessary.) The filtrate was cooled and extracted five times with 40-ml. portions of ether. The water phase was evaporated to approximately 80 ml., a thin layer of ligroin added followed by enough ammonium hydroxide to ensure an excess. The solution was evaporated to dryness as above, and the crude amino acid dissolved in about 150 ml. of hot water containing a little sulfur dioxide. The solution was boiled briefly with a little decolorizing charcoal, filtered and placed in the refrigerator. The amino acid is obtained in a high degree of purity after a single recrystallization from water containing a little sulfur dioxide. The yield of pure material which is obtained in the form of large, colorless crystals containing a molecule of water of crystallization was 7.4 g. (52% yield). The material melts with decomposition between 246 and 254°, depending on the rate of heating.

Anal. Calcd. for $C_9H_{13}NO_5$: C, 50.22; H, 6.09; N, 6.51; H_2O, 8.37. Found: C, 50.20; H, 5.90; N, 6.37; H_2O, 8.68.

The amino acid can be freed of its water of crystallization by drying at 100° for two hours over phosphorus pentoxide at 3 mm. The water was not lost by drying in a desiccator over calcium chloride at room temperature. The amino acid gives a positive ninhydrin reaction, xanthoproteic reaction and ferric chloride solution produces a greenish-black color. Fusion of the material with potassium hydroxide permitted the identification of ammonia. The fusion mass was dissolved in water, acidified with sulfuric acid and extracted with ether. On evaporation of the ether, acetic acid was identified. The *p*-dihydroxyphenyl compound did not survive the treatment with alkali.

When the amino acid was prepared from pure 2-keto-3-acetamino-6-acetoxycoumarin a 63% yield was obtained and from pure 2-phenyl-4-(2,5-diacetoxybenzal)-5-oxazolone the yield was 61%. These yields are equivalent to only 13 and 17%, respectively, when based on starting material 2,5-dihydroxybenzaldehyde.

N-Acetyl-2,5-diacetoxyphenylalanine.—This derivative was prepared because of the general unreliability of the decomposition points of amino acids. Neuberger reports that his product melted at 235° (uncor.). In the purified condition the triacetyl derivative consists of colorless prisms, m. p. 157–158°.

Anal. Calcd. for $C_{15}H_{17}NO_7$: N, 4.33. Found: N, 4.2.

Summary

1. 2,5-Dihydroxyphenylalanine has been prepared from 2-keto-3-acetamino-6-acetoxycoumarin and 2-phenyl-4-(2,5-diacetoxybenzal)-5-oxazolone.

2. The most productive procedure expressed in grams of product and per cent. yields based on starting 2,5-dihydroxybenzaldehyde was: 18.5 g. of 2,5-dihydroxybenzaldehyde yields 25.9 g. of crude 2,5-diacetoxybenzaldehyde (87%); which yields 24.1 g. of crude 2-phenyl-4-(2,5-diacetoxybenzal)-5-oxazolone (49%); which in turn yields 7.4 g. of 2,5-dihydroxyphenylalanine (26%).

ROCHESTER, NEW YORK RECEIVED JUNE 20, 1949

(6) Harington and McCartney, *Biochem. J.*, **21**, 852 (1927).

(7) Lamb and Robson, *ibid.*, **25**, 1231 (1931).

(8) Harington and Randall, *ibid.*, **25**, 1029 (1931).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, PITMAN–MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.]

Some Ethers Derived from Diethylaminoethyl Benzilate[1]

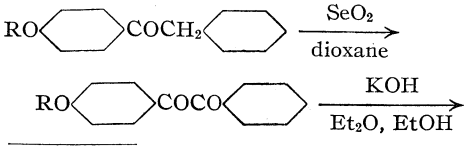
BY EARL R. BOCKSTAHLER AND DONALD L. WRIGHT

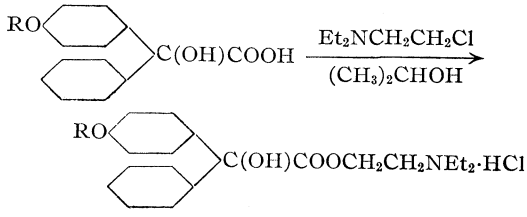
In studies of local anesthetics, it has been demonstrated repeatedly that introducing or varying an alkoxy group on a benzene ring can affect pharmacologic action markedly. For example, the introduction of a butoxy group in one recent instance[2] and of a cyclohexyloxy group in another[3] produced compounds having far greater potency and duration of anesthetic action than was possessed by the ethoxy, methoxy or unsubstituted analogs. Toxicity may or may not be correspondingly altered.

The structural resemblance of the ester type of local anesthetic to antispasmodic aminoalkyl esters suggests that similar enhancement of antispasmodic activity may be possible. Other than scattered instances of methoxy substitution, no data appear to be available in the literature for testing the validity of this conjecture. We therefore undertook the preparation of a homologous series of alkoxy-substituted esters which might be expected to be sufficiently active as antispasmodics to permit judgement on this question.

Diethylaminoethyl benzilate was selected as the parent compound. This substance is known to possess both antispasmodic[4] and local anesthetic[5] as well as mydriatic[6] properties. The 4,4′-dimethoxy derivative has been reported to be inferior to its parent as an antispasmodic.[4] Substitutions which produced the 2,2′-dimethoxy, 3,4,3′,4′-bis-(methylenedioxy), 5,5′-dibromo-2,2′-dimethoxy and 3,3′,4,4′-tetramethoxy derivatives, as ethochlorides, resulted in great reduction or abolition of mydriatic activity.[7]

As a test series, we prepared, as hydrochlorides, ten diethylaminoethyl 4-alkoxybenzilates, in which the number of carbon atoms in the alkyl group was varied from one to seven (Table I). They were obtained from appropriately substituted desoxybenzoins, by the route





For preliminary pharmacological evaluation of these compounds we are indebted to F. H. Schultz, Jr.,[8] W. M. Alexander and W. K. McDonald, of the pharmacology division of this Laboratory, with whose permission we are presenting summarized data. Their results, including additional studies, will be published in detail elsewhere.

As is shown in Table I, the supposition that it would be possible to enhance antispasmodic activity by a suitable choice of alkoxy substituent is not borne out in this series. Activity drops abruptly upon the introduction of a methoxy group, and although some of the later members return to as high a level as the parent compound, none surpass it. A peak is reached with the *n*-amoxy derivative, which possesses activity on the normal gut and against histamine equal to that of the unsubstituted benzilate. Its activity against acetyl-β-methylcholine is two-fifths of that of the parent, and its acute toxicity about half as great.

Enhancement of local anesthetic activity by appropriate alkoxy substitution is clearly apparent, however. A maximum was reached with the *n*-hexyloxy derivative, which produced anesthesia of twenty to thirty minutes duration when applied in 0.01% concentration. At a concentration of 0.25%, which caused temporary irritation (complete recovery by the following day), the duration of anesthesia was approximately three hours.

Because of this favorable finding, nine additional esters containing a variety of nuclear ether substituents were prepared and tested for local anesthetic activity. None was found to surpass the *n*-hexyloxy derivative.

It will be noted that each of the esters except the dibutoxy derivative contains an asymmetric carbon atom. No attempt to resolve these racemic mixtures was made.

Experimental[9,10]

Desoxybenzoins (Table II, A).—The monosubstituted desoxybenzoins, with the exception of the methoxy and

(1) Presented before the Division of Medicinal Chemistry at the 115th meeting of the American Chemical Society at San Francisco, California, March 29, 1949.

(2) M. B.Moore, *J. Am. Pharm. Assoc.*, **33**, 193 (1944).

(3) S. M. McElvain and T. P. Carney, THIS JOURNAL, **68**, 2592 (1946).

(4) *E. g.*, R. R. Burtner and J. W. Cusic, *ibid.*, **65**, 262 (1943).

(5) *E. g.*, A. Gilman, *et al.*, *J. Pharmacol.*, **74**, 290 (1942).

(6) *E. g.*, F. F. Blicke and C. E. Maxwell, THIS JOURNAL, **64**, 428 (1942).

(7) A. H. Ford-Moore, *J. Chem. Soc.*, 952 (1947).

(8) Present address: Commercial Solvents Corporation, Terre Haute, Indiana.

(9) Analyses by Oakwold Laboratories and Dr. Carl Tiedcke.

(10) Melting points are uncorrected.

TABLE I

2-DIETHYLAMINOETHYL BENZILATE HYDROCHLORIDES

$R(R'C_6H_4)C(OH)COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$

R	R′	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	LD_{50},[a] mice, i. p. mg./kg.	Local anesthesia,[b] % MAC[d]	Local anesthesia,[b] % MNIC[e]	Spasmolytic index[c] Normal[f]	Spasmolytic index[c] ABMC[g]	Spasmolytic index[c] Histamine[h]
H	H			$C_{20}H_{25}NO_3 \cdot HCl$					112	0.12	0.12	1	1	1
4-$CH_3OC_6H_4$	H	77	169–171	$C_{21}H_{27}NO_4 \cdot HCl$	64.03	63.97	7.16	7.40	75	.1	.1	0.01	0.04	0.2
4-$C_2H_5OC_6H_4$	H	79	173–174	$C_{22}H_{29}NO_4 \cdot HCl$	64.61	65.03	7.40	7.62	155	.25	< .1	.1	.04	.1
4-*n*-$C_3H_7OC_6H_4$	H	68	140–142	$C_{23}H_{31}NO_4 \cdot HCl$	65.45	65.47	7.65	7.91	228	.1	< .05	.1	.04	.5
4-iso-$C_3H_7OC_6H_4$	H	81	161–162	$C_{23}H_{31}NO_4 \cdot HCl$	65.45	65.41	7.65	8.08	143	.05	.05			.33
4-*n*-$C_4H_9OC_6H_4$	H	69	147–148	$C_{24}H_{33}NO_4 \cdot HCl$	66.10	66.18	7.86	8.20	256	.1	< .05	1	.2	1
4-iso-$C_4H_9OC_6H_4$	H	68	140–142	$C_{24}H_{33}NO_4 \cdot HCl$	66.10	65.97	7.86	7.69	136	.05	.05	0.01		0.5
4-*n*-$C_5H_{11}OC_6H_4$	H	79	136–137	$C_{25}H_{35}NO_4 \cdot HCl$	66.73	66.79	8.06	8.24	(230)[i]	.025	.025	1	.4	1
4-iso-$C_5H_{11}OC_6H_4$	H	37	133–135	$C_{25}H_{35}NO_4 \cdot HCl$	66.73	66.58	8.06	8.29	176	.025	.05	.1	.2	0.5
4-*n*-$C_6H_{13}OC_6H_4$	H	71	123–125	$C_{26}H_{37}NO_4 \cdot HCl$	67.30	67.20	8.24	8.61	148	.01	.025	.1	.25	1
4-*n*-$C_7H_{15}OC_6H_4$	H	67	130–132	$C_{27}H_{39}NO_4 \cdot HCl$	67.83	67.76	8.43	8.48	(235)[i]	.025	.025	.1		
4-*n*-$C_8H_{17}OC_6H_4$	H	55	126–127	$C_{28}H_{41}NO_4 \cdot HCl$	68.35	68.30	8.60	8.86	(460)[i]	.5	.25			
4-*n*-$C_{10}H_{21}OC_6H_4$	H	74	124–125	$C_{30}H_{45}NO_4 \cdot HCl$	69.27	68.81	8.92	8.89	*j*	*j*	*j*			
4-$C_6H_5OC_6H_4$	H	75	152–154	$C_{26}H_{29}NO_4 \cdot HCl$	68.49	68.20	6.63	7.24	205	0.1	0.05			0.5
4-$C_6H_5CH_2OC_6H_4$	H	54	147–149	$C_{27}H_{31}NO_4 \cdot HCl$	69.00	68.80	6.86	6.82	175	.05	.05			.25
2,5-$(C_2H_5O)_2C_6H_3$	H	66	151–153	$C_{24}H_{33}NO_5 \cdot HCl$	63.76	63.65	7.58	7.85	153	.05	.1			
3,4-$(C_2H_5O)_2C_6H_3$	H	56	139–140	$C_{24}H_{33}NO_5 \cdot HCl$	63.76	63.81	7.58	7.88	124	.05	.1			
4-*n*-$C_4H_9OCH_2CH_2OC_6H_4$	H	57	116–117.5	$C_{26}H_{37}NO_5 \cdot HCl$	65.05	64.88	7.99	8.29	82	.05	.1			
4-$C_6H_5OCH_2CH_2OC_6H_4$	H	66	128–130	$C_{28}H_{33}NO_5 \cdot HCl$	67.26	66.88	6.85	6.91	(218)[i]	.025	.025	1	0.2	1
4-*n*-$C_4H_9OC_6H_4$	4-*n*-C_4H_9O	61	122–123	$C_{28}H_{41}NO_5 \cdot HCl$	66.20	66.21	8.33	8.38	(172)[i]	.025	.025			

[a] Dibucaine: 22. Atropine: 300. Papaverine: 117. [b] Dibucaine: MAC, 0.01; MNIC 0.025. [c] Minimum effective concentration of 2-diethylaminoethyl benzilate/M. E. C. of compound being tested. Atropine: normal, 1; ABMC, 2. Papaverine: normal, 0.02; ABMC, 0.0016; histamine, 0.5. [d] Minimum anesthetic concentration; rabbit cornea. [e] Maximum non-irritant concentration; rabbit cornea. [f] Isolated normal rabbit gut. [g] Isolated rabbit gut stimulated by acetyl-β-methylcholine. [h] Isolated guinea pig gut stimulated by histamine. [i] Because of its low solubility, the compound was administered for toxicity determinations in gum acacia suspension. [j] The solubility of the compound, less than 0.01%, was too low for study.

phenoxy, were prepared by refluxing 4-phenylacetylphenol in alcohol or acetone solution with the appropriate bromide or chloride in the presence of potassium carbonate. 4-Phenylacetylphenol was methylated by the use of dimethyl sulfate in aqueous alkaline solution. Phenoxydesoxybenzoin and the two diethoxy derivatives were prepared by Friedel-Crafts reaction of phenylacetyl chloride with appropriate phenol ethers under the usual conditions (aluminum chloride catalyst in carbon disulfide). 4,4′-Di-*n*-butoxydesoxybenzoin was obtained from 4,4′-di-*n*-butoxychalcone according to the scheme described by Rohrmann, Jones and Shonle[11] for lower homologs.

4-*n*-Butoxyacetophenone.—A mixture of 68 g. of 4-hydroxyacetophenone, 72 g. of *n*-butyl bromide, 72.5 g. of potassium carbonate, 8.4 g. of potassium iodide and 25 cc. of 95% ethanol was heated at 75–85° for forty-eight hours. It was then diluted with a little ether and enough water to dissolve the solids. The water layer was discarded. The oil layer was washed with dilute sodium hydroxide solution and with water, dried over sodium sulfate, and distilled, yielding 76 g. (79%) of colorless liquid boiling at 169–170° at 13 mm. *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.06.

4,4′-Di-*n*-butoxychalcone.—A mixture of 70.5 g. of 4-*n*-butoxybenzaldehyde, 76 g. of 4-*n*-butoxyacetophenone and 160 cc. of 95% ethanol was added gradually to a solution prepared from 4 g. of sodium and 40 cc. of methanol. After one hour the mixture was chilled thoroughly and filtered. The crystals were washed with water and recrystallized twice from 95% ethanol; yield, 114 g. (82%) of pale yellow crystals, m. p. 90–92°. *Anal.* Calcd. for $C_{23}H_{38}O_3$: C, 78.35; H, 8.01. Found: C, 78.05; H, 8.15.

α,β-Di-4-*n*-butoxyphenyllactic Acid.—To a stirred suspension of 112 g. of 4,4′-di-*n*-butoxychalcone in 600 cc. of 95% ethanol, 500 cc. of acetone and 41 cc. of 25% aqueous sodium hydroxide warmed to 40°, there was added gradually 98 cc. of 30% hydrogen peroxide; the temperature was kept below 45° by external cooling. After standing for one hour, the mixture was chilled and filtered. After one recrystallization from 95% ethanol, the product (63 g.) was suspended in 212 cc. of 95% ethanol and 66 cc. of 25% aqueous sodium hydroxide and boiled under reflux for three hours. The resulting solution was diluted to 2500 cc. with water and filtered. The filtrate was acidified with hydrochloric acid. The product was removed by filtration and recrystallized twice from methanol; yield, 56 g. (47%); m. p. 135–136°. *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.46; H, 7.82. Found: C, 71.89; H, 7.96.

4,4′-Di-*n*-butoxydesoxybenzoin.—To a stirred suspension of 55 g. of α,β-di-*n*-butoxyphenyllactic acid in 155 cc. of glacial acetic acid, there was added in small portions 99 g. of red lead oxide, at such a rate that the temperature of the mixture did not rise above 65°. The mixture was stirred for thirty minutes after addition was complete, then poured into 1500 cc. of water. The resulting precipitate was removed by filtration, washed with dilute alkali and water, and recrystallized from 95% ethanol; yield, 41 g. (85%).

Benzils (Table II, B).—The desoxybenzoin was refluxed for five to eight hours in one or two times its weight of dioxane with 1.1 molecular proportions of selenium dioxide and water. The mixture was then filtered, and the dioxane was removed by evaporation under reduced pressure. The residue solidified spontaneously, or after it had been cooled and rubbed, and was purified by recrystallization from petroleum ether or methyl, ethyl or isopropyl alcohol. Low yields in several instances are indicative, not of failure of the reaction to proceed, but rather of severe losses in recrystallization of low-melting, readily soluble substances.

Benzilic Acids (Table II, C).—A solution of the benzil in ether was allowed to stand[12] with alcoholic potash

(11) E. Rohrmann, H. G. Jones and H. A. Shonle, THIS JOURNAL, **66**, 1856 (1944).

(12) In most cases occasional shaking of the mixture sufficed for good results. A few of the benzils were not completely soluble in the specified amount of ether; in these instances, the mixture was stirred continuously.

TABLE II

INTERMEDIATE COMPOUNDS

No.	R	R′	A. Desoxybenzoins, RCOCH₂C₆H₄R′ Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	4-$CH_3OC_6H_4$	H	83	74–76	$C_{15}H_{14}O_2$			[a]	
2	4-$C_2H_5OC_6H_4$	H	81	103–104	$C_{16}H_{16}O_2$			[b]	
3	4-*n*-$C_3H_7OC_6H_4$	H	73	94–95[c]	$C_{17}H_{18}O_2$	80.30	79.86	7.13	7.42
4	4-iso-$C_3H_7OC_6H_4$	H	77	105.5–106.5	$C_{17}H_{18}O_2$			[d]	
5	4-*n*-$C_4H_9OC_6H_4$	H	93	84.5–85.5	$C_{18}H_{20}O_2$			[d]	
6	4-iso-$C_4H_9OC_6H_4$	H	47	94–94.5[e]	$C_{18}H_{20}O_2$	80.58	80.64	7.51	7.62
7	4-*n*-$C_5H_{11}OC_6H_4$	H	90	73.5–74.5	$C_{19}H_{22}O_2$	80.81	81.02	7.85	8.16
8	4-iso-$C_5H_{11}OC_6H_4$	H	65	64.5–65.5	$C_{19}H_{22}O_2$	80.81	81.18	7.85	8.22
9	4-*n*-$C_6H_{13}OC_6H_4$	H	59	76–77.5	$C_{20}H_{24}O_2$	81.04	81.22	8.16	8.32
10	4-*n*-$C_7H_{15}OC_6H_4$	H	88	70–71.5	$C_{21}H_{26}O_2$	81.25	81.00	8.44	8.36
11	4-*n*-$C_8H_{17}OC_6H_4$	H	88	69.5–70.5	$C_{22}H_{28}O_2$	81.54	80.47	8.71	8.62
12	4-*n*-$C_{10}H_{21}OC_6H_4$	H	79	70–71	$C_{24}H_{32}O_2$	81.76	81.05	9.16	9.15
13	4-$C_6H_5OC_6H_4$	H	74	88–89[f]	$C_{20}H_{16}O_2$	83.33	81.49	5.55	5.66
14	4-$C_6H_5CH_2OC_6H_4$	H	73	134.5–136	$C_{21}H_{18}O_2$			[g]	
15	2,5-$(C_2H_5O)_2C_6H_3$	H	39	51–52	$C_{18}H_{20}O_3$	76.01	75.72	7.09	7.53
16	3,4-$(C_2H_5O)_2C_6H_3$	H	48	89–91	$C_{18}H_{20}O_3$	76.01	76.24	7.09	6.93
17	4-*n*-$C_4H_5OCH_2CH_2OC_6H_4$	H	52	40–41	$C_{20}H_{24}O_3$	76.89	77.02	7.74	8.01
18	4-$C_6H_5OCH_2CH_2OC_6H_4$	H	71	123.5–124.5	$C_{22}H_{20}O_3$	79.48	79.46	6.06	5.90
19	4-*n*-$C_4H_9OC_6H_4$	4-*n*-C_4H_9O	32[h]	121–122	$C_{22}H_{28}O_3$	77.61	77.89	8.29	8.31

No.	B. Benzils, RCOCOC₆H₄R′ Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	C. Benzilic acid, R(R′C₆H₄)C(OH)COOH Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	65	61.5–63	$C_{15}H_{12}O_3$		[i]			48	147.5–149		[j]		
2	43	69.5–70.5	$C_{16}H_{14}O_3$	75.58	75.67	5.54	5.84	27	112–114	70.58	71.23	5.92	5.90
3	60	102–103	$C_{17}H_{16}O_3$	76.11	76.11	6.01	5.96	32	103–104	71.32	70.91	6.34	6.50
4	6	30–31	$C_{17}H_{16}O_3$	76.11	76.26	6.01	6.62	(15)[k]	120–122	71.32	71.63	6.34	6.72
5	52	58–59	$C_{18}H_{18}O_3$	76.59	77.08	6.43	6.24	30	85–86	72.00	72.29	6.71	6.44
6	69	68.5–69.5	$C_{18}H_{18}O_3$	76.59	76.20	6.43	6.60	39	87–89	72.00	72.00	6.71	6.96
7	20	37–38	$C_{19}H_{20}O_3$	77.00	77.41	6.80	6.55	23	90–91	72.58	72.41	7.05	6.66
8				Not obtained crystalline									
9	91	51.5–52.5	$C_{20}H_{22}O_3$	77.38	77.03	7.15	7.40	15	62–64	73.17	73.28	7.37	7.68
10	96	55–56	$C_{21}H_{24}O_3$	77.75	77.87	7.46	7.77	65	90–91	73.66	73.89	7.65	8.02
11	5	37–38	$C_{22}H_{26}O_3$	78.08	78.34	7.74	8.00	(6)[k]	68–69	74.13	73.86	7.92	8.00
12	14	37–38	$C_{23}H_{30}O_3$	78.64	78.50	8.25	8.04	40	75–77	74.95	74.59	8.39	8.54
13	69	66–67	$C_{20}H_{14}O_3$	79.46	79.53	4.67	4.22	53	127–129	75.00	74.80	5.04	5.62
14	72	95–96	$C_{21}H_{16}O_3$	79.74	79.78	5.10	4.90	73	119–120	75.42	75.43	5.42	5.28
15	76	124–126	$C_{18}H_{18}O_4$	72.48	72.66	6.08	6.44	63	111–113	68.35	68.45	6.37	6.73
16	72	122–123	$C_{18}H_{18}O_4$	72.48	72.54	6.08	5.97	71	123–124	68.35	68.24	6.37	6.22
17	88	68–69	$C_{20}H_{22}O_4$	73.51	73.70	6.80	6.56	70	81–83	69.75	69.81	7.02	7.00
18	72	106–107	$C_{22}H_{18}O_4$	76.27	76.62	5.36	5.65	60	139.5–141	72.50	72.98	5.53	5.35
19	76	88–89	$C_{22}H_{26}O_4$	74.55	74.46	7.40	7.36	63	88–90	70.97	71.26	7.58	7.96

[a] Ney, *Ber.*, **21**, 2450 (1888). [b] C. Torres, *Añales soc. españ. fís. Quím.*, **24**, 82 (1926), (*C. A.*, **20**, 2158 (1926)). [c] Valette, note *d*, gives m. p. 65–66°. [d] M. Valette, *Bull. soc. chim.*, **47**, 289 (1930). [e] Valette, note *d*, gives m. p. 62°. [f] E. R. Bockstahler, Thesis, Yale University, 1934. [g] W. D. McPhee and E. S. Erickson, THIS JOURNAL, **58**, 624 (1946). [h] Calcd. from 4,4′-di-*n*-butoxychalcone. [i] A. McKenzie, E. M. Luis, M. Tiffeneau and P. Weill, *Bull. soc. chim.*, **45**, 414 (1929). [j] E. Christie, A. McKenzie and A. Richtie, *J. Chem. Soc.* 153 (1935). [k] Calcd. from the desoxybenzoin; crude benzil was used.

at room temperature until rearrangement appeared complete, usually overnight. For each 0.1 mole of benzil, 320 cc. of ether, 8 g. of potassium hydroxide and 64 cc. of 95% ethanol were employed. The mixture was then extracted with water, and the extract acidified with hydrochloric acid, which precipitated the benzilic acid. Some unreacted benzil could occasionally be recovered from the ether layer; the recorded yields allow for this.

Our experience is in agreement with the statement of Ford-Moore[6] that "there is a strong tendency for the acid to separate in an obstinately gummy form." Even the purified acids crystallized extremely slowly, sometimes requiring several days for recrystallization, and the freshly precipitated crude products sometimes had to stand for several months before crystallization began spontaneously or after rubbing. The acids were recrystallized from benzene, petroleum ether or mixtures of the two.

2-Diethylaminoethyl Benzilate Hydrochlorides.—Equimolecular quantities of the benzilic acid and freshly distilled 2-diethylaminoethyl chloride were mixed in isopropyl alcohol (about 4 cc. for each gram of acid used), and refluxed for eight hours. The crude products crystallized from the cooled mixture directly or after dilution with ether. For purification, they were redissolved in a small volume of methanol, and isopropyl ether was added gradu-

ally until a permanent precipitate began to form. This, a high-melting impurity, was removed by filtration. The filtrate was diluted further with ether, and the desired product separated. Occasionally it was necessary to repeat this process several times to obtain a constant, sharply-melting product.

Summary

Ten new diethylaminoethyl 4-alkoxybenzilates have been prepared in the form of hydrochlorides and screened for antispasmodic potency. None possesses greater activity than diethylaminoethyl benzilate itself; the *n*-amoxy derivative is approximately as active as the latter, and has half its acute toxicity.

These and nine additional new diethylaminoethyl benzilate hydrochlorides containing various nuclear ether substituents have also been screened for local anesthetic potency. The *n*-hexyloxy derivative is the most active of the series.

Eighteen new benzilic acids, eighteen new benzils and eleven new desoxybenzoins were prepared as intermediates.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUQUESNE UNIVERSITY]

Relative Chloromethylation Rates of Some Aromatic Compounds[1]

BY H. HARRY SZMANT AND JOSEPH DUDEK

Apparently the only extensive study of relative chloromethylation rates of aromatic compounds is that of Vavon, Bolle and Calin[2]; the conclusions of that study are the only ones quoted in authoritative reviews of the chloromethylation reaction.[3] In this paper we wish to point out certain errors in the results of Vavon and co-workers, and to present what we believe to be more nearly correct relative chloromethylation rates of certain compounds studied by these authors. The rates for a few compounds not previously studied are also reported.

The chloromethylation reaction (I) is accompanied by several competitive reactions (II–IV). The situation may be illustrated with the chloromethylation of benzene.

$$C_6H_6 + CH_2O + HCl \longrightarrow C_6H_5CH_2Cl + H_2O \quad (I)$$

$$C_6H_5CH_2Cl + C_6H_6 \longrightarrow C_6H_5CH_2C_6H_5 + HCl \quad (II)$$

$$2C_6H_5CH_2Cl \longrightarrow C_6H_5CH_2C_6H_4CH_2Cl + HCl, \text{ etc.} \quad (III)$$

$$C_6H_5CH_2Cl + C_6H_5CH_2C_6H_5 \longrightarrow C_6H_5CH_2C_6H_4CH_2C_6H_5 + HCl, \text{ etc.} \quad (IV)$$

The course of the chloromethylation reaction can be followed by determining ionic chlorine at certain time intervals. However, the various side reactions liberate ionic chlorine from the initial chloromethylated product; hence to evaluate the chloromethylation rate, one must determine the rate of loss of chloride during the initial period of the reaction before the initial chloromethylation product has accumulated. In arriving at the relative chloromethylation rates in this study we have arbitrarily chosen to compare the time intervals required for the loss of ten per cent. of the initial ionic chlorine. In most of the cases studied, a linear relationship between the rate of chloride loss and elapsed time persisted to the point chosen for the comparison. In a few cases where the curve tended to bend ahead of time, the initial slope was extrapolated to the point chosen for the comparison. The relative chloromethylation rates obtained in this study are listed in Table I, together with the values obtained by Vavon and co-workers. Typical graphs showing per cent. loss of ionic chlorine with time are given in Figs. 1 and 2.

TABLE I

RELATIVE RATES OF CHLOROMETHYLATION

	Compound	$t10\%$[a]	Relative rate[b]	Relative rate[c] of Vavon and co-workers
1	Benzene	9.2	1.0	1
2	Toluene	3.0	3.1	3
3	*n*-Butylbenzene	3.2	2.9	..
4	*t*-Butylbenzene	3.3	2.8	..
5	*p*-Xylene	5.7	1.6	2
6	Mesitylene	0.7	13	600
7	Diphenylmethane	12	0.77	..
8	Bromobenzene	19	0.48	..
9	Diphenyl sulfide	10.5	0.88	..
10	Diphenyl ether	6.1	1.5	100
11	Anisole	0.4	23	1334
12	*p*-Methyl cresyl ether	1.25	7.4	1200

[a] Time (in minutes) required for a 10% decrease in initial chloride concentration. [b] Relative rate ($t10\%$ of benzene)/($t10\%$ of compound). [c] Relative rates reported in ref. 2.

Experimental

All chloromethylation experiments were carried out by allowing 0.1 mole of the aromatic starting material, 0.11 mole of paraformaldehyde and 9 ml. of concd. hydrochloric acid (equivalent to 0.11 mole hydrogen chloride) to react in 125 ml. of glacial acetic acid. In order to avoid any reaction at temperatures other than the desired one, all the formaldehyde, hydrochloric acid and 100 ml. of the acetic acid were heated with stirring in the reaction flask until the desired temperature (85°) was reached, and then (at zero time) the preheated mixture of the compound under study was added in 25 ml. of acetic acid. Samples (2 ml.) were withdrawn from the reaction mixture at desired intervals

(1) Presented at the San Francisco meeting of the American Chemical Society, March, 1949.

(2) Vavon, Bolle and Calin, *Bull. soc. chim.*, **6**, 1025 (1939).

(3) Fuson and McKeever, in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. I, p. 66.

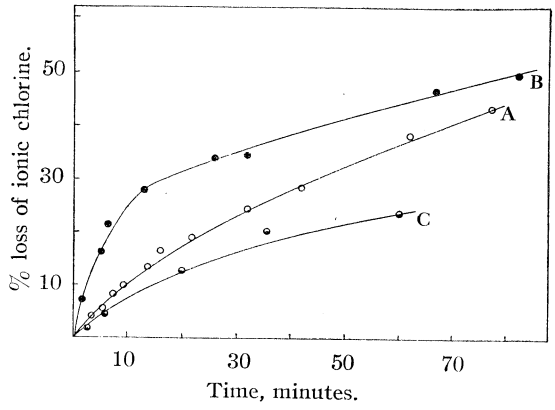

Fig. 1.—Chloromethylation curves at 85°: A, benzene; B, toluene; C, diphenylmethane.

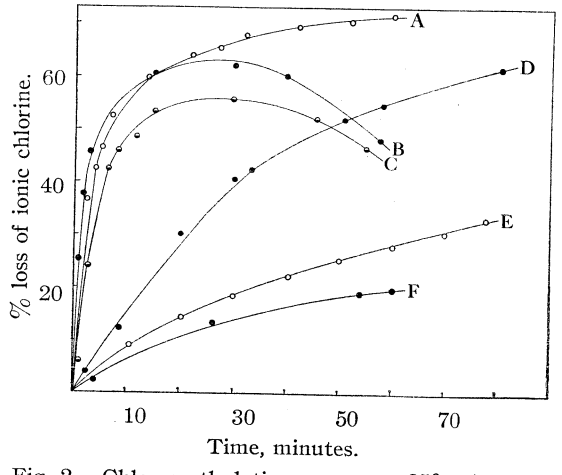

Fig. 2.—Chloromethylation curves at 85°: A, mesitylene; B, anisole; C, *p*-methyl cresyl ether; D, diphenyl ether; E, diphenyl sulfide; F, bromobenzene.

(two to ten minutes, depending on the rate) and introduced into separatory funnels containing 50 ml. of carbon tetrachloride and 25 ml. of water. The contents of the separatory funnel were shaken for approximately thirty seconds, the two layers were allowed to separate, and the lower layer containing the chloromethylation product, starting material, and carbon tetrachloride was drained off. The chloride ion concentration of the aqueous layer was determined in the separatory funnel by means of the conventional Volhard method.[4] The chloride concentration of the reaction mixture was calculated from the relative volumes of the reaction mixture and the sample. The initial chloride concentration was determined in the same fashion by withdrawing a sample of the mixture before the addition of the compound to be chloromethylated. The results of each experiment are plotted as per cent. chloride lost from the reaction mixture against time.

Several possible sources of error resulting from the experimental procedure may be considered. The volume of the reaction mixture at any given time was calculated from the final volume, and possible changes in volume resulting from changes in the composition of the reaction mixture were ignored. This error was minimized, however, by the use of a relatively large volume of solvent. Furthermore, it may be assumed that the changes occurring in the volume of the reaction mixture during the course of the chloromethylation are similar in all the experiments and thus do not affect seriously the *relative* results. In order to check the reliability of the extraction method employed in the analysis, a mixture of the freshly distilled benzyl chloride (0.1 mole), 125 ml. of acetic acid and 9 ml. of water (in place of the hydrochloric acid) was analyzed for chloride ion. The amount of chloride ion was found to be 1–2% of the chloride ion concentration in the chloromethylation experiments. Since the critical part of the chloromethylation reaction is the initial stage during which there is relatively little chloromethylated product, it is believed that the hydrolysis of the product during the extraction does not affect seriously the results obtained.

(4) Caldwell and Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935).

Discussion

Inspection of Table I reveals that the results obtained in the present study are not in agreement with those of Vavon and co-workers in the cases of compounds which tend to chloromethylate very readily (as compared with benzene). These discrepancies may be accounted for, at first glance, by the fact that the reagent used by Vavon was chloromethyl ether rather than a mixture of paraformaldehyde and hydrochloric acid. Otherwise, both studies employed the same solvent, and used essentially the same method of analysis. While the absolute chloromethylation rates are, no doubt, affected by the difference in the reagent, we believe that the discrepancies in the relative rates are explained by the method by which the previous workers arrived at the relative chloromethylation rates. They chose as a point of comparison the time required for the loss of 30% of ionic chlorine at a temperature of 65°. However, in order to obtain convenient time intervals their experiments were carried out in a temperature range of 15–100°, and the time intervals required for 30% loss of ionic chlorine were then converted to time intervals corresponding to a temperature of 65°, by methods not indicated in the publication. It seems reasonable to assume that such calculations are not valid since the activation energies of the various reactions (I–IV) are not known, and since the temperature coefficients of these reactions are not necessarily the same. This view is supported by the fact that satisfactory agreement between the two sets of results is found only in the case of compounds which Vavon and co-workers studied at the same temperature. Compounds 1, 2 and 5 were all studied at 100° and since this set includes benzene, the rates obtained for these compounds agree with those of the present study. Compounds 6, 10, 11 and 12 were studied at 65° and while the relative rates reported differ from ours by a great margin, the relative rates *within* this set of compounds are in closer agreement with our results. This is brought out clearly by comparing Vavon's relative rates with ours, taking the rate of diphenyl ether[5] as unity. His relative rates then become for mesitylene, anisole and *p*-methylcresyl ether: 6, 13.3 and

(5) Additional information on the temperature coefficients of the various reactions occurring during the chloromethylation process will be presented in a forthcoming publication dealing with the chloromethylation of diphenyl sulfide.

12, as compared with our rates of 8.7, 15 and 4.9, respectively.

While the exact mechanism of chloromethylation of aromatic compounds is not known, and probably depends on the nature of the chloromethylation reagent which is employed, it can be safely assumed that the chloromethylation reaction falls into the broad class of substitution reactions brought about by electrophilic reagents.[6] Thus, the relative chloromethylation rates are in accord with those to be expected from the usual effect of substituent groups on the reactivity of the benzene ring in other substitution reactions involving an electrophilic reagent.

The initial slope of the curves depicting the change in ionic chlorine with time is directly related to the rate of chloromethylation; the actual shape of the curves, on the other hand, depends on the extent to which the competing reactions interfere with the principal chloromethylation process. Work is in progress to determine how the competing reactions are related to the chemical structure of the compound being chloromethylated. The effect of the competitive reactions on the shape of the chloromethylation curve is clearly demonstrated in the comparison of anisole and mesitylene (Fig. 2). Both compounds are very reactive in the principal chloromethylation reaction, but the initial chloromethylated product of anisole undergoes further reactions which restore ionic chlorine to the mixture. Since chloromethylmesitylene is capable of undergoing further substitution reactions[7] the lack of side-reactions in this case may be due to the relative inertness of chloromethylmesitylene as an aralkylating agent.

(6) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 90.

Acknowledgment.—The authors wish to express their appreciation to Mr. Joseph Anzenberger for his technical assistance in several of the experiments, and to Drs. T. H. Dunkelberger and O. Gawron for their interest in this work and helpful suggestions. Dr. Gawron originally suggested the kinetic approach to the chloromethylation study of diphenyl sulfide.

Summary

The relative chloromethylation rates of twelve aromatic compounds have been determined. The relative rates of six compounds have been critically compared with those previously reported, and the discrepancies between the new and old rates have been explained. The relative order of the chloromethylation rates was found to be in general agreement with that expected from the effect of the substituent on the substitution reactions of benzene involving an electrophilic reagent.

(7) Excellent yields of the dichloromethylated mesitylene can be obtained (ref. 3, p. 76).

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[CONTRIBUTION NO. 62 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Catalytic Hydrogenation of Terpenes

BY HILTON A. SMITH, JOHN F. FUZEK AND HENRY T. MERIWETHER

Introduction

While a number of studies dealing with the catalytic hydrogenation of terpenes have been reported, few investigations have been concerned with the kinetics of this process. Furthermore, much of the work has been done with mixtures of terpenes, rather than with pure compounds. The present work was undertaken in order to study the kinetics of the catalytic hydrogenation of certain terpenes which could be obtained in a reasonably pure state.

Experimental

Dipentene, terpinolene, α- and β-pinenes and camphene were all furnished in relatively pure form by the Hercules Powder Company of Wilmington, Delaware. Four of these terpenes were fractionated before use through an eight-foot Vigreux column in an atmosphere of carbon dioxide. The other, β-pinene, was fractionated in the same column under vacuum. Constant boiling cuts were obtained for each material. *d*-Limonene was purchased from the Eastman Kodak Company, and carefully fractionated in an atmosphere of carbon dioxide. The constant boiling fraction used had an optical rotation $\alpha^{20}D$ of 104°. Head temperatures and refractive indices of the terpenes used are given in Table I.

Tank hydrogen[1] was used without further purification. Methanol and acetic acid, which were used as solvents, were prepared by fractionation of du Pont methanol or C. P. glacial acetic acid in a five-foot helix-packed still. Sodium oleate and palmitic acid were Merck U.S.P. and Eastman Kodak Co. best grade materials, and were used without further purification. The nickel catalyst was prepared from Raney alloy and the platinum catalyst from platinic chloride in the standard manner.[2,3] The nickel was stored under ethanol.

(1) Purchased from the National Cylinder Gas Co. of Chattanooga, Tenn.

(2) Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(3) Adams, Voorhees and Shriner, "Organic Syntheses," Coll, Vol. I, 463 (1944).

TABLE I

PROPERTIES OF THE TERPENES AND HYDROGENATED PRODUCTS CONSIDERED IN THIS INVESTIGATION

Compound	B. p., °C.	Mm.	$n^{20}D$
Diphentene	176.9	745	1.4729
d-Limonene	176.9	745	1.4729[a]
α-Pinene	155.3	740	1.4659
β-Pinene	166.1	744	1.4758
Terpinolene	102.5	50	1.4898
	119.2	95	
Camphene	91.5	100[b]	
d-Carvomenthene (from *d*-limonene)	179.0	737	1.4572[c]
p-Menthane (from dipentane or terpinolene)	168.0	745	1.4395
Pinane (from α-pinene)	166.0	745	1.4624
Pinane (from β-pinene)	165.7	735	1.4625
iso-Camphane (from camphene)	166.5	740[d]	....
p-Menthene-3 (from terpinolene)	169.0	745	1.4501
	85.0	50	

[a] $\alpha^{20}D$ 104°. [b] M. p. 48.7°. [c] $\alpha^{20}D$ 96°. [d] M. p. 63.5°.

High pressure hydrogenation experiments were carried out in bombs of 45-ml. capacity. These were constructed according to the directions of Adkins.[4] They were equipped with gages of 0–1000 p. s. i. range in 10 p. s. i. subdivisions, or of 0–2000 p. s. i. range in 20 p. s. i. subdivisions. Room temperatures were used except for camphene where the bomb was heated to 65° so as to have the terpene in the liquid state.

For most of the rate work a conventional shaker was used. This shaker completed 42 cycles per minute through an angle of 30° per stroke. For experiments with varying shaking speeds, a similar shaker was constructed having a Mixmaster motor for driving power. With this instrument, any shaking speed between 20 and 70 cycles per minute could be obtained. The shakers were equipped with conventional heating jackets.

In making rate studies, the nickel catalyst was placed in the hydrogenation bomb along with a small amount of the ethanol under which it was stored. This alcohol was removed by evaporation under vacuum. While the bomb was still under vacuum, the terpene was admitted in such a way that it covered the catalyst before any air entered the bomb. The bomb was then sealed, hydrogen admitted to the desired pressure, and the reaction started by shaking the bomb.

After the hydrogenation, the bomb was opened and the contents transferred to a beaker. Any catalyst remaining in the bomb was washed out by acetone. The catalyst was then filtered from the liquid and from the washings in an atmosphere of carbon dioxide, dried in a vacuum desiccator and weighed under carbon dioxide.

Low pressure hydrogenations using either nickel or platinum catalysts were carried out in a standard Parr low-pressure catalytic reduction apparatus. Platinum catalyst was weighed as platinic oxide before use. The nickel catalyst was weighed after each run in the same manner as that described for high-pressure experiments.

(4) Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wisconsin, 1937, pp. 29–45.

Reaction Mechanisms

α-Pinene, β-pinene and camphene each absorbed one mole of hydrogen per mole of terpene to form pinane from the pinenes, and isocamphane from the camphene. Each of these products distilled through an efficient fractionating column at a constant head temperature. Their physical constants are given in Table I.

Dipentene and terpinolene each absorbed two moles of hydrogen per mole of terpene. The hydrogenation of one double bond proceeds quite readily. That of the second bond takes place more slowly. The dipentene hydrogenation proceeded first to carvomenthene and then to *p*-menthane. This was shown by use of the optically active isomer of dipentene, *d*-limonene. If the hydrogenation proceeds by the path *d*-limonene → dihydrodipentene → *p*-menthane, the absorption of one mole of hydrogen will lead to an optically inactive product. If the hydrogenation proceeds by the path *d*-limonene→carvomenthene →*p*-menthane, the absorption of one mole of hydrogen will form carvomenthene, the asymmetric carbon will not be affected, and the intermediate product, *d*-carvomenthene, should have an optical activity comparable to that of the unhydrogenated material. If both bonds are saturated simultaneously, the activity of the half-hydrogenated material should be one-half of that of the starting terpene. Figure 1 indicates that the product formed by the absorption of one mole of hydrogen per mole of terpene is definitely *d*-carvomenthene.[5]

When one equivalent of hydrogen is absorbed by terpinolene, the product would presumably be either carvomenthene or dihydroterpinolene. The half-hydrogenated terpinolene contains no carvomenthene, and it appears that the product is actually an equimolecular mixture of two *p*-menthenes. This mixture was separated by fractionation in an eight foot Vigreux column. The lower-boiling fraction was identified as 3-*p*-menthene by its physical properties, and by the formation of its nitroso derivative. The higher boiling fraction was not positively identified. It forms a low-melting solid nitroso derivative, and its physical properties conform more closely to those published for 2-*p*-menthene than for any other known *p*-menthene. A summary of such data is given in Table II. Apparently the 1,2 bond in terpinolene is first saturated, and the 4-8 bond shifts, partly to the 3-4 position, and partly in some other manner.

The mechanisms for the hydrogenation of both dipentene and terpinolene were the same whether the catalyst was platinum or nickel, whether or not

(5) *Cf.* Vavon, *Compt. rend.*, **152**, 1675 (1911); **158**, 409 (1914).

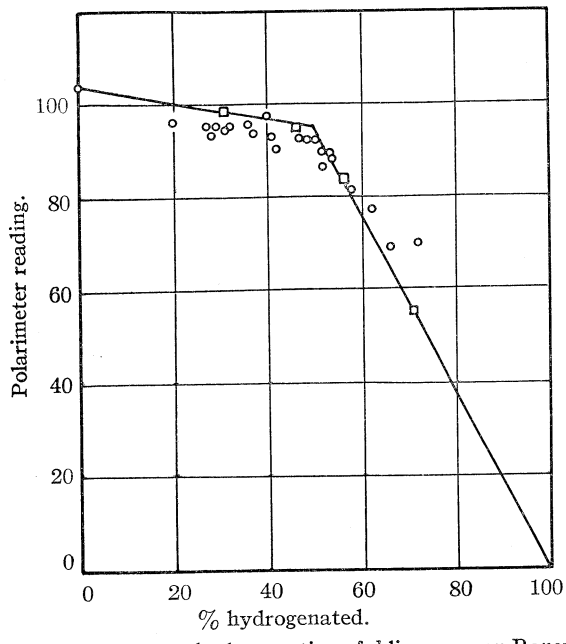


Fig. 1.—Per cent. hydrogenation of *d*-limonene on Raney nickel catalyst as a function of optical rotation ($\alpha^{20}D$ in 10-cm. tube): O, hydrogenation at high pressures; □, hydrogenation at low pressures.

a solvent was present, and whether low or high hydrogen pressures were used. However, when nickel was used as a catalyst (with methanol as a solvent at low pressures, or with no solvent at high pressures) the hydrogenations of dipentene and terpinolene virtually ceased after one mole of hydrogen had been absorbed per mole of terpene.

TABLE II

PROPERTIES OF THE *p*-MENTHENES

Compound	$n^{20}D$	B. p., °C.	M. p. of nitroso-chloride derivative, °C.
1-*p*-Methene[a] (carvomenthene)	1.4563	177	95–96
2-*p*-Menthene[a]	1.461	56 (12 mm.)	.....
3-*p*-Menthene[b]	1.4532	168.0	127
Dihydroterpinolene[a]	1.4568	174	101–103
Dihydrodipentene[a]	1.4523	170	.....
Fractions of the one-half hydrogenated terpinolene			
Fraction 1	1.4501	169	122–123
		85 (50 mm.)	
Fraction 2	1.4640	177	22–23
		92 (50 mm.)	
		58 (12 mm.)[c]	

[a] I. M. Heilbron, "Dictionary of Organic Compounds," Vols. I–III, Oxford University Press, London, 1934. [b] J. Zelikow, *Ber.*, **37**, 1374 (1904). [c] This value was obtained by extrapolation from a plot of log *p versus* $1/T$.

Experimental Calculations and Results

Preliminary experiments indicated that the high pressure hydrogenation reactions were independent of the amount of terpene used, and that the low pressure hydrogenations did not depend on the concentration of the hydrogen acceptor. They also showed that, for all of the reactions studied, the rate was directly proportional to the pressure of hydrogen gas, and also directly proportional to the weight of catalyst used, provided shaking equilibrium was maintained. This was true whether the hydrogenation was carried out without solvent, with methanol or acetic acid as solvent, or in the presence of certain additives. The latter are such materials as fatty acids and soaps, which greatly influenced the rate of reduction. This being true, a plot of log p_0/p against time should result in a straight line.

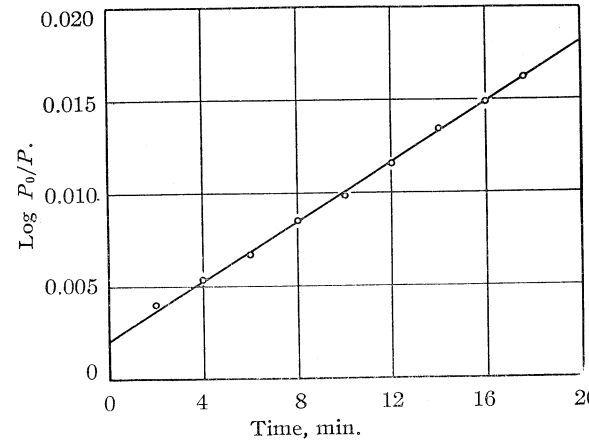


Fig. 2.—Sample hydrogenation curve for *d*-limonene on Raney nickel catalyst.

Figure 2 gives such a plot for the high pressure hydrogenation of *d*-limonene on nickel while Figs. 3 and 4 show similar plots for low pressure hydrogenations using Adams platinum catalyst and acetic acid or methanol as solvents. Since straight lines are obtained, rate constants for these hydrogenations can be calculated from the equation

$$\log p^0/p = kt/2.303\ V$$

where p is the pressure at any time t, p^0 is the initial pressure, V is the volume of the system, and k is the reaction rate constant.[6] Since k is directly proportional to the amount of catalyst used, it is divided by the weight of catalyst to give a k which represents the rate constant referred to one gram of catalyst.

Figure 5 demonstrates the necessity of maintaining shaking equilibrium. In all high pressure experiments for which rate constants are reported here, the shaking speed was maintained at 42 cycles per minute for catalyst weights of 0.3 to 0.5 g. The rate of shaking for the low pressure experiments was 180 cycles per minute, which was shown to be fast enough to maintain equilibrium conditions.

(6) Fuzek and Smith, THIS JOURNAL, **70**, 3743 (1948).

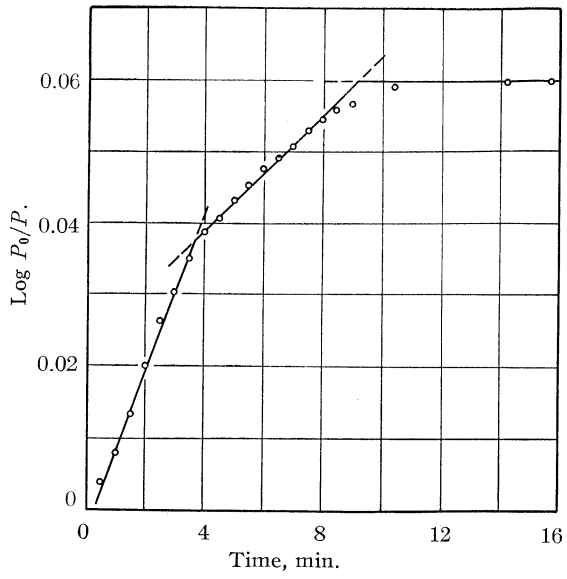


Fig. 3.—Sample hydrogenation curve for dipentene on Adams platinum catalyst in acetic acid at 64.3 p. s. i. a., t, 25°.

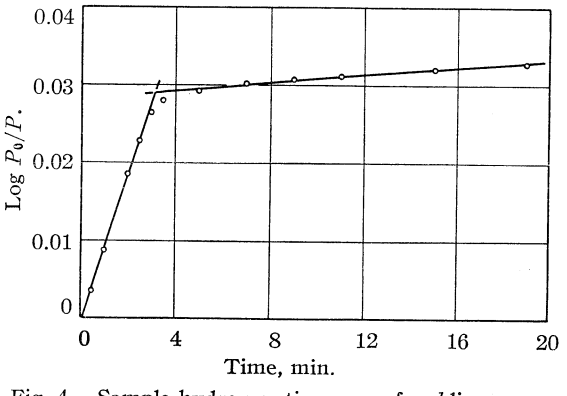


Fig. 4.—Sample hydrogenation curve for d-limonene on Adams platinum catalyst in ethanol at 64.2 p. s. i. a., t, 28°.

Tables III and IV show that the rate constants calculated from such plots are constant over a wide range of conditions. Table V gives the rate constants for the terpenes studied when they are hydrogenated over Raney nickel or Adams platinum catalyst. For the monocyclic terpenes, the rate constants are for the hydrogenation of the first bond only. Hydrogenation of the second bond over nickel is negligible under the experimental conditions employed.

TABLE III

INFLUENCE OF THE AMOUNT OF d-LIMONENE ON ITS RATE OF HYDROGENATION ON NICKEL AT 100 P. S. I. PRESSURE AND AT ROOM TEMPERATURE

Moles d-limonene used	No solvent or additive	$k \times 10^4$ (liters min.$^{-1}$ g.$^{-1}$) With 0.0004 mole palmitic acid per g. of catalyst	With 10 ml. methanol as solvent
0.025	1.93	31.2	123.5
.050	1.84	32.2	127.0
.075	1.84	32.6	127.3
.100	1.93	33.1	126.8

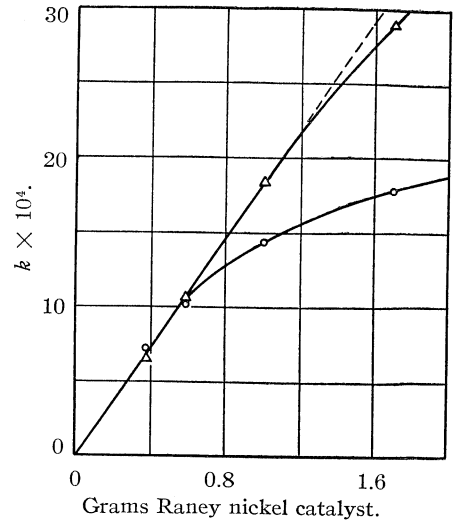


Fig. 5.—Hydrogenation of d-limonene on Raney nickel with 0.100 g. of sodium oleate: shaking speed, (⊙), 41 cycles/min.; (△), 96 cycles/min.

TABLE IV

INFLUENCE OF PRESSURE ON THE RATE OF HYDROGENATION OF d-LIMONENE ON NICKEL USING 0.05 MOLE OF TERPENE AT ROOM TEMPERATURE

Initial pressure, p. s. i.	No solvent or additive	$k \times 10^4$ (liters min.$^{-1}$ g.$^{-1}$) With 0.0004 mole palmitic acid per g. of catalyst	With 10 ml. methanol as solvent
300	1.93	..	127.9
360	..	32.6	..
945	1.84	..	..
980	1.93	..	126.8
1100	..	31.3	..
1720	1.84	30.4	128.9

TABLE V

RATE CONSTANTS FOR HYDROGENATION OF TERPENES AT ROOM TEMPERATURE

Terpene	Rate constant (liters min.$^{-1}$ g.$^{-1}$): On platinum with 50 ml. acetic acid solvent and 64 p. s. i. hydrogen pressure k	On nickel with no solvent and 100 p. s. i. hydrogen pressure $k \times 10^4$	On nickel with 0.0004 mole palmitic acid per g. nickel and 1000 p. s. i. hydrogen $k \times 10^4$
d-Limonene[a]	5.7	1.84	29.4
Dipentene[a]	5.7	1.84	29.4
Terpinolene[a]	1.3	1.47	6.1
Camphene	8.8	1.93[b]	12.7[b]
α-Pinene	2.7	1.10	0.9
β-Pinene	4.3	1.01	9.1

[a] For hydrogenation to the p-menthene only. [b] These runs were made at 65°.

Discussion

Not very much can be said concerning the effect of the structure of the terpene on its rate

of hydrogenation, other than the fact that in general those containing an exocyclic double bond undergo hydrogenation more readily than do those where all of the unsaturation is in the ring. Whether or not the terpene is monocyclic or bicyclic appears to be unimportant since there is no apparent difference in the rates of hydrogenation of the *p*-menthadienes, dipentene and terpinolene, when compared with the pinenes and camphene which are bicyclic terpenes.

It is interesting to note that the *p*-menthadienes undergo hydrogenation on either platinum or nickel more readily than do the *p*-menthenes, since it has already been shown that cyclohexene adds hydrogen much more quickly than does either the conjugated or unconjugated cyclohexadiene.[7] In this connection it would be interesting to study one of the *p*-menthadienes which has both double bonds in the ring.

(7) Smith and Meriwether, THIS JOURNAL, **71**, 413 (1949).

As would be expected, the rates of hydrogenation of dipentene and the optically active *d*-limonene are identical in all cases.

Acknowledgment.—The authors are indebted to the Hercules Powder Company for a fellowship which made this research possible.

Summary

Dipentene, *d*-limonene, terpinolene, α- and β-pinenes and camphene have been hydrogenated over Adams platinum or Raney nickel catalyst, and the results subjected to kinetic analysis. It has been shown that carvomenthene is an intermediate in the hydrogenation of dipentene or *d*-limonene, while terpinolene yields a mixture of 3-*p*-menthene and another *p*-menthene (perhaps 2-*p*-menthene) as intermediates. The factors influencing the rates of hydrogenation of these terpenes have been discussed.

KNOXVILLE, TENNESSEE RECEIVED APRIL 25, 1949

[CONTRIBUTION NO. 64 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Preparation and Aging of Raney Nickel Catalysts

BY HILTON A. SMITH, WILLIAM C. BEDOIT, JR., AND JOHN F. FUZEK

Several different methods for the preparation of Raney nickel catalyst from the standard alloy have been described. Mozingo[1] describes a preparation from the nickel–aluminum alloy according to which the aluminum is dissolved in sodium hydroxide leaving the active catalyst. It is stated that the temperature during the reaction should not rise above 25°. The catalyst is then digested on a hot-plate for twelve hours, and washed by decantation. Pavlic and Adkins[2] have indicated a revision of this method, according to which the alloy is treated with caustic at 50°, and washing is accomplished by a continuous process. The catalyst is claimed to be much more active than that prepared by the method of Mozingo. In a still more recent paper, Adkins and Billica[3] described a further modification in which the washing process was carried out under about 1.5 atmospheres hydrogen pressure. This catalyst (designated as W-6) is described as the most active catalyst known to the authors.

In connection with Mozingo's preparation, it is stated that the catalyst may lose much of its activity if it is kept too long. The purpose of the research reported here was to study the activity of various Raney nickel catalysts, considering both their method of preparation and the length of time which they had been kept.

Experimental

Raney nickel catalyst was prepared by the methods of Mozingo,[1] Pavlic and Adkins[2] and Adkins and Billica.[3] Special care was taken to follow the directions explicitly as given by the authors. In addition, several modifications were introduced. The alloy was taken from a single drum of commercial product furnished by Mr. Raney of the Gilman Paint and Varnish Company, Chattanooga, Tennessee.[4]

The activity of the catalyst was determined by measuring the rate of hydrogenation of freshly distilled *d*-limonene at a hydrogen pressure of 1000 p. s. i. by the method previously described.[5] The latter material was prepared by fractionation under carbon dioxide of Eastman Kodak Co. technical grade product. In addition, the surface areas of a number of these preparations were measured by the adsorption of palmitic acid from benzene solution as previously described.[6]

Experimental Calculations and Results

The rate of hydrogenation of the *d*-limonene has been shown to follow the equation

$$\log p_0/p = k't/2.303\ V$$

where p is the hydrogen pressure at any time, t, p_0 is the initial pressure, V is the volume of hydrogen gas in the system, *i.e.*, the total void which is constant for any system, and k' is the reaction rate constant.[5] (By dividing the value of k' by the weight of catalyst employed rate constants (k) referred to one gram of catalyst

(1) Mozingo, *Org. Syntheses*, **21**, 15 (1941).
(2) Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).
(3) Adkins and Billica, *ibid.*, **70**, 695 (1948).
(4) According to Mr. Raney, this alloy had the following analysis: Ni, 51.06; Al, 48.19; Si, Fe, and Cu combined, 0.75. It was further stated that these latter three elements have percentages approximately as follows: Fe, 0.5; Si, 0.15; and Cu, 0.1.
(5) Smith, Fuzek and Meriwether, *ibid.*, **71**, 3765 (1949).
(6) Smith and Fuzek, *ibid.*, **68**, 229 (1946).

TABLE I

PREPARATION AND PROPERTIES OF RANEY NICKEL CATALYSTS

Temp. of reaction of alloy and caustic, °C.	Subsequent treatment	$k \times 10^4$ (l./g. × min.) for hydrogenation of *d*-limonene	Surface area, sq. meters/g.
10–25	Digested at room temperature for one hour; heated overnight on hot-plate; washed by decantation[1]	134	..
−5–+5		115	31.8
35–45		115	35.0
60 ± 2	Digested at 60–70° for one hour; heated overnight on hot-plate; washed by decantation	97	35.3
35–45	Digested at 35–40° for one hour; washed mechanically; digestion incomplete	55	27.7
35–45	Digested at room temperature for one hour; heated overnight on hot-plate; washed mechanically	106	37.5
50 ± 2	Digested at 50–60° for one hour; washed mechanically[2]	120	..
50 ± 1	Digested at 50–70° for one hour; washed mechanically	115	26.6
50 ± 2	Digested at 50–55° for one hour; washed mechanically	124	25.9
50 ± 2	Treated exactly as recommended by Adkins and Billica[3]	132	18.2

may be obtained.) It was found that slight impurities in the *d*-limonene caused variation in its rate of hydrogenation, and that a simple test could be applied to tell whether the terpene was sufficiently pure. When k' is plotted against the weight of catalyst used, a straight line passing through the origin should be obtained as long as equilibrium conditions are maintained. However, when the terpene is impure, the straight line is displaced so that it no longer passes through the origin. This is shown in Fig. 1. The deviations from linearity shown when catalyst weights greater than 0.3 g. are used are caused by inability to maintain shaking equilibrium. For this reason catalyst weights were kept below 0.3 g. Figure 2 shows a typical hydrogenation plot. It gives evidence that good results may be obtained even with the active catalysts used here.

All surface areas were calculated on the assumption that, under the conditions of adsorption of palmitic acid from benzene, the catalyst surface is covered with a unimolecular layer of palmitic acid, and that the cross section of each fatty acid molecule in the layer is 20.5 square ångström units.

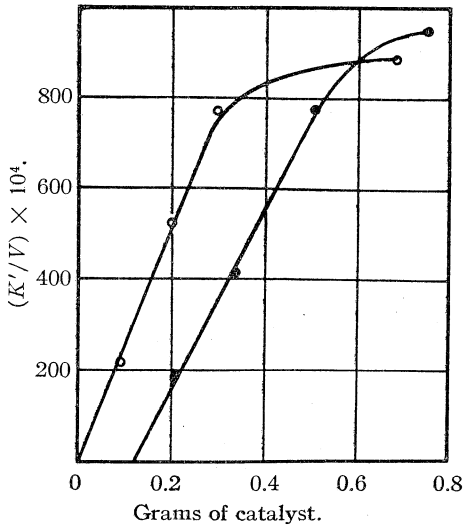


Fig. 1.—Influence of impurities on rate of hydrogenation of *d*-limonene: O, pure sample; ●, impure sample.

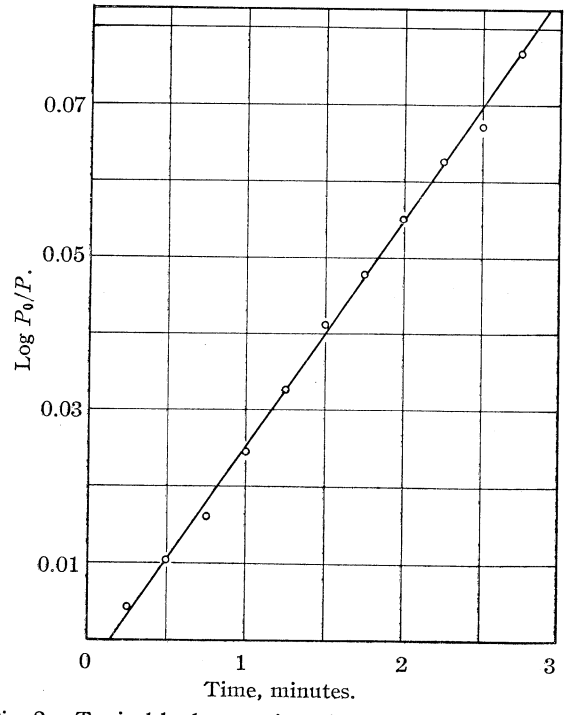


Fig. 2.—Typical hydrogenation plot for hydrogenation of *d*-limonene on an active sample of Raney nickel.

The results of both kinetic and surface measurements for a number of catalyst preparations are given in Table I. The influence of aging on the activity and surface area of such catalysts are shown in Figs. 3 and 4.

Discussion

A study of Table I shows that neither the method of reaction of the alloy with the sodium hydroxide solution, the time or temperature of the

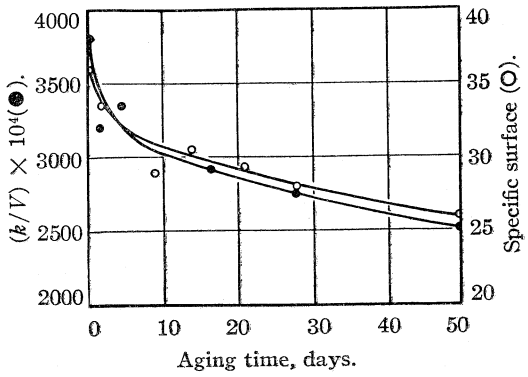


Fig. 3.—Influence of aging on surface area and catalytic activity of Raney nickel.

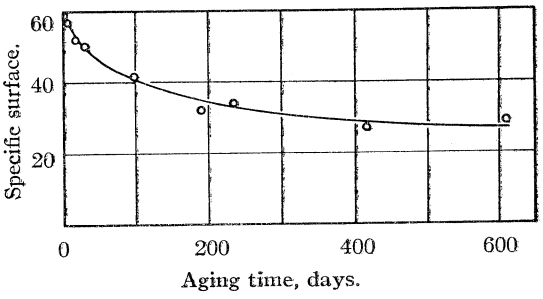


Fig. 4.—Influence of aging on surface area of Raney nickel. (These data were obtained in the course of work done under a fellowship from the Hercules Powder Company.)

digestion beyond a minimum of one hour at 50°, or the method of washing of the catalyst have any very noticeable effect on the activity of the nickel produced as measured by the rate of hydrogenation of *d*-limonene. On the other hand, differences in the original alloy may result in considerable differences in activity of the catalyst. Thus in some earlier work using different alloy rate constants much lower than those reported here were found.[6]

There seems to be no correlation whatever between surface area and initial catalyst activity. The catalyst used in connection with Fig. 4 was made from a different alloy, and had an initial activity only about 1% as great as that used for Fig. 3, although its specific surface was more than 50% greater. However, as Fig. 3 shows, there does seem to be a direct correlation between the decrease in catalytic activity and the decrease in surface area as the catalyst ages.

An examination of Figs. 3 and 4 indicates that the catalyst activity and the specific surface both decrease rather rapidly at first, but much more slowly over longer periods of time.

It has been previously shown that the activity of Raney nickel catalyst as measured by the rate of hydrogenation of *d*-limonene may be greatly affected by the presence of a small amount of additive such as palmitic acid.[7] The activity of a rather poor catalyst is increased and that of a rather good catalyst is decreased to a common value. Furthermore, the increase or decrease is proportional to the amount of fatty acid used until enough is present to cover the nickel surface, after which increasing amounts have little further effect. The catalysts prepared in connection with the work reported here were more active than those made from early samples of alloy. Therefore, a study of the influence of palmitic acid on this catalyst was undertaken. Figure 5 shows that the activity of the catalyst decreases with increasing amounts of fatty acid till it reaches about the same activity as that previously obtained, after which further addition of acid has little effect. The dotted lines in the figure are taken from earlier work[7] for comparison purposes.

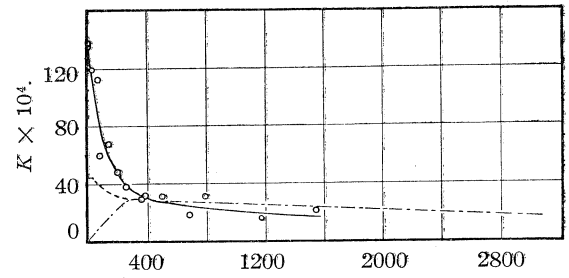


Fig. 5.—Hydrogenation of *d*-limonene on Raney nickel in the presence of palmitic acid: dotted lines represent behavior of less active catalyst samples; *cf.* Smith and Fuzek, ref. 7.

Acknowledgment.—The authors are indebted to the Office of Naval Research for financial support which made this research possible.

Summary

A study has been made of the activity of Raney nickel catalyst as affected by its method of preparation from the alloy and its age. It has been shown that different temperatures of solution of the alloy, different temperatures and times of digestion, and different methods of washing have little effect on catalytic activity as measured by the rate of hydrogenation of *d*-limonene. It has been further shown that, while the original specific surface of a catalyst has little influence on its initial activity, the change in surface with time is closely paralleled by the change in catalytic activity.

KNOXVILLE, TENNESSEE RECEIVED MAY 16, 1949

(7) Smith and Fuzek, unpublished results.

[CONTRIBUTION NO. 69 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Catalytic Hydrogenation of the Benzene Nucleus. VI. The Hydrogenation of Compounds with Two Benzene Rings

BY HILTON A. SMITH, DAVID M. ALDERMAN, JR., COMER D. SHACKLETT AND CLARK M. WELCH

In earlier publications in this series, the kinetics of the catalytic hydrogenation of the benzene nucleus in compounds containing only one phenyl group have been reported. The purpose of the present paper is to report similar studies on a number of compounds containing more than one such group. In a compound such as diphenyl or diphenylmethane, the hydrogenation curve shows no discontinuity at the half-hydrogenation point, when the reaction is carried out in acetic acid using Adams platinum catalyst. This might be due to the fact that once the compound is adsorbed on the catalyst, both rings are reduced before desorption occurs. If, on the other hand, the reaction proceeds by steps, with all of the original compound being hydrogenated to an intermediate containing one phenyl and one cyclohexyl group, and subsequently the intermediate being hydrogenated to the fully reduced product, then the lack of a break in the hydrogenation curve could only be explained if the rates of hydrogenation of the original and the intermediate compounds were the same.

The rates for diphenylacetic acid and phenylcyclohexylacetic acid have already been reported,[1] and are equal, within experimental error. The hydrogenation of methyl and ethyl diphenylacetate has also been studied by two other workers using nickel catalysts.[2,3] The hydrogenation was reported to proceed only as far as the ester of phenylcyclohexylacetic acid, although the second benzene nucleus can be reduced in the presence of platinum. Methyl benzilate could also be reduced only to the methyl ester of phenylcyclohexylacetic acid when nickel was used as a catalyst. Miescher and Hoffmann[4] have reported that benzilic acid can be hydrogenated to phenylcyclohexylglycolic and dicyclohexylglycolic acids using platinum as a catalyst. However, experimental details are not given, and there is some question as to the identity of their products.

Experimental

Diphenyl, diphenylmethane, dibenzyl, diphenylacetic acid, mandelic acid, and triphenylmethane were obtained from the Eastman Kodak Company. The diphenyl was recrystallized from methanol and then distilled through an 18-inch Vigreux column. Dibenzyl and triphenylmethane were recrystallized from ethanol. The diphenylmethane was fractionated before use. Mandelic acid and diphenylacetic acid were used directly. 1,1-Diphenylethane was obtained by the catalytic hydrogenation over nickel of 1,1-diphenylethylene, which had been prepared from bromobenzene and ethyl acetate by a Grignard reaction.[5] The diphenylethane was fractionated in an eight-foot Vigreux column. **1,6-Diphenylhexane** was prepared from γ-phenyl-*n*-propyl alcohol, which was converted to the bromide using phosphorus tribromide, and thence to the desired product by means of sodium in dry ether.[6] The product was fractionated in a small Vigreux column.

Phenylcyclohexylmethane, 1-phenyl-1-cyclohexylethane, cyclohexyldiphenylmethane, and phenylcyclohexylacetic acid were all prepared by partial hydrogenation of the corresponding diphenyl or triphenyl compound. **Phenylcyclohexane** was synthesized from cyclohexene and benzene.[7] The product was fractionated in the eight-foot column.

Benzilic acid was prepared as follows: Benzoin was prepared from benzaldehyde by the method of Adams and Marvel.[8] This was converted to benzil by oxidation with nitric acid.[9] Rearrangement to benzilic acid using alcoholic potassium hydroxide[10] with subsequent recrystallizations from benzene, water, and methanol–water mixtures gave a product which melted from 148–150°. Oxidation of the benzoin by the method of Ballard and Dehn[11] with subsequent conversion to benzilic acid and recrystallization gave a product with similar melting range. A sample of benzilic acid was converted to ethyl benzilate by the reaction of potassium benzilate with ethyl iodide. The ester was fractionated under reduced pressure in an eight-foot Vigreux column, and the middle 60% of the distillate saponified. The acid obtained from this process was treated with active charcoal (in ethanol solution), and recrystallized three times from benzene, three times from methanol–water mixtures, and twice from ligroin. The resulting material melted from 148–150° as before. It was concluded that the melting range was caused by decomposition of the acid, and not by extraneous impurities.

Phenylcyclohexylglycolic acid was prepared as follows: Benzoyl cyanide (100 g.)[12] was dissolved in 400 ml. of absolute ethanol, and the solution saturated at 10° with hydrogen chloride. After standing five days it was diluted with water, and extracted with ether. The ether layer was washed with sodium bicarbonate solution and distilled under reduced pressure, yielding 56 ml. of ethyl phenylglyoxylate, b. p. 105–106° (1 mm.). To 40 g. of this ester dissolved in dry ether was added slowly with vigorous stirring a solution of cyclohexylmagnesium bromide[13] made from one mole of bromocyclohexane and one equivalent of magnesium. The mixture was heated under reflux for one hour, poured into a mixture of ice and dilute sulfuric acid and the ether layer dried and evaporated. The remaining liquid was distilled under reduced pressure, yielding 45 ml. of ethyl phenylcyclohexylglycolate, b. p. 172–173° (10 mm.). Thirty grams of phenylcyclohexylglycolic acid was obtained from this ester by saponifica-

(1) Smith, Alderman and Nadig, THIS JOURNAL, **67**, 272 (1945).

(2) Miescher and Hoffmann, *Helv. Chim. Acta*, **24**, 458 (1941); *cf.* Swiss Patent 217,225.

(3) L. Sandoval, *Ciencia (Mex.)*, **4**, 107 (1943).

(4) Miescher and Hoffmann, U. S. Patents 2,265,184 and 2,265,185.

(5) Allen and Converse, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1941, p. 226.

(6) The authors are indebted to Mr. Sigmund Wolfson who carried out this preparation.

(7) Corson and Ipatieff, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 151.

(8) Adams and Marvel, *Org. Syntheses*, **1**, 33 (1920).

(9) *Ibid.*, **1**, 25 (1920).

(10) *Ibid.*, **1**, 29 (1920).

(11) Ballard and Dehn, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 89.

(12) Oakwood and Weisgerber, "Org. Syntheses," **24**, 14 (1944).

(13) Gilman and Zoellner, THIS JOURNAL, **53**, 1945 (1931).

TABLE I

BOILING POINTS, MELTING POINTS AND NEUTRAL EQUIVALENTS OF COMPOUNDS HYDROGENATED

Reactant	B. p. cor. °C.	Mm.	M. p. cor., °C.	Neutral equivalent Found	Theory
Diphenyl			68.9–69.6		
Diphenylmethane	264.0	743	26.6		
1,1-Diphenylethane	150.9–151.4	29			
Dibenzyl			52.5–53.0		
1,6-Diphenylhexane	203.8–204.1	16			
Triphenylmethane			92.6–93.8		
Phenylcyclohexane	135.2	46.5			
Phenylcyclohexylmethane	132.7	19			
1-Phenyl-1-cyclohexylethane	131.6	10			
Cyclohexyldiphenylmethane			62.0–63.6		
Diphenylacetic acid[a]			147.5	212.0	212.2
Di-(γ-phenylpropyl)-acetic acid[a]			52.5	294.2	296.4
Phenylcyclohexylacetic acid			142.5	217.7	218.3
Benzilic acid			148–150	228.0	228.2
Phenylcyclohexylglycolic acid			167–168	234.0	234.3
Mandelic acid			120.3–120.8	151.9	152.1

[a] Smith, Alderman and Nadig, THIS JOURNAL, 67, 272 (1945).

TABLE II

MELTING POINTS, BOILING POINTS AND NEUTRAL EQUIVALENTS OF HYDROGENATION PRODUCTS

Completely reduced product	B. p. cor. (distn. temp.) °C.	Mm.	M. p. cor.	Neutral equivalent Found	Theory
Dicyclohexyl	131.4–132.0	31			
Dicyclohexylmethane	131.0	19			
1,1-Dicyclohexylethane	128.4–128.8	10			
1,2-Dicyclohexylethane	273.6	736			
1,6-Dicyclohexylhexane	197.6–198.0	16			
Tricyclohexylmethane	200.7	7	58.2–59.4		
Dicyclohexylacetic acid[a]			138.6	224.8	224.3
Di-(γ-cyclohexylpropyl)-acetic acid[a]			49.0	309.9	308.5
Dicyclohexylglycolic acid			173	240	240.3
Cyclohexylglycolic acid			137.2–137.6	158.7	158.2

[a] Smith, Alderman and Nadig, THIS JOURNAL, 67, 272 (1945).

tion procedures. The acid, when recrystallized from benzene and methanol–water mixtures, melted from 167–168°, and had a neutral equivalent of 234. Upon hydrogenation, it yielded dicyclohexylglycolic acid.

Dicyclohexylglycolic acid was obtained in 97–99% yields by hydrogenation of either benzilic acid or the phenylcyclohexylglycolic acid using platinum catalyst and acetic acid solvent. If the recrystallized acid was heated slowly, it underwent a change of state at 160°. The crystals melted, and almost immediately recrystallized in a different modification. The resulting solid melted sharply at 173°. Miescher and Hoffmann[1] claim a melting point of 143–144° while Danilow and Venus-Danilowa[14] obtained a value of 162–163°. For proof of structure of the compound resulting from this research, the following evidence was obtained: neutral equivalent, 240 (theoretical 240); molecular weight by boiling point elevation in ethyl acetate, 239 (theoretical 240). Reaction with methylmagnesium iodide showed two active hydrogens. The product obtained by complete hydrogenation over Raney nickel at 150° was dicyclohexylacetic acid, m. p. 138°, mixed melting point with an authentic sample, 138°.

Table I gives the reactants used together with their melting points, boiling points, and neutral equivalents.

The acetic acid used as a solvent in hydrogenation runs was prepared by fractionation in a five-foot helix-packed still. The platinum catalyst was prepared by standard methods.[15] The hydrogenations were carried out in a standard low-pressure Parr catalytic reduction apparatus.

After the reaction was complete, the product was recovered either by distilling the acetic acid solvent or by diluting it with water to make the product insoluble. The product was then recrystallized or distilled. The pertinent data are given in Table II.

Experimental Calculations and Results

As in previous hydrogenation experiments dealing with the benzene nucleus, all of the reactions were zero order with respect to the hydrogen acceptor, first order with respect to hydrogen pressure, and directly proportional to the weight of catalyst used. Therefore rate constants were calculated from the equation

$$\log p^0_{H_2}/p_{H_2} = kt/2.303\ V$$

where $p^0_{H_2}$ represents the initial hydrogen pressure, p_{H_2} represents the hydrogen pressure at time t, and V is the volume of the hydrogen gas in the system. Individual values of the rate constant, k, were obtained by plotting $\log p^0_{H_2}/p_{H_2}$ against t, and multiplying the slope of the line thus ob-

(14) Dᵉnilow and Venus-Danilowa, *Ber.*, **62**, 2653 (1929).

(15) Adams, Voorhees and Shriner, "Org. Syntheses," **8**, 92 (1928).

tained by $2.303V$.[16] Figure 1 shows typical plots from which rate constants were calculated. These constants, all referred to one gram of standard catalyst,[1] are given in Table III. The values are given at 30°, although the actual runs were made at temperatures varying from 25 to 32.5°. Corrections to 30° were made by means of the Arrhenius equation, using an activation energy of 7400 calories per mole.[17]

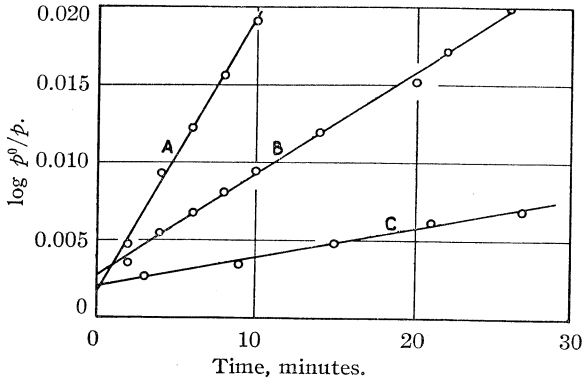


Fig. 1.—Hydrogenation plots for A, dibenzyl; B, diphenyl; and C, cyclohexyldiphenylmethane. For each run, 50 ml. of acetic acid, 0.2 g. of PtO_2 and 64 p. s. i. initial H_2 pressure were employed.

Discussion of Rate Data

An examination of the results given in Table III indicates two significant facts. First, substitution of a benzene nucleus into a molecule already containing one such nucleus usually causes a considerable decrease in the hydrogenation rate. This fact is clearly shown in Table IV. It appears that, in general, the retarding influence is reduced as the phenyl groups are removed farther away from each other.

TABLE III

RATE CONSTANTS FOR THE HYDROGENATION OF COMPOUNDS STUDIED

Compound	k (liters/g. min.)
n-Alkylbenzenes[a]	0.1152
Biphenyl	.0541
Diphenylmethane	.0629
1,1-Diphenylethane	.0474
1,2-Diphenylethane (dibenzyl)	.0806
1,6-Diphenylhexane	.1143
Triphenylmethane	.0135
Phenylcyclohexane	.0614
Phenylcyclohexylmethane	.0665
1-Phenyl-1-cyclohexylethane	.0366
Cyclohexyldiphenylmethane	.0129
Phenyl-substituted normal aliphatic acids[b]	.1108
Diphenylacetic acid[b]	.0182
Di-(phenylpropyl)-acetic acid	.0554
Benzilic acid	.0146
Mandelic acid	.0481
Phenylcyclohexylacetic acid[b]	.0191
Phenylcyclohexylglycolic acid	.0163

[a] For propylbenzenes and higher homologs. *Cf.* Smith and Pennekamp, THIS JOURNAL, **67**, 276 (1945).
[b] *Cf.* Smith, Alderman and Nadig, *ibid.*, **67**, 272 (1945).

(16) Fuzek and Smith, THIS JOURNAL, **70**, 3743 (1948).
(17) Smith and Meriwether, *ibid.*, **71**, 413 (1939).

The second interesting result is shown clearly in Table V. It appears that the substitution of a cyclohexyl group for a phenyl group has essentially no influence on the rate of hydrogenation. With the exception of 1,1-diphenylethane, the substitution of a cyclohexyl for a phenyl group results in a value of the rate constant which is unchanged almost within experimental error. It is possible that a trace of catalyst poison is responsible for the one exception, although great care was taken to prevent this.

These results can be explained if one assumes that only one benzene nucleus is adsorbed on the catalyst in any of the polyphenyl compounds, and that the remaining nucleus decreases the rate because of steric factors. Thus, an increase in the number of benzene nuclei would cause a decrease in the hydrogenation rate and, in addition, the substitution of the cyclohexyl group for the phenyl group would have little influence. This suggestion is particularly interesting in reference to biphenyl, where the two benzene rings are in resonance with each other, and where one would probably expect that both of these groups would be simultaneously adsorbed on the catalyst surface in a flat position. However, it has already been suggested that resonance in a single benzene ring is destroyed when adsorption on platinum takes place,[17] and a similar condition would probably be indicated for the biphenyl molecule.

Partial Hydrogenation Experiments

In view of the previous finding that the substitution of a cyclohexyl group for one of the phenyl groups in a polyphenyl compound did not affect the rate of hydrogenation, it follows that rate measurements can give no evidence as to whether these compounds are hydrogenated completely before they are desorbed from the catalyst, or whether one phenyl is hydrogenated, the compound then desorbed, and subsequently the other phenyl or phenyls are reduced. In order to investigate the mechanism of hydrogenation of such materials, several polyphenyl compounds were hydrogenated to that point which would be equivalent to the saturation of one ring only. The hydrogenations were then stopped, and the products analyzed. Four methods of analysis were used; they were fractional distillation, spectrophotometry, esterification and identification of the products.

The half-hydrogenation products of biphenyl, diphenylmethane, 1,1-diphenylethane and 1,2-diphenylethane were analyzed by fractional distillation methods. Figure 2 shows the results for diphenylmethane and Figure 3 those for biphenyl. The fractionations were carried out in a

TABLE IV

INFLUENCE OF PHENYL SUBSTITUTION ON HYDROGENATION RATE

Mono-substituted	k_m	Di-substituted	k_d	Ratio, k_m/k_d
Benzene	0.290	Biphenyl	0.0541	5.4
Toluene	.178	Diphenylmethane	.0629	2.8
Ethylbenzene	.130	1,1-Diphenylethane	.0474	2.7
Diphenylmethane	.0629	Triphenylmethane	.0135	4.7
Phenylcyclohexylmethane	.0665	Cyclohexyldiphenylmethane	.0129	5.2
Phenylacetic acid	.1108	Diphenylacetic acid	.0182	6.1
Mandelic acid	.0481	Benzilic acid	.0146	3.3
Ethylbenzene	.130	1,2-Diphenylethane	.0806	1.6
n-Hexylbenzene	.115	1,6-Diphenylhexane	.1145	1.0

TABLE V

COMPARISON OF RATES OF HYDROGENATION OF CORRESPONDING PHENYL- AND CYCLOHEXYL-SUBSTITUTED COMPOUNDS

Phenyl-substituted	k_p	Cyclohexyl-substituted	k_c	Ratio k_p/k_c
Biphenyl	0.0541	Phenylcyclohexane	0.0614	0.88
Diphenylmethane	.0629	Phenylcyclohexylmethane	.0665	0.95
1,1-Diphenylethane	.0474	1-Phenyl-1-cyclohexylethane	.0366	1.3
Triphenylmethane	.0135	Diphenylcyclohexylmethane	.0129	1.05
Diphenylacetic acid	.0182	Phenylcyclohexylacetic acid	.0191	0.95
Benzilic acid	.0146	Phenylcyclohexylglycolic acid	.0163	0.90

twenty-inch Vigreux column. The platinum catalyst was filtered from the acetic acid solution of the partially hydrogenated material, and the solvent removed by distillation in the same column. A synthetic mixture containing diphenylmethane and dicyclohexylmethane, and one containing 1,1-diphenylethane and 1,1-dicyclohexylethane were also fractionated in order to show that separation could be achieved with the apparatus employed.

The results of the fractionation experiments showed that the half-hydrogenated products of diphenylmethane and 1,1-diphenylethane were essentially pure phenylcyclohexylmethane and 1-phenyl-1-cyclohexylethane respectively. Half-hydrogenated diphenyl yielded about 60% of phenylcyclohexane. The distillation curve for 1,2-diphenylethane was unsatisfactory for analytical purposes, but indicated that a mixture was present.

Analysis of half-hydrogenated diphenylacetic acid depended on the fact that diphenylacetic acid is esterified at a measurable rate under conditions where dicyclohexylacetic acid is not esterified at all.[18] If one assumes that phenylcyclohexylacetic acid does not esterify at all, then the total esterification rate of a mixture of the three acids will be caused by any diphenylacetic acid present.

Two samples of diphenylacetic acid were hydrogenated until an amount of hydrogen gas equivalent to half that necessary to saturate both rings had been adsorbed. The catalyst was removed by filtration, and the acetic acid solvent

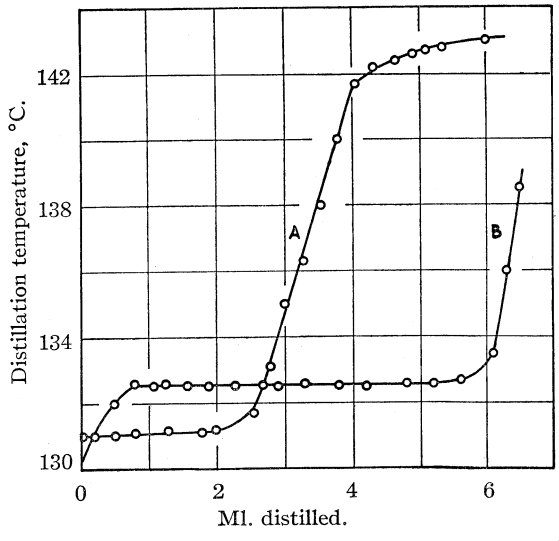


Fig. 2.—Distillation curves at 19 mm. pressure: A, synthetic mixture of 3 ml. of dicyclohexylmethane plus 4 ml. of diphenylmethane; B, 6.5 ml. of half-hydrogenated diphenylmethane.

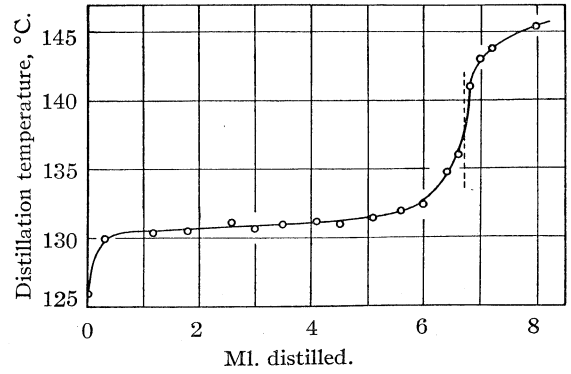


Fig. 3.—Distillation of 8.5 ml. of half-hydrogenated diphenyl; fraction between 0 and 6.7 ml. is a mixture of dicyclohexyl and phenylcyclohexane; remainder is diphenyl.

(18) Smith and Burn, THIS JOURNAL, **66**, 1494 (1944).

completely evaporated. Esterification analyses were made by treating samples from each run with methanol at 50° in the presence of hydrochloric acid catalyst. The method was essentially that used in earlier experiments,[18] except that the concentrations of organic acid and of catalyst were different from those previously used. Runs were made under comparable conditions with diphenylacetic acid, mixtures of diphenylacetic and dicyclohexylacetic acids, and with phenylcyclohexylacetic acid. The results are given in Table VI.

TABLE VI

ESTERIFICATION OF DIPHENYLACETIC ACID AND HYDROGENATED PRODUCTS IN METHANOL

For all runs, the temperature was 50.0° and the concentration of the HCl catalyst was 0.01 *M*.

Material esterified	Original concn., moles/liter	Rate constant[a]
Diphenylacetic acid	0.10	0.00957
Diphenylacetic acid plus phenylcyclohexylacetic acid	.05 .05	.00490
Half-hydrogenated diphenylacetic acid, no. 1	.10[b]	.00059
Half-hydrogenated diphenylacetic acid, no. 2	.10[b]	.00047
Phenylcyclohexylacetic acid	.10	.00054

[a] The rate constants were calculated from the equation

$$k = \frac{(r + a)\ln a/(a - x) - x}{(\text{catalyst})rt}$$

where a is the initial concentration of organic acid, x is the concentration of ester formed after time, t, and $r = 0.42$ [*cf.* Smith and Reichardt, THIS JOURNAL, **63**, 605(1941)]. The units of the rate constants are liters moles^{-1} sec.$^{-1}$

[b] These concentrations were calculated assuming a molecular weight of 218.3.

On the basis of the runs with diphenylacetic acid, it appears that the half-hydrogenated product can have a maximum of 5% of this material, and hence a minimum of 90% phenylcyclohexylacetic acid. The experiments with samples of the latter acid indicate that essentially all of the esterification rate can be accounted for by the reactivity of this material and hence the half-hydrogenated product is essentially pure phenylcyclohexylacetic acid.

When triphenylmethane was reduced with enough hydrogen to saturate only one benzene ring, the platinum filtered out, and the acetic acid solution poured into water, an oily layer separated which on standing in the refrigerator for several days became crystalline. The melting range of the crystalline material indicated that it was primarily a single compound. When recrystallized several times from methanol, the product melted at 62.0–63.6°. The literature reports a melting point of 56.5° for diphenylcyclohexylmethane.[19]

When di-(phenylpropyl)-acetic acid was half-hydrogenated, and the product recovered in the usual manner, an oily layer was obtained which could not be crystallized. This was thought to indicate that a mixture was present.

The half-hydrogenated benzilic acid was analyzed by a colorimetric method, details of which will be given later. The analysis showed that approximately 65% of the material present when enough hydrogen had been taken up to reduce one benzene nucleus was phenylcyclohexylglycolic acid.

Thus, for every compound for which satisfactory analysis was made, the partial hydrogenation product was found to be mainly a compound with only one ring saturated, and in three cases this was essentially the only material present. It would appear that the polyphenyl compound must be desorbed after one ring is saturated, and that the original material is adsorbed in preference to the partially saturated material, even though the rates of hydrogenation of the two are the same. If the differences in these adsorptions are sufficiently great, one may obtain practically pure material with only one saturated benzene nucleus.

The fact that, on nickel catalyst, the esters of diphenylacetic and benzilic acids may be hydrogenated only as far as the esters of phenylcyclohexylacetic acid[2,3] may be explained on the same basis.

Summary

The kinetics of the catalytic hydrogenation of sixteen compounds each containing more than one benzene nucleus have been investigated. All hydrogenations were carried out in acetic acid solution using Adams platinum catalyst, and first order rate constants referred to one gram of standard catalyst were tabulated.

The results indicate that, in general, the rate of hydrogenation decreases with the number of phenyl groups present. In addition, substitution of a cyclohexyl group for a phenyl group has no influence on the rate of hydrogenation.

Partial hydrogenation experiments indicate that the mechanism of the hydrogenation of compounds containing several nuclei is a stepwise reaction involving saturation of only one benzene nucleus at a time. In some cases it is possible to isolate intermediate cyclohexyl compounds in almost the theoretical quantities even though no change in rate occurs.

KNOXVILLE, TENNESSEE RECEIVED MAY 18, 1949

(19) Schmidlin and von Escher, *Ber.*, **45**, 892 (1912).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Reaction between Ferrous Iron and Peroxides. I. Reaction with Hydrogen Peroxide in the Absence of Oxygen[1]

BY I. M. KOLTHOFF AND A. I. MEDALIA[1a]

In a previous paper[2] the mechanisms which have been proposed for the reaction between ferrous iron and hydrogen peroxide have been reviewed. Two mechanisms which appear equally satisfactory are those of Bray and Gorin[3] and of Haber and Weiss.[4,5] In both mechanisms the primary step is assumed to be unimolecular in ferrous iron and hydrogen peroxide, and to result in the formation of a highly active intermediate. This intermediate is ferryl iron, FeO^{++}, in the former mechanism, and the hydroxyl radical, HO·, in the latter. For simplicity, attention is focused in the present paper upon the more familiar mechanism of Haber and Weiss. The steps proposed by Haber and Weiss are

$$Fe^{++} + H_2O_2 = Fe^{+3} + OH^- + HO\cdot \quad (1)$$

$$HO\cdot + H_2O_2 = H_2O + HO_2\cdot \quad (2)$$

$$HO_2\cdot + H_2O_2 = O_2 + H_2O + HO\cdot \quad (3)$$

$$HO\cdot + Fe^{++} = Fe^{+3} + OH^- \quad (4)$$

The active intermediate (HO·) can react with ferrous iron, hydrogen peroxide or other components contained in the reaction mixture. Reaction with ferrous iron leads to the stoichiometric over-all reaction (sum of steps (1) and (4))

$$2Fe^{++} + H_2O_2 + 2H^+ = 2Fe^{+3} + 2H_2O \quad (I)$$

while reaction with hydrogen peroxide leads to induced decomposition of hydrogen peroxide (sum of steps (2) and (3))

$$2H_2O_2 = 2H_2O + O_2 \quad (II)$$

If the reaction mixture contains only ferrous iron, hydrogen peroxide, water and sulfuric acid, the free radical reaction with ferrous iron predominates, unless hydrogen peroxide is present in large excess over ferrous iron. Under the latter circumstances some of the intermediates decompose hydrogen peroxide. Consideration of the reaction in this simple system, on the basis of either mechanism mentioned above, leads to the following expression for the instantaneous consumption ratio, n

$$n = \frac{d(H_2O_2)}{d(Fe^{++})} = 0.5 + \frac{k_a}{k_b}\frac{(H_2O_2)}{(Fe^{++})} \quad (5)$$

where k_a and k_b represent the rate constants for reaction of the active intermediate with hydrogen peroxide or ferrous iron, respectively. This expression was derived theoretically and confirmed experimentally by Haber and Weiss; the value of k_a/k_b is of the order of 2×10^{-2} at 20°, depending somewhat upon the acidity.

The rate law for the *stoichiometric* reaction (I) which would be expected on the basis of either of the above mechanisms

$$-\frac{d(Fe^{++})}{dt} = \frac{2d(H_2O_2)}{dt} = k_4(Fe^{++})(H_2O_2) \quad (5a)$$

was established experimentally by Baxendale, Evans and Park,[6] who found an average value of k_4 of 62 liters mole^{-1} sec.$^{-1}$ at 25°.

The reaction between hydrogen peroxide and ferrous iron becomes of special interest when carried out in the presence of other compounds with which the active intermediate can react. The polymerization of vinyl monomers may be initiated in this way,[6] the free radical reacting with the monomer and thus initiating the polymerization. The oxidation of many organic compounds by hydrogen peroxide is induced by the ferrous iron–hydrogen peroxide reaction; this is known as a Fenton reaction. For example, it is shown in the experimental part that ethanol is oxidized to acetaldehyde when it is present in the reaction mixture of hydrogen peroxide and ferrous iron.

The reaction between ferrous iron and organic hydroperoxides is widely used for the determination of these compounds, especially when they are present in very small amounts. This reaction results in a ratio of moles of ferrous iron to hydroperoxide reacted which may be much smaller or much larger than the stoichiometric ratio dependent on whether oxygen is absent or present. Similar deviations from the stoichiometric ratio are found in the reaction between hydrogen peroxide and ferrous iron in the presence of various organic substances. The present paper deals with a study of these deviations in the absence of oxygen; in a subsequent paper the results of a similar study in the presence of oxygen will be presented. These studies have yielded insight into the side reactions which occur in the reaction between ferrous iron and organic hydroperoxides, which will be reported in a future paper.

Experimental

In adopting a technique for the study of the re-

(1) This investigation was started under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Synthetic Rubber Program of the United States Government.

(1a) From a thesis submitted by A. I. Medalia to the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the doctor's degree (July 1948).

(2) A. I. Medalia and I. M. Kolthoff, *J. Polymer Sci.*, **4**, 377 (1949).

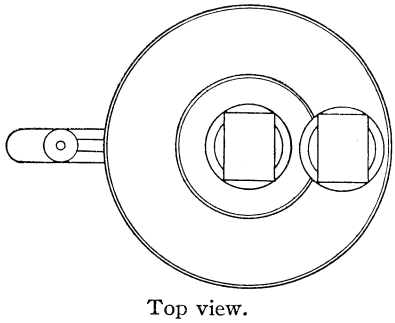
(3) W. C. Bray and M. H. Gorin, THIS JOURNAL, **54**, 2124 (1932).

(4) F. Haber and J. Weiss, *Naturwiss.*, **20**, 948 (1932).

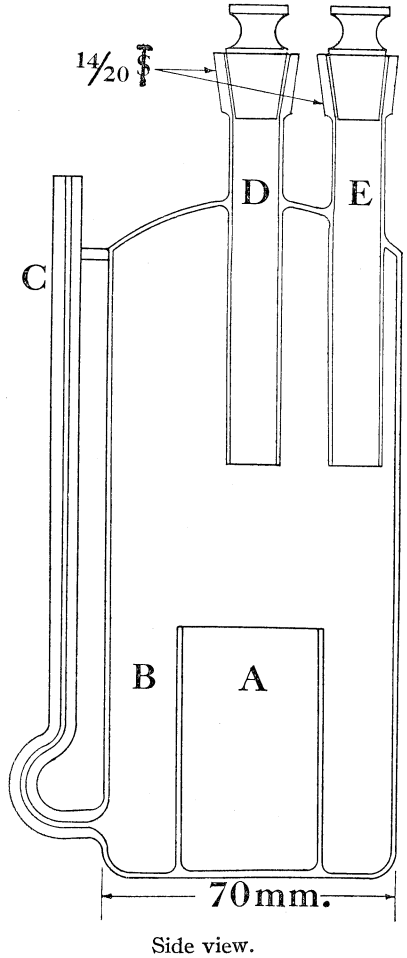
(5) F. Haber and J. Weiss, *Proc. Roy. Soc.*, **A147**, 332 (1934).

(6) J. H. Baxendale, M. G. Evans and G. S. Park, *Trans. Faraday Soc.*, **42**, 155 (1946).

action between hydrogen peroxide and ferrous iron in the absence of oxygen, the following factors were considered: (1) exclusion of oxygen must be thorough, (2) mixing should be rapid, (3) the reaction vessel should be free from contamination by organic matter, such as stopcock grease. Reaction vessels were constructed as shown in Fig. 1. Experiments in the absence of oxygen have been carried out as follows.



Top view.



Side view.

Fig. 1.—Reaction vessel.

Procedure.—Purified nitrogen is passed through the capillary side-tube C, and through inlet tubes inserted through the tubes D and E, for at least ten minutes. The solutions which are to be added are flushed with nitrogen, in vessels provided with tubes similar to D and E, for at least thirty minutes. Aliquots are withdrawn with nitrogen-filled pipets, which are then inserted all the way through tubes D and E before draining. Solutions are introduced into compartment A through inlet tube D, and into compartment B through inlet tube E. The nitrogen inlet tube is removed from D or E immediately before inserting the pipet; however, nitrogen is continually passed through the other of these tubes, and through the capillary side-arm. When the solutions have all been added, the tubes D and E are flushed with nitrogen by keeping one tube stoppered tightly and the other loosely (alternately) while passing nitrogen through the capillary. The tubes are then stoppered tightly and the vessel is shaken vigorously for about fifteen seconds. One stopper is then loosened and nitrogen is passed through the side-arm. Aliquots are removed with a pipet, and the ferrous iron is titrated. Evidently the total volume of solution added to the vessel must be known accurately.

When the above procedure is followed, complete mixing appears to be brought about in one second (three strokes). Calculation on the basis of the rate law[4] and rate constant given above shows that in a solution initially 2×10^{-3} M in ferrous iron and 5×10^{-4} M in hydrogen peroxide (typical conditions used in the present work), the stoichiometric reaction is 11.4% complete in one second. Thus under the experimental conditions, only a minor portion of the reaction can take place before mixing is complete.

In the experiments reported in this paper, 25 ml. of acid (generally 1.5 N sulfuric) was placed in A and 75 ml. in B. Solutions of the organic substance and ferrous iron were placed in B and of hydrogen peroxide in A. The total volumes of solution were 120–130 ml., and 50-ml. aliquots were titrated ten and twenty minutes (or fifteen and thirty minutes), respectively, after mixing, with ceric sulfate solution of the proper concentration, using ferrous *o*-phenanthroline perchlorate as indicator. Good end-points were obtained with 0.001321 N cerate solution, which was the most dilute cerate solution used, using comparison flasks in the detection of the end-point. No interference in the titration of iron was found in the presence of ethanol or acetaldehyde. All experiments were carried out at room temperature (25–30°).

To test completeness of removal of oxygen by the above procedure, solutions of ferrous iron and alkali pyrophosphate were flushed with nitrogen in the separate compartments of the reaction vessel, then mixed and allowed to stand for fifteen minutes. Titration of aliquots showed that the extent of air oxidation of ferrous iron was negligible.

Reagents.—Water: Twice-distilled water was redistilled from alkaline permanganate in an all-

glass still; the middle three-fifths portion was used. Sulfuric acid was du Pont (Grasselli) reagent grade; ferrous sulfate heptahydrate, Merck reagent grade; hydrogen peroxide, Merck Superoxol (30%), C.P.; sodium perchlorate, G. F. Smith Co. Other inorganic compounds were C.P. or reagent grade. Ethanol, absolute ethanol was refluxed with aluminum and sodium hydroxide, then distilled; acetic acid, du Pont (Grasselli) reagent grade; acetone, C.P., freshly distilled; acetaldehyde, Eastman Kodak Co. "White Label" grade; methanol, C.P., freshly distilled; nitrogen, pre-purified nitrogen, obtained from Air Reduction Co. (Seaford works) and from Linde Air Co.

The dilute cerate solutions for titration were made up daily by dilution with 1 N sulfuric acid of a 0.1321 N stock solution (standardized against Bureau of Standards arsenious oxide). Both the ferrous solution and the hydrogen peroxide solution were standardized daily against the dilute cerate solution. The ferrous *o*-phenanthroline end-point was not sharp in the titration of dilute hydrogen peroxide with dilute cerate, and for this reason a known amount of ferrous solution was added after the approximate end-point, and the excess ferrous iron was back-titrated with cerate.

Results and Discussion

Results Obtained in the Presence of Sulfuric Acid and Ethanol.—In the present experiments attention is focused upon the stoichiometry of the reaction between ferrous iron and hydrogen peroxide in the presence of various other compounds, while in a later section there is described a brief study of the products formed. The stoichiometry was determined simply by titration of the ferrous iron remaining after carrying out a reaction under conditions such that the hydrogen peroxide taken was completely consumed; completeness of reaction was tested by titration of aliquots taken after two different reaction times; qualitative tests (with titanic sulfate or potassium ferricyanide) established whether ferrous iron or hydrogen peroxide remained in the mixture after completion of the reaction.

Results obtained for the reaction in sulfuric acid solutions in the presence of various concentrations of ethanol are shown in Table I. This table, as well as all other tables in this paper, gives analytical data obtained for the reaction between ferrous iron and hydrogen peroxide, in the absence of oxygen, according to the above procedure. The initial concentrations of ingredients given are those which would be present immediately after mixing if no reaction had taken place during mixing. The column headed "Molar ratio, (Fe^{++}) reacted/(H_2O_2) taken" gives the results of the titrations. Each figure given in this column is an average obtained with aliquots from a single reaction mixture after reaction times differing by a factor of two. Since in all experiments, therefore, the concentration of hydrogen peroxide taken was equal to the concentration of hydrogen peroxide reacted, this column gives the values of the overall reaction ratio, which may be designated as

$$R = \frac{\text{moles } (Fe^{++}) \text{ reacted}}{\text{moles } (H_2O_2) \text{ reacted}} = \frac{\Delta(Fe^{++})}{\Delta(H_2O_2)} = \frac{1}{\bar{n}}$$

The stoichiometric value of R is 2. The significance of the induction factor is discussed below.

TABLE I

REACTION IN 1.5 N SULFURIC ACID IN THE PRESENCE OF ETHANOL

Initial concentrations Ethanol, M	Fe^{++} ($M \times 10^3$)	Molar ratios: Initial $(Fe^{++})/(H_2O_2)$ taken	(Fe^{++}) reacted $/(H_2O_2)$ taken	Induction factor
.....	0.52	3.8	1.98	0.01
1.0×10^{-4}	.52	3.8	1.64	0.22
1.0×10^{-3}	.52	3.8	0.54	2.7
1.0×10^{-3}	.52	7.6	.56	2.6
1.0×10^{-3}	.52	1.9	.58	2.5
1.0×10^{-2}	.52	3.8	.15	12.3
1.0×10^{-1}	.52	3.8	.18	10.1
1.0×10^{-2}	.90	0.85	.19	9.5
.....	2.0	4.1	1.96	0.02
1.0×10^{-4}	2.0	4.1	1.64	0.22
1.0×10^{-3}	2.0	4.1	0.70, 0.71	1.86
1.0×10^{-2}	2.0	4.1	0.19, 0.24, 0.23	8.5
1.0×10^{-2}	2.0	2.0	0.21	8.5
1.0×10^{-1}	2.0	4.1	0.11	17.2
5.0×10^{-5}	4.4	3.5	1.90	0.05
1.0×10^{-2}	2.0	8.2	0.21	8.5
1.0×10^{-4}	8.7	8.2	1.88	0.064
.....	9.5	3.8	1.99	0.005
1.0×10^{-3}	9.5	3.8	1.16	0.72
1.0×10^{-2}	9.5	3.8	0.36	4.56
1.3×10^{-4}	23	3.5	1.94	0.03
1.0×10^{-3}	2.0	3.8	0.89[a]	1.25
1.0×10^{-3}	2.0	3.8	0.49[b]	3.08

[a] In 2.1 N sulfuric acid. [b] In 0.045 N sulfuric acid.

The above data show that in the presence of ethanol, less ferrous iron is oxidized than would correspond to the hydrogen peroxide initially present, on a stoichiometric basis. Thus hydrogen peroxide must be consumed by some reaction which is induced by the ferrous iron–hydrogen peroxide reaction. It is shown further in this paper that this induced reaction is principally the oxidation of ethanol to acetaldehyde; that is, a Fenton reaction. The extent of this induced reaction increases with increasing concentrations of ethanol, when the initial concentrations of iron and peroxide are kept constant. With given concentrations of ethanol and iron (10^{-3} and 0.52×10^{-3} M, respectively), the reaction ratio was found to be independent of the initial concentration of peroxide, over a fourfold range; while with a given concentration of ethanol and a given initial ratio of iron to peroxide, the reaction ratio increased (*i. e.*, the extent of the induced reaction decreased) with increasing concentrations of iron. The effect of the concentration of sulfuric acid is discussed

later. The slight deviations from the stoichiometric reaction ratio found in the absence of ethanol may be due to traces of organic impurities.

The induction factor is defined as the number of equivalents of the induced reaction divided by the number of equivalents of the primary reaction.[7] In the present experiments, R equivalents (or moles) of ferrous iron react per mole (or per 2 equivalents) of hydrogen peroxide. Thus the number of equivalents of hydrogen peroxide consumed in the primary reaction is R, and the number consumed in the induced reaction is $2 - R$; so that the induction factor is $(2 - R)/R$. The large values of the induction factor are significant from an analytical standpoint. If a determination of hydrogen peroxide with ferrous iron were attempted in the presence of ethanol, the percentage error (based on the amount of hydrogen peroxide found) would be given by 100 times the induction factor. It is seen that the error in the presence of sufficient ethanol would be over one thousand per cent.

The Fenton oxidation of ethanol may be interpreted either on the basis of the Haber and Weiss[4,5] mechanism or the Bray and Gorin[3] mechanism. On the former basis, the mechanism would be

$$Fe^{++} + H_2O_2 = Fe^{+3} + HO\cdot + OH^- \quad (1)$$
$$HO\cdot + CH_3CH_2OH = CH_3\dot{C}HOH + H_2O \quad (6)$$
$$CH_3\dot{C}HOH + Fe^{+3} = CH_3CHO + H^+ + Fe^{++} \quad (7)$$
$$Fe^{++} + HO\cdot = Fe^{+3} + OH^- \quad (4)$$

Steps (1), (6) and (7) form a chain mechanism for the reaction between hydrogen peroxide and ethanol, with ferrous iron, hydroxyl radical and hydroxyethyl radical as chain-carriers; step (4) is the termination step. The sum of steps (1), (6) and (7) gives the over-all induced oxidation of ethanol by hydrogen peroxide

$$CH_3CH_2OH + H_2O_2 = CH_3CHO + 2H_2O \quad (8)$$

In a qualitative interpretation of the results, termination by reaction between the organic radical and ferrous iron, though possible, need not be assumed for compounds, such as ethanol, which are oxidized during the course of the peroxide–iron reaction. Termination by reaction with the organic radical is found with acetic acid, as shown in step (15). Direct reaction between hydrogen peroxide and the hydroxyethyl radical may also take place, as shown in step (9), which is equivalent to the sum of steps (7) and (1).

$$CH_3\dot{C}HOH + H_2O_2 = CH_3CH(OH)_2 + HO\cdot =$$
$$CH_3CHO + H_2O + HO\cdot \quad (9)$$

On the basis of the mechanism of Bray and Gorin, the pertinent steps would be

$$Fe^{++} + H_2O_2 = FeO^{++} + H_2O \quad (10)$$
$$FeO^{++} + CH_3CH_2OH = Fe^{+3} + CH_3\dot{C}HOH + OH^- \quad (11)$$

(7) I. M. Kolthoff and V. A. Stenger, "Volumetric Analysis," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1942.

$$CH_3\dot{C}HOH + Fe^{+3} = CH_3CHO + H^+ + Fe^{++} \quad (7)$$
$$Fe^{++} + FeO^{++} + 2H^+ = 2Fe^{+3} + H_2O \quad (12)$$

Steps (10), (11) and (7) form a chain reaction with the ferryl ion as a chain-carrier; the chain is terminated by step (12). It is also possible that hydrogen peroxide is consumed by steps (16) and (17) discussed later in this paper. We are indebted to Professor M. S. Kharasch of the University of Chicago for the suggestion that acetaldehyde is the reaction product.

We have attempted to derive expressions for the stoichiometry of the reaction in the presence of ethanol, based on the above mechanisms[8]; however, agreement of any of these expressions with the experimental data of Table I is only fair. A complicating factor is the induced oxidation of acetaldehyde to acetic acid, as shown below; that is, as soon as some acetaldehyde is formed by oxidation of ethanol, it will compete with both ethanol and ferrous iron for reaction with the active intermediate (ferryl iron or hydroxyl radical), so that the kinetic treatment becomes very complicated and difficult to test experimentally.

Results Obtained in the Presence of Sulfuric Acid and Organic Compounds other than Ethanol.—Some experiments have been carried out using the apparatus and technique described above, but with acetic acid, acetone or acetaldehyde in place of ethanol. The data are given in Table II.

TABLE II

REACTION IN 1.5 N SULFURIC ACID IN THE PRESENCE OF VARIOUS ORGANIC COMPOUNDS

Initial concentrations				Molar ratios		
Acetic acid, M	Acetone, M	Acetaldehyde, M	Fe^{++} ($M \times 10^3$)	Initial (Fe^{++}) (H_2O_2) taken	(Fe^{++}) reacted (H_2O_2) taken	Induction factor
...	..	..	0.51	3.9	1.99	0.005
10^{-4}	..	..	.51	3.9	1.97	.015
10^{-2}	..	..	.51	3.9	1.91	.047
10^{-1}	..	..	.51	3.9	1.92	.042
10^{-1}[a]	..	..	.51	3.9	1.91	.047
10[a]	..	..	2.0	3.8	1.97	.015
...	10^{-2}	..	2.0	3.8	1.95	.025
...	..	10^{-3}	8.7	3.5	1.54	.30

[a] In 0.045 N sulfuric acid.

The behavior of acetaldehyde, as indicated in Table II, is qualitatively similar to that of ethanol; that is, a significant deviation from the stoichiometric reaction is found in the presence of a small concentration of acetaldehyde. In preliminary experiments with a less refined experimental technique, methanol was also found to behave similarly.

In contrast, even relatively high concentrations of acetic acid or acetone give rise to practically no deviation from the stoichiometric reaction. In terms of the mechanisms given above, this means that these compounds either fail to react with the active intermediates, or that, if reaction does oc-

(8) A. I. Medalia, Ph.D. Thesis, University of Minnesota, 1948.

cur, the organic radicals thus formed react with ferrous iron in preference to ferric iron or hydrogen peroxide; this is illustrated in equations (13)–(15), with acetic acid.[9a]

$$HO\cdot + CH_3COOH = CH_3COO\cdot + H_2O \quad (13)$$

$$FeO^{++} + CH_3COOH = Fe^{+3} + CH_3COO\cdot + OH^- \quad (14)$$

$$CH_3COO\cdot + Fe^{++} = CH_3COO^- + Fe^{+3} \quad (15)$$

The sum of steps (1), (13) and (15) or of steps (10), (14) and (15), gives the stoichiometric reaction (I), which in the absence of added organic compounds results from the combination of steps (1) and (4), or (10) and (12). Thus, while the reaction between ferrous iron and hydrogen peroxide is stoichiometric in either the presence or absence of acetic acid (or acetone), the reaction may proceed through a different path in the two cases. Strong evidence that this is the correct interpretation is derived from the work described in the second paper of this series, in which it is shown that both acetic acid and acetone give rise to considerable induced oxygen oxidation of ferrous iron when the peroxide–iron reaction is carried out in the presence of dissolved oxygen. Additional evidence is given in the following section. Independent evidence that acetic acid reacts with the hydroxyl radical comes from a study of the hydrogen peroxide–ozone system, by Taube and Bray.[9b] Using the values of relative rate constants for the reaction of hydroxyl radical with acetic acid, hydrogen peroxide and ferrous iron, as determined by Taube and Bray and by Haber and Weiss, a simple kinetic treatment shows that in the experiments of Table II with 0.1 *M* acetic acid, where a reaction ratio of 1.91 was found, a reaction ratio of only 0.59 would be expected if the acetate radicals reacted with ferric iron or hydrogen peroxide rather than with ferrous iron; this is of significance, of course, only if the Haber and Weiss mechanism is adopted rather than that of Bray and Gorin.

Results Obtained in the Presence of Sulfuric Acid and Mixtures of Organic Compounds.—As shown above, it appears that when the active intermediates which are formed in the ferrous iron–hydrogen peroxide reaction react with acetic acid, then the over-all reaction is stoichiometric, while if these intermediates react with ethanol, then induced reduction of hydrogen peroxide takes place. In a mixture containing both ethanol and acetic acid, competition between these compounds (and ferrous iron) for reaction with the active intermediates would be expected to result in a reaction ratio intermediate between that found with the same concentrations of either organic compound separately. Data illustrating this are shown in Table III.

TABLE III

REACTION IN SULFURIC ACID IN THE PRESENCE OF A MIXTURE OF ACETIC ACID AND ETHANOL

Initial concentrations				Molar ratios		
H_2SO_4, *N*	Acetic acid, *M*	Ethanol, *M*	Fe^{++} ($M \times 10^3$)	Initial $(Fe^{++})/(H_2O_2)$ taken	(Fe^{++}) reacted $/(H_2O_2)$ taken	Induction factor
2.1	..	10^{-3}	2.0	3.8	0.89	1.25
2.1	10^{-1}	10^{-3}	2.0	3.8	1.27	0.57
1.5	..	10^{-3}	2.0	3.8	0.71	1.86
1.5	1	10^{-3}	2.0	3.8	1.79	0.12
0.045	..	10^{-3}	2.0	3.8	0.49	3.09
.045	10[a]	..	2.0	3.8	1.97	0.015
.045	10[a]	10^{-3}	2.0	3.8	1.95	.025
.045	10[a]	10^{-4}	2.0	3.8	1.97	.015

[a] Reaction medium approximately 60% acetic acid.

These data strongly support the view that acetic acid and ethanol compete for the active intermediates formed in the reaction between ferrous iron and hydrogen peroxide. The acetate free radicals do not give rise to decomposition of hydrogen peroxide (equations (13) to (15)), while the hydroxyethyl free radicals do. Thus acetic acid suppresses the induced oxidation of ethanol observed in the reaction between ferrous iron and hydrogen peroxide. Interaction between a hydroxyethyl radical and acetic acid, or an acetate radical and ethanol, while possible, need not be considered in the qualitative interpretation.

On a purely experimental basis, ethanol may be said to promote the decomposition of hydrogen peroxide during the course of the ferrous iron–hydrogen peroxide reaction, while acetic acid suppresses the promoting action of ethanol. The classification of compounds as "promoting" or "suppressing" is of great utility in considering chain reactions such as those between ferrous iron and hydrogen peroxide, organic hydroperoxides or persulfate. From an analytical standpoint, the above results are significant as indicating the use which can be made of the suppressing action of certain compounds in overcoming the induced decomposition caused by other compounds. Application of this principle to the determination of organic peroxides may be of considerable importance, as will be shown in a subsequent paper.

Reaction in the Presence of Inorganic Compounds other than Sulfuric Acid.—The experiments described above were carried out in the presence of sulfuric acid. This acid is convenient to use, since it is available in pure form and is quite stable, and extensive previous study of the ferrous iron–hydrogen peroxide reaction has been carried out in sulfuric acid medium. However, some study of the reaction in the presence of perchloric rather than sulfuric acid seemed desirable in view of the comparatively slight tendency of

(9a) If the acetate radical would decompose appreciably (to $CH_3\cdot$ and CO_2) before reacting with ferrous iron, the stoichiometry would require oxidation of ferrous iron by the methyl radical:

$$CH_3\cdot + Fe^{++} + H^+ = CH_4 + Fe^{+3} \quad (15a)$$

Because of the low concentrations of peroxide and ferrous iron used in the present experiments, no attempt was made to detect the presence of methane or carbon dioxide. Reaction between hydroxyl radical and acetic acid might form the radical $\cdot CH_2COOH$ instead of the acetate radical (step (13)); *cf.* the following paper.

(9b) H. Taube and W. C. Bray, THIS JOURNAL, **62**, 3357 (1940).

perchloric acid to form complexes with ferrous and ferric iron. Some difficulty was encountered in these experiments, apparently as a result of impurities present in several of the samples of perchloric acid which were used. In selecting a sample of perchloric acid for use in further experiments, the criterion of purity which was used was the reaction ratio of ferrous iron to hydrogen peroxide found in the presence of perchloric acid (1 *M*) in nitrogen, in the absence of other added substances. The sample which gave the reaction ratio closest to the theoretical (J. T. Baker C.P. vacuum distilled, 20%) was used in subsequent work. The reaction ratio obtained with this sample was 1.94 (theoretical, 2.0); other ratios obtained are as follows: Merck 60%, two different lots, 1.03 and 1.23; Baker and Adamson 60%, 1.82.

The reaction has also been studied in the presence of sodium perchlorate, sodium chloride, potassium nitrate and phosphoric acid. Experiments with each compound were carried out both in the absence and presence of ethanol. The data are given in Table IV.

TABLE IV

REACTION IN THE PRESENCE OF VARIOUS INORGANIC COMPOUNDS IN THE PRESENCE AND ABSENCE OF ETHANOL

Initial concentrations				Molar ratios		
$HClO_4$, *M*	Ethanol, *M*	Fe^{++} (*M* × 10^3)	Other compound	Initial $(Fe^{++})/(H_2O_2)$ taken	(Fe^{++}) reacted $/(H_2O_2)$ taken	Induction factor
1.0	..	1.6	.....	2.69	1.94	0.03
1.0	10^{-3}	1.6	.....	2.69	0.55, 0.53	2.70
0.14	10^{-3}	1.6	.....	2.69	0.51	2.92
.02	..	1.9	.....	3.28	1.98	0.01
.02	10^{-3}	1.9	.....	3.28	0.50	3.00
.02	..	1.9	$NaClO_4$, 1 *M*	3.28	1.89	0.06
.02	10^{-3}	1.9	$NaClO_4$, 1 *M*	3.28	0.51	2.92
.14	..	1.6	NaCl, 1 *M*	2.69	1.96	0.02
.14	10^{-3}	1.6	NaCl, 1 *M*	2.69	1.95	.03
.14	10^{-2}	1.6	NaCl, 1 *M*	2.69	1.87	.07
.14	..	1.6	KNO_3, 1 *M*	3.25	1.95	.03
.14	10^{-3}	1.6	KNO_3, 1 *M*	3.25	0.79	1.53
..	..	1.6	H_3PO_4, 1 *M*	3.25	1.93	0.04
..	10^{-3}	1.6	H_3PO_4, 1 *M*	3.25	0.67	1.99
..	10^{-3}	2.0	H_2SO_4, 1.5 *N*	4.1	.70	1.86
..	10^{-3}	2.0	H_2SO_4, 0.045 *N*	3.8	.49	3.08

The above data show definitely that with perchloric acid the extent of the induced reaction in nitrogen is practically independent of the amount of acid over a fifty-fold range. The coincidence of the value obtained in perchloric acid with that obtained in dilute (0.045 *N*) sulfuric acid makes it appear that these values are limiting values, without interference by the anions. The data obtained with sodium perchlorate substantiate the conclusion that there is no salt effect upon the reaction ratio with perchlorate as the anion. The extent of the induced reaction depends upon the competition between ethanol and ferrous iron for reaction with the active intermediates. Absence of a salt effect indicates that the active intermediate is uncharged; this supports the free-radical mechanism. If ferryl iron were the active intermediate, then a salt effect would be expected for the reaction of ferryl iron with ferrous iron, but not for the reaction of ferryl iron with ethanol; thus the reaction ratio would be expected to depend upon salt concentration. It is, however, possible that hydrolysis or complex formation may obscure the expected salt effect.

Chloride ion is seen to act as a powerful suppressor, comparable with acetic acid. Reaction of hydroxyl radical with chloride ion, to form atomic chlorine, was described by Taube and Bray.[9b] From our results it follows that atomic chlorine must react more readily with ferrous iron than with ferric iron, hydrogen peroxide or ethanol.

With high concentrations of sulfuric acid, phosphoric acid or potassium nitrate, slightly higher values are found for the reaction ratio in the presence of 10^{-3} *M* ethanol than are found in dilute sulfuric acid or in perchloric acid. The effect of these compounds may be regarded as mild "suppression," either by the mechanism assumed for suppression by acetic acid, acetone and chloride ion, namely, by reaction of these compounds with the active intermediate; or possibly by protection of the ferrous ion by complex formation, resulting in a decreased rate of reaction between ferrous iron and the active intermediate.

Detection of Acetaldehyde Formed from Ethanol.—In the above presentation it has been assumed that the role of ethanol in the ferrous iron–hydrogen peroxide reaction is to reduce hydrogen peroxide. It also appeared possible that ethanol could serve simply as a chain-carrier, without itself being oxidized. A mechanism for this behavior, based on the mechanism of Haber and Weiss, would include steps (1) and (6) followed by (16) and (17).

$$CH_3\dot{C}HOH + H_2O_2 = CH_3CH_2OH + HO_2\cdot \quad (16)$$

$$HO_2\cdot + H_2O_2 = H_2O + O_2 + HO\cdot \quad (17)$$

It has been reported by Goldschmidt and Pauncz[10] that acetaldehyde, acetic acid and a small amount of oxygen are formed upon slow addition of ferrous iron to relatively concentrated solutions of hydrogen peroxide and ethanol. The conditions under which these experiments were carried out are quite different from those described in this paper. In order to decide by which mechanism hydrogen peroxide disappears when ethanol is present in the reaction mixture it was decided to determine the amount of acetaldehyde formed. It was assumed that if acetaldehyde were formed in the presence of a large amount of ethanol, ethanol would be attacked by the active intermediates rather than the small amounts of acetaldehyde. The experimental results show that the assumption is justified. The most suitable method for the detection and determination of acetaldehyde

(10) S. Goldschmidt and S. Pauncz, *Ann.*, **502**, 1 (1933).

in the presence of ferrous and ferric iron appeared to be that based on reaction with Schiff reagent.

A solution of Schiff reagent was prepared by dissolving 0.50 g. of basic fuchsin (National Aniline Co.) in 1 l. of water, together with 0.31 ml. of 6 N sulfuric acid and 0.58 g. of sodium sulfite. The solution was still pink, and sulfur dioxide was passed through very slowly until the color just turned to yellow. The solution was thus 1.5×10^{-3} M in the fuchsin reagent. Tests were carried out with various buffer solutions, using the following procedure: 5 ml. of buffer solution was mixed with 1 ml. of Schiff reagent solution, and the colors developed in various solutions after five to fifteen minutes were compared visually. At a pH of greater than 3.0, a rose color of fuchsin was visible in the absence of aldehyde. The sensitivity of the test for acetaldehyde decreased with decreasing pH below 3.0. A biphthalate buffer of pH 3.0 was unsuitable, owing to the formation of orange hydrous ferric oxide upon addition of ferric iron in a concentration of 10^{-3} M. In a phosphate buffer, at a pH of 3.0 or 2.4, a white turbidity was formed on addition of ferric iron (ferric phosphate) which did not, however, interfere with the Schiff test under the present conditions. In a phosphate buffer of pH 2.0, no precipitate was formed on addition of ferric iron, but the sensitivity of the test was lower than at the higher values of pH. Ferrous iron did not interfere with the test in the pH range 2–3. The procedure which was adopted for testing reaction mixtures was as follows.

Procedure.—To 5 ml. of reaction mixture, containing up to 0.05 N acid (sulfuric or perchloric), was added sufficient sodium dihydrogen phosphate to give a pH of 3.0 (calculated). One ml. of the solution of Schiff reagent was added and the color was observed after fifteen minutes.

By means of this test, acetaldehyde could be detected in concentrations as low as 10^{-4} M. By visual comparison with controls containing various amounts of acetaldehyde, the concentration could be estimated to $\pm 10^{-4}$ M in the range between 2 and 5×10^{-4} M. More concentrated solutions were diluted before carrying out the test.

Reactions were carried out as described previously. The conditions and results are given in Table V.

TABLE V

ALDEHYDE DETERMINATIONS

Acid[a]	Initial concentrations: Ethanol, M	Initial concentrations: Fe^{++} ($M \times 10^3$)	Molar ratios: Initial (Fe^{++}) / Initial (H_2O_2)	Molar ratios: (Fe^{++}) reacted / Initial (H_2O_2)	Acetaldehyde found, M
Sulfuric	10^{-1}	2.9	2.1	0.13	1×10^{-3}
Perchloric	10^{-3}	2.0	3.3	.50	4×10^{-4}
Perchloric[b]	10^{-3}	2.0	3.3	.51	3×10^{-4}

[a] The sulfuric acid was 0.05 N; the perchloric acid was 0.02 N. [b] With sodium perchlorate (1 M) in addition to perchloric acid (0.02 N).

The concentration of hydrogen peroxide consumed by reaction with ethanol in the first experiment of Table V is 1.3×10^{-3} M, and in the last two experiments, 0.45×10^{-3} M. It is seen that the concentrations of acetaldehyde found correspond to the concentrations of hydrogen peroxide consumed by the induced reaction. Thus the induced reaction is, at least principally, induced oxidation of ethanol to acetaldehyde.

Acknowledgment.—The authors wish to acknowledge the advice and interest of Professor R. S. Livingston of this University.

Summary

An apparatus and procedure are described with which the reaction between ferrous iron and hydrogen peroxide has been investigated, with rapid mixing, in the absence of oxygen. Ethanol, in concentrations of 10^{-4} to 10^{-1} M, has been added to reaction mixtures in acid solution, with concentrations of the primary reactants generally of the order of 10^{-3} M; in these mixtures, the primary reaction between ferrous iron and hydrogen peroxide induces the reaction between hydrogen peroxide and ethanol, with the formation of acetaldehyde; this is known as a Fenton reaction. Mechanisms for this reaction are presented. No induced reaction is found between hydrogen peroxide and acetic acid; but when acetic acid is added to a mixture containing ethanol, the extent of the induced reduction of hydrogen peroxide by the latter is decreased. Apparently there is competition between acetic acid and ethanol for reaction with the active intermediates formed in the primary reaction; the radicals formed from the two organic compounds differ in their subsequent reactions. Ethanol is termed a promoter, and acetic acid a suppressor.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Reaction between Ferrous Iron and Peroxides. II. Reaction with Hydrogen Peroxide, in the Presence of Oxygen[1]

BY I. M. KOLTHOFF AND A. I. MEDALIA

In the preceding paper of this series,[2] the course of the reaction between ferrous iron and hydrogen peroxide, in the absence of oxygen, but in the presence of various other compounds, was described. Evidence was given that several compounds react with active intermediates formed in the course of this reaction; thus, ethanol is believed to form the hydroxyethyl radical, and acetic acid, the acetate radical. It is known[3,4] that organic radicals are extremely reactive toward oxygen. It is shown in the present paper that not only quantitatively, but also qualitatively, quite different results are obtained in the presence of oxygen than in its absence.

Experimental

Many of the experiments described in this paper were carried out with the reaction vessel and technique described in the preceding paper,[2] but flushing the vessel with oxygen or air, in place of nitrogen, for at least ten minutes before mixing, as well as between mixing and titration. This technique will be referred to as the "shaking" procedure. Other experiments were carried out by a "stirring" procedure, described below.

"Stirring" Procedure.—The ferrous sulfate solution was added from a 10-ml. "Exax" pipet to 45 ml. of hydrogen peroxide solution in a 125-ml. erlenmeyer flask. The contents of the flask was stirred vigorously during addition of the ferrous solution by means of a flattened twisted stirring rod rotating at 1800 r. p. m. In many experiments the reverse order of mixing was used. With either order of mixing, the solution originally in the flask contained acid as well as any added substances other than the primary reactants; the ferrous sulfate solution was always acid. After standing for a short time, the entire content of the flask was titrated with ceric sulfate solution. The reaction mixtures of duplicate experiments were allowed to stand for different lengths of time (generally ten and twenty minutes) before titrating.

Reagents.—The following reagents were used in the experiments described in this paper in addition to those described in the preceding one.

t-Butyl alcohol	Laboratory supply, distilled through a fractionating column with a reflux ratio of 2:1, in all-glass apparatus
Perchloric acid	J. T. Baker C. P. (20%)
Ferrous perchlorate	Prepared by solution of pure iron wire (B and A reagent) in perchloric acid
Oxygen	Air Reduction Co. (99.5%), filtered through glass wool

Results and Discussion

Reaction in the Presence of Sulfuric Acid and Ethanol.—Results of experiments carried out by the "shaking" procedure are given in Table I. If desirable, before titration with ceric sulfate, small portions of the reaction mixtures were tested for hydrogen peroxide by addition of titanic sulfate solution. The column headed "gas" indicates the gas with which the solutions and gas space were flushed before and after mixing.

TABLE I

EXPERIMENTS IN 1.5 *N* SULFURIC ACID, WITH VARIOUS CONCENTRATIONS OF ETHANOL

Each figure is an average obtained with aliquots from a single reaction mixture after 15 and 30 minutes reaction time. Experiments carried out by "shaking" technique.

Initial concentrations Ethanol, *M*	Fe^{++} (*M* × 10^3)	Molar ratio, initial $\frac{(Fe^{++})}{(H_2O_2)}$ taken	Gas	Molar ratio, $\frac{(Fe^{++})}{(H_2O_2)}$ reacted / taken	Titanium sulfate test	Induction factor
..	0.51	3.92	Oxygen	2.06	.....	0.03
10^{-4}	.51	3.92	Oxygen	2.74	Negative	0.37
10^{-2}	.51	3.92	Oxygen	2.69[a],10.4[b]	Positive	4.2[b]
10^{-2}	.51	7.84	Oxygen	7.46	Negative	2.73
10^{-4}	1.0	3.60	Air	2.42,2.44	.....	0.21
10^{-2}	1.0	15.7	Oxygen	6.71	Negative	2.35
..	2.2	4.38	Oxygen	2.04	.....	0.02
10^{-4}	2.0	3.64	Air	2.20	.....	0.10
10^{-4}	2.0	3.64	Oxygen	2.34	.....	0.17
10^{-2}	2.2	4.38	Oxygen	4.16[a],4.89[b]	Positive	1.45[b]
10^{-2}	2.2	7.30	Oxygen	5.15	Negative	1.57
10^{-2}	2.2	10.95	Oxygen	5.46	Negative	1.73
10^{-1}	2.2	10.95	Oxygen	5.51	Negative	1.75
10^{-2}	2.2	4.38	Air	2.92	Negative	0.46
10^{-2}	2.2	7.30	Air	3.39	Negative	0.70
..	13.1	4.38	Oxygen	2.00	Negative	0.00
10^{-4}	13.1	4.38	Oxygen	2.06	Negative	0.03
10^{-2}	13.1	4.38	Oxygen	2.08	Negative	0.04
10^{-2}	9.5	3.76	Air	0.79	Negative	..

[a] These values are calculated on the incorrect assumption that all the hydrogen peroxide has been consumed by reaction with ferrous iron. [b] Calculated on the assumption that all the ferrous iron has been consumed by reaction with hydrogen peroxide.

The results given in Table I show that considerable induced oxygen oxidation of the ferrous iron can take place during the reaction between hydrogen peroxide and ferrous iron in the presence of ethanol and oxygen. The induction factor for this reaction is $(R - 2)/2$, where R is the reaction ratio

(1) This work was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Synthetic Rubber Program of the United States Government. From a thesis submitted by A. I. Medalia to the Graduate School of the University of Minnesota in partial fulfillment of the requirements of the degree of Doctor of Philosophy (1948).

(2) I. M. Kolthoff and A. I. Medalia, THIS JOURNAL, **71**, 3777 (1949).

(3) F. A. Bovey and I. M. Kolthoff, *Chem. Rev.*, **42**, 491 (1948).

(4) W. A. Waters, "The Chemistry of Free Radicals," Clarendon Press, Oxford, England, 1946.

given in the fifth column of the table. In dilute solutions (0.001 M) saturated with oxygen, induction factors greater than 2 may be found. Even when the concentration of ethanol is only one-twentieth as great as that of the ferrous iron, an appreciable induced reaction is found. The mechanism of the induced oxidation of ferrous iron is discussed in the following section.

Under certain circumstances the extent of induced air oxidation of ferrous iron may be so great that hydrogen peroxide rather than ferrous iron is left after completion of the reaction. This was found to be the case in the experiments reported in the third and seventh lines of Table I. Since hydrogen peroxide can be titrated with ceric sulfate in the same manner as ferrous iron, titration values are obtained which might be mistaken as corresponding to the amount of iron present, if no test is made for hydrogen peroxide.

With higher concentrations of ferrous iron and hydrogen peroxide, lower induction factors or reaction ratios are found at the same ethanol concentrations. Comparison of the results obtained in oxygen and in air suggests that the magnitude of the reaction ratio is limited by the amount of oxygen available to the system, with initial concentrations of ferrous iron of 2×10^{-3} M or greater. The ratio of the amount of dissolved oxygen to the amount of ferrous iron becomes smaller, of course, as the concentration of ferrous iron is increased. The concentration of oxygen in a solution of 1.5 N sulfuric acid, saturated with oxygen at 25° at atmospheric pressure, is 1.07×10^{-3} M.[5] Also as the concentrations of ferrous iron and of hydrogen peroxide are increased, the ferrous iron–hydrogen peroxide reaction goes to completion more rapidly, so that less oxygen can enter the solution from the gas phase during the course of the reaction. For both reasons it is not surprising that a very low induction factor is found with 0.013 M ferrous iron and 0.0029 M peroxide in the presence of oxygen, while in the presence of air, the reaction ratio is actually lower than the stoichiometric value, with 0.0095 M ferrous iron and 0.0025 M peroxide. Apparently both induced reduction of the peroxide (*cf.* preceding paper[2]) and induced air oxidation of the ferrous iron can take place in the course of a given experiment; if relatively little oxygen is present, the reduction may predominate over the oxidation.

In Table II are given data obtained by the "stirring" technique. Hydrogen peroxide was added to ferrous iron ("reverse" addition), to prevent the error which would result, even in the absence of ethanol, from induced decomposition of hydrogen peroxide in solutions containing a large excess of hydrogen peroxide over ferrous iron.[6] All results are averages of duplicate experiments, titrated after different times, which checked closely. When more than one result is given for a given experiment each figure is the result of a single determination. In all the experiments reported, ferrous iron was in excess to hydrogen peroxide at the time of titration with ceric sulfate.

TABLE II

EXPERIMENTS IN 1.5 N SULFURIC ACID WITH VARIOUS CONCENTRATIONS OF ETHANOL IN THE PRESENCE OF AIR, USING THE "STIRRING" TECHNIQUE

Concentration of ethanol, M	Initial concentration of Fe^{++} ($M \times 10^3$)	Molar ratio Initial (Fe^{++}) / (H_2O_2) taken	Molar ratio (Fe^{++}) reacted / (H_2O_2) taken
.....	1.0	4.16	2.04
3×10^{-6}	1.0	3.38	2.07
10^{-5}	1.0	3.38	2.12
3×10^{-5}	1.0	3.38	2.20
10^{-4}	1.0	4.16	2.19
10^{-3}	1.0	4.16	2.77, 2.94
.....	2.0	4.24	2.04
10^{-4}	2.0	4.24	2.22
10^{-3}	2.0	4.24	2.32
10^{-2}	2.0	4.24	2.06, 2.11, 1.95
10^{-1}	2.0	4.24	2.05 (single expt.)
1	2.0	4.24	2.07, 2.18
10	2.0	4.24	3.10
.....	10.5	4.38	1.99
2×10^{-4}	10.5	4.38	1.98
2×10^{-3}	10.5	4.38	1.44 ..
2×10^{-2}	10.5	4.38	0.91, 0.95
.....	17	3.74	2.00[a]
10^{-2}	17	3.74	0.66[a]
.....	172	3.70	2.00
10^{-2}	172	3.70	1.45

[a] In 0.046 N sulfuric acid.

Qualitatively, the deviations from the stoichiometric reaction ratio correspond to those given in Table I. With low concentrations of ethanol, ferrous iron, and hydrogen peroxide, the error is due mainly to induced air oxidation of the ferrous iron. When the concentrations of ferrous iron and peroxide are high relative to the concentration of oxygen in the solution, the induced reduction of hydrogen peroxide becomes of greater importance, leading to values of R less than the stoichiometric value of 2. Thus under typical analytical conditions, in the presence of air and ethanol, peroxide values may be found which are low, high, or by chance approximately correct, depending on the concentrations of peroxide and ferrous iron.

With an initial concentration of ferrous iron of 2×10^{-3} M, results within 5% of the stoichiometric are found over a wide range of concentrations of ethanol, due to compensation of the induced oxygen oxidation of ferrous iron and the induced reduction of the peroxide. The high values of R found with 10 M (46% by weight) ethanol may be partly due to the increased solubility of oxygen in this solvent as compared to dilute aqueous solutions.

Reaction in the Presence of Sulfuric Acid and Organic Compounds Other than Ethanol.—In

(5) G. Geffcken, *Z. phys. Chem.*, **49**, 257 (1904).

(6) F. Haber and J. Weiss, *Proc. Roy. Soc.* (*London*), **A147**, 332 (1934).

the preceding paper[2] it was shown that acetic acid suppresses the induced reaction between hydrogen peroxide and ethanol in the absence of oxygen. It seemed of interest to investigate the behavior of acetic acid in the presence of oxygen. Results of experiments carried out by the "shaking" procedure are given in Table III.

TABLE III

EXPERIMENTS IN 1.5 *N* SULFURIC ACID, USING THE "SHAKING" TECHNIQUE, WITH OXYGEN-SATURATED SOLUTIONS

Initial concentrations			Molar ratios	
Acetic acid, *M*	Ethanol, *M*	Fe^{++} ($M \times 10^3$)	Initial $(Fe^{++})/(H_2O_2)$ taken	(Fe^{++}) reacted $/(H_2O_2)$ taken
..	..	0.51	3.92	2.02
10^{-2}	..	0.51	3.92	2.60
10^{-2}	..	0.51	7.84	2.47
..	..	2.0	3.76	2.04
1	10^{-3}	2.0	3.76	3.44

The data of Table III show that, like ethanol, acetic acid also gives rise to induced oxygen oxidation of ferrous iron in the peroxide–iron reaction. This confirms the hypothesis that acetic acid reacts with the active intermediates which are formed in the ferrous iron–hydrogen peroxide reaction. Since acetic acid itself can give rise to induced oxygen oxidation of ferrous iron, acetic acid would not be expected to suppress the induced oxygen oxidation caused by ethanol; this is brought out by comparison of the data of Tables I and III.

TABLE IV

EXPERIMENTS IN 1.5 *N* SULFURIC ACID, IN THE PRESENCE OF AIR AND VARIOUS ORGANIC SUBSTANCES, USING THE "STIRRING" TECHNIQUE

Substance added	Concentration, moles/liter	Initial concn. Fe^{++} $M \times 10^3$	Molar ratio Initial $(Fe^{++})/(H_2O_2)$ taken	Molar ratio (Fe^{++}) reacted $/(H_2O_2)$ taken
Nothing	..	1.0	3.75	2.04
Methanol	10^{-5}	1.0	3.75	2.06
Methanol	10^{-4}	1.0	3.75	2.22
Methanol	10^{-3}	1.0	3.75	2.46
Methanol	10^{-2}	1.0	3.75	2.10
Methanol	10^{-1}	1.0	3.75	2.16[a], 2.51[a]
Nothing	..	1.3	4.64	2.02
Methanol	10^{-3}	1.3	4.64	2.49
Methanol	10^{-2}	1.3	4.64	2.37
Methanol	10^{-2}	1.3	9.28	3.21
Methanol	10^{-1}	1.3	4.64	2.31
Acetic acid	10^{-4}	1.0	3.75	2.07
Acetic acid	10^{-3}	1.0	3.75	2.11
Acetic acid	10^{-2}	1.0	3.75	2.41
Acetic acid	1	1.3	4.64	3.00
Acetone	10^{-4}	1.0	3.75	2.09
Acetone	10^{-3}	1.0	3.75	2.38
Acetone	2×10^{-3}	1.0	3.75	2.59
Acetone	10^{-2}	1.0	3.75	3.04
t-Butyl alcohol	10^{-4}	1.0	3.66	2.11
t-Butyl alcohol	10^{-3}	1.0	3.66	2.46
t-Butyl alcohol	10^{-2}	1.0	3.66	2.45

[a] Single experiments.

Results obtained by the "stirring" technique, in air-saturated solutions, in the presence of various organic susbstances, are given in Table IV. The "reverse" mode of addition was used throughout. All results (except as noted) are averages of duplicate experiments titrated after different times, which checked closely.

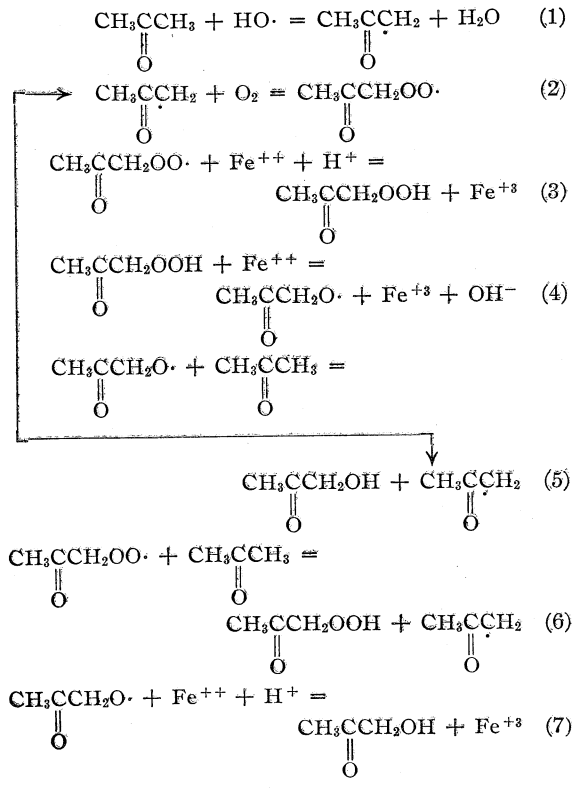
The reaction between ferrous iron and hydrogen peroxide leads to induced oxygen oxidation of ferrous iron when carried out in the presence of dissolved oxygen and any of the five organic compounds tested, as shown in the preceding tables: namely, ethanol, methanol, acetic acid, acetone and *t*-butyl alcohol. It is of particular interest that even relatively stable substances such as acetic acid and *t*-butyl alcohol can bring about considerable induced reaction. As was observed with ethanol (Table II), the extent of the induced oxidation found with a given initial concentration of ferrous iron and peroxide may vary irregularly with increasing concentrations of the added organic compound. In many of the present experiments in Table IV the extent of the induced air oxidation is limited by the amount of oxygen present, while the extent of induced decomposition of the peroxide increases with increasing concentrations of the organic compound. Thus it is seen qualitatively that the net extent of induced oxidation may be expected to pass through a maximum with increasing concentrations of the organic compound. A more exact treatment of the complex reactions involved cannot be given (*v. i.*).

Mechanism of the Induced Oxygen Oxidation of Ferrous Iron.—When the reaction between ferrous iron and hydrogen peroxide is carried out in the presence of various organic compounds, organic radicals apparently are formed, which can react with oxygen (if present in the system), forming peroxide radicals. These can in turn react with molecules of the organic compound present, leading to a chain autoxidation of this compound, with the formation of considerable quantities of peroxides[7,8]; or the peroxide radicals may react with ferrous iron or with hydrogen peroxide; or they may decompose spontaneously. The steps which are possible in the presence of oxygen are much more numerous than in the absence of oxygen, and a detailed analysis of the results does not seem possible. As an illustration, some of the reactions which may take place are given below. For simplicity, the formation of hydroxyl radical in the primary step of the peroxide–iron reaction will be assumed.[2]

In the case of acetone, the hydrogen atoms are labilized by the keto group, so that autoxidation is facilitated. We would expect the following reactions to be possible.

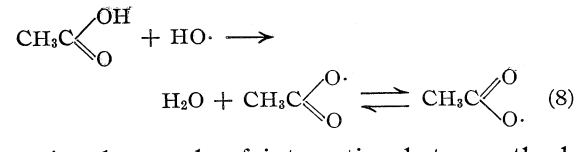
Steps (3), (4) and (7) predict the oxidation of three ferrous ions by each peroxide radical formed

(7) J. L. Bolland, *Proc. Roy. Soc.* (*London*), **A186**, 218 (1946).
(8) E. H. Farmer and D. A. Sutton, *J. Chem. Soc.*, 119 (1943).



in step (1); however, since the initial formation of the peroxide radical (step (1)) consumes a hydroxyl radical which would otherwise oxidize a ferrous ion, only two *additional* ferrous ions are oxidized by the peroxide radical formed in this manner; so that, barring autoxidation (steps (5) and (2), or (6) and (2)), the highest possible induction factor should be unity. Induction factors greater than unity are accounted for by the chain autoxidation reactions, in which a very large number of peroxide radicals can be formed, each of which oxidizes two additional ferrous ions.

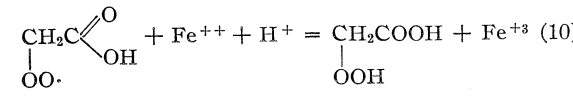
With acetic acid, removal of a hydrogen atom from the hydroxyl group leads to formation of a radical (acetate radical) which is stabilized by resonance.



Another mode of interaction between the hydroxyl radical and acetic acid would be

$$CH_3COOH + HO\cdot \longrightarrow H_2O + \cdot CH_2COOH \quad (9)$$

this radical could add molecular oxygen to form a peroxide radical, which would oxidize ferrous iron as shown in step (10). Formation of the radical, $\cdot CH_2COOH$, by intramolecular rearrangement of



the acetate radical, or by reaction of the acetate radical with acetic acid, also appears possible.

The hydroperoxide formed in step (10) could react further, in a manner similar to steps (4)–(7).

Reaction in the Presence of Various Inorganic Compounds, in the Presence and Absence of Ethanol.—Experiments have been carried out by the "stirring" technique in 1.5 *N* sulfuric acid solutions in the presence of air, with various inorganic compounds present in low concentrations, but in the absence of organic compounds. None of the inorganic compounds investigated gave rise to induced oxygen oxidation of ferrous iron in the reaction between the latter (10^{-3} *M*) and hydrogen peroxide (3×10^{-4} *M*); these compounds include $NaHCO_3$ (1.5×10^{-4} *M*), $CuSO_4$ (5×10^{-5} *M*), $(NH_4)_2SO_4$ (up to 10^{-3} *M*), KCl (10^{-4} *M*), $MnSO_4$ (5×10^{-5} *M*), and $SnCl_4$ (up to 10^{-4} *M*); C.P. or reagent grade salts were used.

A study of the effects of various common inorganic acids or salts upon the reaction in question, in the presence and absence of ethanol, has been carried out, using the "shaking" technique, with oxygen-saturated solutions. The data, given in Table V, show that with the exception of phosphoric acid, none of the compounds studied leads to any significant induced reaction, in the absence of organic compounds. The small effect found with phosphoric acid may be due to traces of impurities in the sample used, as indicated from the data obtained in the absence of oxygen,[2] or to direct reaction between oxygen and ferrous iron.

TABLE V

EFFECT OF SOME INORGANIC COMPOUNDS ON THE INDUCED OXYGEN OXIDATION. EXPERIMENTS IN OXYGEN-SATURATED SOLUTIONS, BY THE "SHAKING" TECHNIQUE

Initial concentrations				Molar ratios	
$HClO_4$, *M*	Ethanol, *M*	Fe^{++} (*M* × 10^3)	Other compound	Initial $(Fe^{++})/(H_2O_2)$ taken	(Fe^{++}) reacted $/(H_2O_2)$ taken
1.0	..	1.5	.....	6.5	2.05
1.0	10^{-2}	1.5	.....	6.5	7.19
..	..	1.5	H_2SO_4 (1.5 *N*)	6.7	2.04
..	10^{-2}	1.5	H_2SO_4 (1.5 *N*)	6.7	6.08
..	..	1.5	HCl (1 *N*)	6.7	1.95
..	10^{-3}	1.5	HCl (1 *N*)	6.7	2.12
..	10^{-2}	1.5	HCl (1 *N*)	6.7	2.18
0.14	..	1.5	KNO_3 (1 *M*)	6.5	2.02
0.14	10^{-2}	1.5	KNO_3 (1 *M*)	6.5	4.76
..	..	1.5	H_3PO_4 (1 *M*)	6.5	2.12
..	10^{-2}	1.5	H_3PO_4 (1 *M*)	6.5	11.7

In the presence of ethanol, the extent of induced oxygen oxidation of ferrous iron depends markedly upon the anion present. This behavior may be correlated with the suppressing action in nitrogen, except for phosphoric acid. The strong suppressing action of chloride ion in the presence of oxygen is particularly striking and may be of practical importance in the determination of peroxides by re-

action with ferrous iron; it is planned to investigate whether chloride ion exerts this suppressing action in the presence of oxygen in the reaction between ferrous iron and organic hydroperoxides. Evidently atomic chlorine, formed from the chloride ion during the course of the peroxide–iron reaction, does not react with oxygen to form reactive peroxides under the experimental conditions used. Neither do the chlorine free radicals formed activate the organic compounds present in the reaction mixture. The above reactions may be possible, but under our experimental conditions the chlorine free radicals apparently react faster with ferrous iron than with other constituents of the reaction mixture.

It is evident that traces of organic impurities in the reagents used may give rise to considerable induced reactions, especially when the concentration of the primary reactants is small (of the order of 10–3 M). In a previous paper[2] it has been shown that various samples of reagent grade perchloric acid from different sources contained impurities which caused considerable induced reduction of hydrogen peroxide. Even traces of organic impurities in the water used may exert a considerable effect on the ferrous iron–hydrogen peroxide reaction. When the present work was started we used twice-distilled water; however, no permanganate was present in the still. When this water was used reaction ratios greatly deviating from 2 were found, as shown in Table VI.

TABLE VI

EXPERIMENTS WITH IMPURE WATER IN THE PRESENCE OF AIR (EXCEPT AS NOTED). "STIRRING" TECHNIQUE

Acid and concentration, N	Initial concentration of Fe^{++} ($M \times 10^3$)	Molar ratios: Initial $\frac{(Fe^{++})}{(H_2O_2)}$ taken	Molar ratios: $\frac{(Fe^{++})\ reacted}{(H_2O_2)\ taken}$
1.5 N H_2SO_4	0.42	4.0	2.64
0.15 N H_2SO_4	.42	4.0	2.26
1 N $HClO_4$	.46	4.5	2.72
0.1 N $HClO_4$	.46	4.5	2.28
0.005 N $HClO_4$	.46	4.5	2.12
1 N $HClO_4$	.46	4.5	1.54[a]
0.005 N $HClO_4$	.46	4.5	1.72[a]

[a] Nitrogen was passed through the solutions before mixing; however, oxygen was only partially removed by the technique employed.

The impure water gave results similar to those found with pure water in the presence of small amounts of various organic compounds. Systematic investigation showed that the induced reaction could be almost completely eliminated by distillation of the water from alkaline permanganate, whereas no significant change in the extent of the induced reaction was found upon changing any of the other ingredients. Thus, similar results were found in impure water with ferrous solutions from two different sources (reagent grade $FeSO_4 \cdot 7H_2O$ and pure iron wire dissolved in perchloric acid); with three different brands of hydrogen peroxide (Merck, Baker, and Buffalo Electrochemical Co.); and with perchloric or sulfuric acid. While in the experiments of Table VI, increasing concentrations of acid led to increasing induced reaction, this effect cannot be due to impurities in the acids used, since no induced reaction was found when these same acids were used in purified water. The deviations from stoichiometric results found with the impure water must be attributed to the presence of traces of organic impurities in the water.

Summary

The reaction between hydrogen peroxide and ferrous iron in dilute solutions in the presence of oxygen and organic compounds leads to induced oxygen oxidation of ferrous iron. The extent of the induced oxidation may be quite large, particularly in oxygen-saturated solutions of the order of 10^{-3} M in peroxide and iron, in which the concentration of oxygen is relatively high. The amount of ferrous iron oxidized by the induced reaction may be two to three times as great as the amount oxidized by the stoichiometric reaction, under certain circumstances. It appears that the organic radical formed can add molecular oxygen, forming a peroxide radical, which can react with three ferrous ions, or can lead to autoxidation of the organic compound by a chain reaction. In the presence of oxygen, all the organic compounds tested show qualitatively similar behavior, without distinction between "promoting" and "suppressing" compounds. On the other hand, chloride ion is a suppressor in the presence as well as the absence of oxygen.

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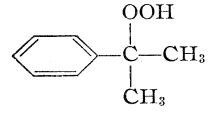
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Reaction between Ferrous Iron and Peroxides. III. Reaction with Cumene Hydroperoxide, in Aqueous Solution[1]

BY I. M. KOLTHOFF AND A. I. MEDALIA[1]

In previous publications[2,3] the authors have presented the results of an experimental study of the reaction between hydrogen peroxide and ferrous iron, in very dilute aqueous solution, in the presence of various compounds. In the absence of oxygen, it has been shown[2] that the peroxide–iron reaction induces the oxidation of certain organic compounds (termed "promoters") by hydrogen peroxide; several compounds (termed "suppressors") suppress this induced reaction. In the presence of oxygen,[3] induced oxygen oxidation of ferrous iron occurs in the presence of various organic compounds, apparently through the intermediate formation of organic peroxides; this induced oxygen oxidation is suppressed by chloride ion, but not by any of the organic compounds studied. Mechanisms for these reactions were presented in these papers, and in a review paper[4] on the reaction between ferrous iron and peroxides. It is likely that in the reaction between ferrous iron and organic peroxides, particularly hydroperoxides, active intermediates are formed, through mechanisms similar to that of the ferrous iron–hydrogen peroxide reaction. The present paper deals with a study of the reaction between ferrous iron and a hydroperoxide, under conditions similar to those used with hydrogen peroxide.[2,3] The results obtained are of particular importance in view of the wide use of the reaction between ferrous iron and organic hydroperoxides in the determination of these hydroperoxides, and in the initiation of the polymerization of vinyl monomers.

The hydroperoxide chosen for the present study is cumene hydroperoxide (phenyldimethyl methyl hydroperoxide), designated below as CHP. This compound is a typical organic hydroperoxide, of structure



The preparation of this compound from cumene (isopropylbenzene) by photochemical autoxidation at 60–70° has been described by Hock and Lang.[5] Cumene hydroperoxide is an oily liquid which is quite stable at room temperature. As shown below, its solubility in water is sufficient (0.09 *M*) to permit study of its reactions in dilute aqueous solutions. CHP is used in oxidation–reduction polymerization recipes which have proved to be of considerable practical importance.[6,7] Determination of CHP by both ferrous and iodometric methods has been studied recently.[8]

Experimental

Reagents.—The reagents used were as described previously.[2,3] The water used in all experiments was purified by distillation from alkaline permanganate. Benzene (Mallinckrodt reagent grade) and CHP (purified as below) were also used.

Purification of CHP.—A sample of CHP (Sample No. X5557–47) prepared from cumene was kindly furnished by the Hercules Powder Co. Iodometric analysis of this sample by a macro procedure (*v. i.*) corresponded to 71.4% pure CHP. It has been pointed out by Hock and Lang[5] that the impurities in a sample of cumene hydroperoxide prepared by autoxidation of cumene may consist largely of the decomposition products of cumene hydroperoxide, namely, dimethylphenylcarbinol, phenol, and acetone, in addition to the unchanged cumene.

Purification of the Hercules sample of cumene hydroperoxide was carried out by the alkali extraction procedure of Hock and Lang,[5] with the omission of the final vacuum distillation used by these authors. Iodometric analysis by the above procedure corresponded to 94.2% pure CHP. It should be pointed out that both Hock and Lang[5] and Wagner, *et al.*,[8] obtained samples of 95% purity. Further purification does not seem feasible by this method.

Iodometric Analysis of CHP.—Two methods of iodometric analysis have been investigated for use with CHP. The first of these is a macro method, developed in this Laboratory[9] for determination of *t*-butyl hydroperoxide.

Procedure.—Accurately weigh a 1.2 to 1.6 g. sample into a weighing bottle, transfer the sample to a 100-ml. volumetric flask and dilute to the mark with glacial acetic acid. Pipet a 25-ml. aliquot into a 125-ml. iodine flask, and then bubble nitrogen through the solution for five minutes. Add 2 g. of finely divided sodium iodide, flush the air space above the solution with nitrogen, and stopper the flask. Allow the solution to stand in the dark at room temperature for twenty minutes. Add 50 ml. of water, and titrate with 0.1 *N* thiosulfate solution, using starch indicator near the end-point. A blank solution should require less than about 0.02 ml. of thiosulfate solution. The reaction time of twenty minutes was found to be sufficient, by comparison with determinations carried out in sealed flasks at 100°.

The method of Kokatnur and Jelling[10] was used for the

(1) This investigation was started under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Synthetic Rubber Program of the United States Government. From a thesis submitted by A. I. Medalia to the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the doctor's degree, 1948.

(2) I. M. Kolthoff and A. I. Medalia, THIS JOURNAL, **71**, 3777, (1949).

(3) I. M. Kolthoff and A. I. Medalia, *ibid.*, **71**, 3784 (1949).

(4) A. I. Medalia and I. M. Kolthoff, *J. Polymer Sci.*, **4**, 377 (1949).

(5) H. Hock and S. Lang, *Ber.*, **77B**, 257 (1944).

(6) E. J. Vandenberg and G. E. Hulse, *Ind. Eng. Chem.*, **40**, 932 (1948).

(7) W. A. Schulze, W. B. Reynolds, C. F. Fryling, L. R. Sperberg and J. E. Troyan, *India Rubber World*, **117**, 739 (1948).

(8) C. D. Wagner, R. H. Smith and E. D. Peters, *Ind. Eng. Chem., Anal. Ed.*, **19**, 976, 982 (1947); C. D. Wagner, H. L. Clever and E. D. Peters, *ibid.*, **19**, 980 (1947).

(9) I. M. Kolthoff and T. S. Lee, private communication.

(10) V. R. Kokatnur and M. Jelling, THIS JOURNAL, **63**, 1432 (1941).

determination of small amounts of cumene hydroperoxide. In this method the peroxide is dissolved in about 75 ml. of boiling absolute ethanol in a 150-ml. beaker; after addition of 1 ml. each of glacial acetic acid and saturated aqueous potassium iodide, boiling is continued for five minutes, and then the iodine formed is titrated immediately with 0.005 *N* thiosulfate. The accuracy of the method was improved by amperometric determination of the end-point, using the procedure developed by the late Dr. L. S. Guss of this laboratory. In this procedure a rotating platinum microelectrode at the potential of a saturated calomel electrode serves as an indicator of the iodine concentration; titration is continued until the current, which is due to reduction of iodine at the microelectrode, decreases to zero. With amounts of CHP as small as 5 mg. (0.03 millimole) in 75 ml., the accuracy and precision were found to be of the order of 2%.

Results and Discussion

Solubility of Purified Cumene Hydroxide in Water.—The solubility in water of the purified sample of cumene hydroperoxide, and its distribution between benzene and water and between benzene and aqueous alkali, have been determined. The method used was to shake various amounts of water, cumene hydroperoxide, and (in some cases) benzene for two minutes in an ungreased separatory funnel; 2-ml. portions of the filtered aqueous layer were then analyzed by the method of Kokatnur and Jelling. The results are given in Table I.

TABLE I

SOLUBILITY OF CUMENE HYDROPEROXIDE IN WATER AND AQUEOUS ALKALI AT 25°

Benzene taken,[a] ml.	Concn. of NaOH in aqueous phase initially, *N*	CHP[b] taken,[a] g.	CHP[b] diss. in 100 ml. of aqueous phase, g.	Mole % CHP in aqueous phase	Mole % CHP in organic phase[c]
..	....	2.60	1.36	0.161	(95)
..	....	13.0	1.35	.160	(95)
2.0	....	2.60	0.731	.0865	36.3
6.0	....	2.60	.441	.0522	17.6
14.0	....	1.95	.238	.0282	6.67
28.0	0.0506	3.91	.466	.0551	6.70
28.0	.253	3.91	1.11	.132	5.51

[a] Per 100 ml. of water. [b] Based on 100% purity. [c] Corrected for the solubility of benzene in water.

The solubility of the sample of purified CHP in water does not depend upon the amount of CHP taken; this is indicative of the purity of this sample. The data for the distribution of CHP between benzene and water show that the behavior does not follow the ideal distribution equation

$$(\text{Mole \% in water}) = K\,(\text{mole \% in benzene}) \quad (1)$$

Graphical extrapolation of the data to 100% purity gives for the solubility of pure CHP in water a value of 0.165 mole %, or 0.0914 molar, or 1.39 g. per 100 ml. of solution.

From the data for the distribution of CHP between benzene and aqueous alkali the ionization constant, K_a, is calculated to be 2.6×10^{-13} (0.0506 *N* alkali) and 2.4×10^{-13} (0.253 *N* alkali), respectively, at 25°. By way of comparison, the ionization constant of hydrogen peroxide is given[11] as 2.4×10^{-12} at 25°.

Approximate Determination of the Rate of Reaction between Ferrous Iron and CHP. Procedure.—Solutions of CHP and ferrous iron in 1.5 *N* sulfuric acid (total volume, 120 ml.) were mixed in the absence of air, in a reaction vessel with two compartments, described in a previous publication.[2] After the desired time of reaction 20 ml. of air-free benzene was added to the inner compartment and the mixture was shaken for ten seconds. After standing for one to two minutes to allow separation of the phases, a 15-ml. aliquot of the benzene phase was analyzed by the procedure of Kokatnur and Jelling,[9] and 50-ml. portions of the aqueous phase were titrated with ceric sulfate. The results of experiments carried out as above are given in Table II.

TABLE II

REACTION BETWEEN FERROUS IRON AND PURIFIED CHP IN 1.5 *N* H_2SO_4 AT 27°, IN THE ABSENCE OF OXYGEN. INITIAL CONCENTRATIONS: $(Fe^{++})_0 = 5.31 \times 10^{-4}$ *M*; $(CHP)_0 = 2.21 \times 10^{-4}$ *M*

Time of reaction, sec.	Concn. remaining at given time ($M \times 10^4$) Fe^{++}	CHP	Molar reaction ratio $\frac{\Delta(Fe^{++})}{\Delta(CHP)}$	Approximate rate constant, k_1 (l. mole^{-1}sec.$^{-1}$)
30	4.52	1.38	0.95	30
40	4.36	1.36	1.15	28
75	4.10	1.00	1.00	22

In Table II the reaction times given are from the instant of mixing the ferrous iron and CHP to the midpoint of the period of shaking with benzene. In calculating the rate constant, it was assumed that, as in the reaction between hydrogen peroxide and ferrous iron, the rate-determining step is first-order in both reactants. The calculation of the rate constant is complicated by the fact that the reaction between ferrous iron and CHP is not stoichiometric, as is evident from Table II; the average reaction ratio under the experimental conditions is 1.05. The calculation of the approximate rate constant has been based upon the rate of disappearance of ferrous iron only, taking an average value of the concentration of CHP. Thus if

$$-\,d(Fe^{++})/dt = k_1(Fe^{++})(CHP) \quad (2)$$

then

$$\int_0^t \frac{-d(Fe^{++})}{(Fe^{++})} = -\ln\left[\frac{(Fe^{++})}{(Fe^{++})_0}\right] = k_1 t(CHP)_{average} \quad (3)$$

The values of k_1 given in Table II were calculated on the basis of equation (3). The agreement between the values obtained is probably as good as can be expected in view of the inaccuracy of the reaction times and the large changes in the concentrations of CHP over the ranges in which average values were taken. The average value of k_1 is 27 l. mole^{-1} sec.$^{-1}$, or slightly less than half the

(11) R. A. Joyner, *Z. anorg. Chem.*, **77**, 103 (1912).

value (62) given by Baxendale, Evans and Park[12] for the corresponding rate constant in the hydrogen peroxide–ferrous iron reaction.

Reaction in the Absence of Oxygen: Determination of Over-all Reaction Ratios.—The experiments described below were carried out using the reaction vessels and technique described previously. After rapid mixing of the ingredients, the reaction was allowed to go to completion, and then aliquots were removed after twenty and forty minutes and titrated with ceric sulfate. It was not necessary to extract the reaction mixture with benzene before the titration, since the CHP was completely consumed. Purified (94%) CHP was used throughout. Results obtained in the presence and absence of various added substances are given in Table III. Reactions were carried out at room temperature.

TABLE III

REACTION BETWEEN FERROUS IRON AND PURIFIED CHP IN 1.5 N H_2SO_4, IN THE ABSENCE OF OXYGEN

Initial concentrations				Molar ratios	
Ethanol, M	Acetic acid, M	Acetone, M	Fe^{++} ($M \times 10^3$)	Initial $(Fe^{++})/(CHP)$ taken	(Fe^{++}) reacted $/(CHP)$ taken
..	..	..	0.53	2.41	1.15
..	..	..	1.9	3.28	1.12
10^{-2}	..	..	1.9	3.28	1.06
10^{-1}	..	..	1.9	3.28	0.76
..	10^{-1}	..	1.9	3.28	1.40
..	10	..	1.9	3.28	1.92
10^{-1}	10	..	1.9	3.28	1.79
..	..	10	1.9	3.28	1.93

In the absence of added substances, the molar reaction ratio is considerably less than the stoichiometric value of 2.00 (see also Table II). It is of interest that the same reaction ratio of 1:1 is found with two different initial concentrations of reactants. The results indicate that the reaction between ferrous iron and CHP induces the decomposition of CHP. In this respect the behavior is similar to that of hydrogen peroxide in its reaction with ferrous iron in the presence of an organic compound of the "promoting" type.[2]

Addition of ethanol increases the extent of the induced decomposition of CHP. The reaction ratios found with the concentrations of ethanol employed in the experiments of Table III are higher than those found in the hydrogen peroxide–ferrous iron reaction when carried out in the presence of these concentrations of ethanol, under comparable conditions.[2]

Addition of acetic acid diminishes the extent of induced decomposition of CHP, both in the presence and absence of ethanol. Qualitatively, acetic acid exerts the same "suppressing" action on the ferrous iron–CHP systems as was found in the hydrogen peroxide–ferrous iron–ethanol system.[2] With 0.1 M acetic acid, the induced decomposition of CHP is only partially suppressed, while with 10 M acetic acid (62% by weight) suppression is virtually complete, in the absence of ethanol, but only partially complete in the presence of 0.1 M ethanol. Similarly, suppression is virtually complete with 10 M acetone, in the absence of ethanol. The importance of these results from the standpoint of peroxide analysis is obvious, as will be demonstrated in a subsequent paper.

In the experiments carried out in 10 M acetic acid, it was necessary to dilute the solutions with approximately an equal volume of water before titrating, in order to obtain a sharp end-point. In the experiment with acetone, a sharp end-point was obtained by diluting the 50-ml. aliquot with 100 ml. of water before titrating. In this experiment, correction was made for loss of acetone by volatilization during the hour-long flushing with nitrogen, by weighing the vessel before and after flushing.

As has been discussed elsewhere,[4] the mechanism of the reaction between ferrous iron and hydrogen peroxide is not known with certainty, despite the extensive studies of this reaction. Much less study has been devoted to the reaction between hydroperoxides and ferrous iron, and the possible reaction steps are much more numerous. Presentation of such speculative mechanisms would be premature at this time. The course of the reaction cannot be established definitely without determination of the products. However, it is certain on the basis of the above data, together with results of reactions carried out in the presence of oxygen (*v. i.*), that in the course of the reaction between CHP and ferrous iron, some active intermediate is formed. By analogy with the mechanism of Haber and Weiss[13,14] for the reaction between hydrogen peroxide and ferrous iron, it is likely that the first step of the reaction is as shown below

$$C_6H_5C(CH_3)_2 + Fe^{++} = C_6H_5C(CH_3)_2 + Fe^{+3} + OH^- \quad (4)$$
$$\quad\quad\quad

used as in the experiments of Table III, except that the solutions were flushed with air or oxygen rather than nitrogen. In the "stirring" technique, one reactant is added by pipet to a solution of the other reagents, with vigorous stirring. In each experiment carried out by the "shaking" technique, the vessel was shaken for eighty seconds, to allow access of the solution to the oxygen of the gas phase during the greater part of the reaction. Aliquots of the reaction mixture were titrated with ceric sulfate after ten and twenty-five minutes reaction time. The titrations agreed closely, showing that under the conditions used, the CHP had been completely reduced within ten minutes. The results are given in Table IV.

TABLE IV

REACTION BETWEEN FERROUS IRON AND PURIFIED CHP, IN 1.5 N H_2SO_4, IN THE PRESENCE OF OXYGEN. EXPERIMENTS CARRIED OUT BY "SHAKING" TECHNIQUE

Initial concentrations				Molar ratios	
Ethanol, M	Acetic acid, M	Fe^{++} ($M \times 10^3$)	Gas	Initial $\frac{(Fe^{++})}{(CHP)}$ taken	$\frac{(Fe^{++})}{(CHP)}$ reacted taken
..	..	0.51	Air	3.82	3.50
..	..	.51	Air	7.64	4.64
..	..	.51	Air	12.7	4.70
..	..	.51	Oxygen	12.7	4.70
10^{-4}	..	.51	Air	12.7	4.90
10^{-3}	..	.51	Air	12.7	6.50
..	..	1.9	Oxygen	3.28	3.05
..	10	1.9	Oxygen	3.28	2.94

The results of Table IV show that considerable induced oxygen oxidation of ferrous iron takes place during the course of the reaction between ferrous iron and CHP, in the presence of oxygen. With a given initial concentration of ferrous iron, the reaction ratio is practically independent of the initial ratio of reactants, provided that ferrous iron is in sufficient excess over CHP. With 0.51×10^{-3} M ferrous iron and 0.40×10^{-4} M CHP, the same results were obtained in air as in oxygen. Addition of ethanol has a definite effect in increasing the induction factor. The addition of acetic acid (10 M) does not materially affect the extent of the reaction, in the single experiment performed. The results found for the reaction between CHP and ferrous iron in the presence of oxygen are qualitatively similar to those found for the reaction between hydrogen peroxide and ferrous iron in the presence of both oxygen and an organic compound.[3]

Results obtained by the "stirring" technique are given in Table V. The "reverse" mode of addition was used (CHP added to ferrous iron). Titrations carried out on duplicate reaction mixtures after ten and twenty minutes agreed closely; only the average values are given.

TABLE V

REACTION BETWEEN FERROUS IRON AND PURIFIED CHP, IN 1.5 N H_2SO_4. EXPERIMENTS CARRIED OUT BY "STIRRING" TECHNIQUE IN THE PRESENCE OF AIR

	Molar ratios	
Initial concn. of Fe^{++} ($M \times 10^3$)	Initial $\frac{(Fe^{++})}{(CHP)}$ taken	$\frac{(Fe^{++})}{(CHP)}$ reacted taken
1.0	2.97	2.45
2.0	2.97	1.83

With 10^{-3} M ferrous iron, induced air oxidation of ferrous iron is found, while with 2×10^{-3} M ferrous iron, induced decomposition of CHP predominates over the induced air oxidation, in the experiments of Table V. This behavior is similar to that found with hydrogen peroxide in the presence of ethanol.[3]

Summary

The solubility of cumene hydroperoxide (CHP) in water at 25° is 0.0914 M. The distribution ratio of CHP between water and benzene is a function of the concentration of CHP. The ionization constant (acid dissociation constant) of CHP is 2.5×10^{-13} at 27°. The rate constant of reaction between CHP and ferrous iron in aqueous solution (1.5 N sulfuric acid) at 27°, taken as first order in each reactant, is roughly 27 l. mole^{-1} sec.$^{-1}$.

The behavior of cumene hydroperoxide in its reaction with ferrous iron is qualitatively similar to that of a mixture of hydrogen peroxide and an organic compound such as ethanol. Thus, the reaction between cumene hydroperoxide and ferrous iron in pure aqueous solution leads to considerable induced decomposition of the peroxide, in the absence of oxygen, and to considerable induced oxidation of ferrous iron, in the presence of oxygen. Addition of ethanol to the system increases the extent of both induced reactions; while addition of acetic acid suppresses the induced decomposition of peroxide in the absence of oxygen, but does not suppress the induced oxidation in the presence of oxygen.

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[CONTRIBUTION FROM THE INSTITUTE OF POLYMER RESEARCH AT THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Intramolecular Condensations in Vinyl Copolymers[1]

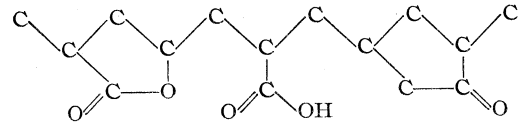
BY TURNER ALFREY, JR., CHARLES LEWIS AND BERNARD MAGEL

Intramolecular condensation reactions have been successfully employed to elucidate the structure of polymers such as polyvinyl chloride[2] polyvinyl methyl ketone[3,4,5] and polyisopropenyl methyl ketone.[6] These reactions have been subjected to statistical treatment, and the agreement between experimental results and theoretical calculations based on a 1,3-structure has established a head-to-tail addition mechanism for vinyl polymerization.

It has been suggested[7] that the copolymer of vinyl acetate and acrylic acid could be studied by hydrolyzing the acetate group and allowing the resulting hydroxyl to lactonize with the carboxyl groups present. The Flory statistical treatment[2a] is not directly applicable to such a system. It is the purpose of this paper to extend these statistics to cover the case of intramolecular condensations between unlike substituents. The example given above will be used as a model in the subsequent derivation.

We will assume a head-to-tail configuration for the copolymer, giving rise to a γ-hydroxy acid structure along the chain. We will further assume that γ-lactonization takes place to the complete exclusion of cross-linking by esterification. This is in accord with the known behavior of γ-hydroxy acids.

It is clear that lactonization cannot be quantitative since an acrylic acid segment flanked by two other acid segments is incapable of reaction. A similar situation exists for the vinyl alcohol segments. Furthermore, there exists the possibility of isolation of functions in alternating sequences. Thus we may find a carboxyl group whose neighbors are lactonized hydroxyl groups and which consequently cannot react.



In the discussion which follows we will focus our attention on the carboxyl groups, as these are the more readily determinable. We will use M_1 and M_2 to designate vinyl alcohol and acrylic acid segments, respectively. Thus an alternating sequence is of the form $M_1M_2M_1M_2M_1M_2$. Starting from a point in the chain where we find an M_1–M_2 (or an M_2–M_1) pair we advance along the chain in both directions until we reach breaks in the alternation pattern (*i. e.*, an M_1–M_1 or an M_2–M_2 pair). We next draw lines which separate the members of the like pairs thus found. By continuing this operation throughout the system, we will divide it into sequences which are either pure alternating or "straight" (*i. e.*, all M_1 or all M_2). The length of an alternating sequence is defined as the number of M_1 or M_2 groups (whichever is the smaller) that it contains.

We see that there are four possible types of alternating sequence.

I	M_1 ¦	$(M_1M_2)_nM_1$ ¦	M_1
II	M_1 ¦	$(M_1M_2)_n$ ¦	M_2
III	M_2 ¦	$(M_2M_1)_nM_2$ ¦	M_2
IV	M_2 ¦	$(M_2M_1)_n$ ¦	M_1

Let

N = total number of monomer molecules that have polymerized

m_1 = mole fraction of M_1 in copolymer

m_2 = mole fraction of M_2 in copolymer

Therefore

Nm_1 = total M_1 in copolymer

Nm_2 = total M_2 in copolymer

The total number of sequences of type I and length n is given by the product of the number of M_1 segments and the probability that an M_1 segment is followed by an alternating sequence of the desired type. Representing this quantity by A_n^{I} we have[8]

$$(1)\quad A_n^{\mathrm{I}} = Nm_1P_{11}^{2}P_{12}^{n}P_{21}^{n}$$

Similarly

$$(2)\quad A_n^{\mathrm{II}} = Nm_1P_{11}P_{22}P_{12}^{n}P_{21}^{n-1}$$

$$(3)\quad A_n^{\mathrm{III}} = Nm_2P_{22}^{2}P_{12}^{n}P_{21}^{n}$$

$$(4)\quad A_n^{\mathrm{IV}} = Nm_2P_{22}P_{11}P_{12}^{n-1}P_{21}^{n}$$

The constants P_{11}, P_{12}, etc., in the above equations are the propagation probabilities of the copolymer system. Thus P_{12} is the probability that, during the copolymerization process, a growing free radical chain of the type M^{1*} will react with a monomer molecule of type M_2.[8]

The number of alternations of type M_1M_2 must obviously be equal to the number of type M_2M_1.

(1) Presented before the High Polymer Forum at the 115th Meeting of the American Chemical Society, San Francisco, California, March–April, 1949.

(2) (a) P. Flory, THIS JOURNAL, **61**, 1518 (1939); (b) C. S. Marvel, Sample and Roy, *ibid.*, **61**, 3241 (1939).

(3) P. Flory, *ibid.*, **64**, 177 (1942).

(4) F. T. Wall, *ibid.*, **64**, 269 (1942).

(5) C. S. Marvel and C. L. Levesque, *ibid.*, **60**, 280 (1938).

(6) C. S. Marvel, Riddle and Corner, *ibid.*, **64**, 92 (1942).

(7) E. Merz, T. Alfrey and G. Goldfinger, *J. Polymer Sci.*, **1**, 75 (1946).

(8) The propagation probabilities used here refer to the system vinyl acetate–acrylic acid. P_{12} is the probability that, during the copolymerization process, a growing free radical chain of the type M_1 will react with a monomer molecule of type M_2, and similarly for the other P terms. A complete discussion of these propagation probabilities may be found in T. Alfrey, *Trans. N. Y. Acad. Sci.*, **10**, 298 (1948). An earlier paper discusses the same subject but employs a different type of symbolism, T. Alfrey and G. Goldfinger, *J. Chem. Phys.*, **12**, 205 (1944).

This is expressed mathematically by the equation

$$(5)\quad m_2P_{21} = m_1P_{12}$$

We may consequently rewrite equations (1) and (2) in the form

$$(6)\quad A_n^{\mathrm{I}} = Nm_2P_{11}^2P_{12}^{n-1}P_{21}^{n+1}$$
$$(7)\quad A_n^{\mathrm{II}} = Nm_2P_{11}P_{22}P_{12}^{n-1}P_{21}^{n}$$

It is now necessary to calculate on a statistical basis the number of carboxyl groups that will be isolated in the various alternating sequences. Flory[2a] has derived an expression for the average number of chlorine atoms remaining in a sequence of v nyl chloride segments after the random removal of chlorine from 1,3-positions (*e. g.*, by the action of metallic zinc). According to this treatment, S_n chlorine atoms will remain after exhaustive dechlorination of a sequence of n vinyl chloride groups, where

$$S_n = \sum_{i=0}^{n-1}(n-i)\frac{(-2)^i}{i!}$$

Let us consider an alternating sequence of type I and length n. The lactonization of such a sequence is statistically identical with the removal of chlorine from a sequence of $2n + 1$ vinyl chloride groups. Thus S_{2n+1} gives the total number of uncombined alcohol and acid groups. Since the number of alcohol groups is greater by one than the number of acid groups both before and after lactonization, we may write for the number of remaining acid groups

$$(9)\quad S_n^{\mathrm{I}} = (S_{2n+1} - 1)/2$$

A similar treatment for the other types of alternating sequences gives

$$(10)\quad S_n^{\mathrm{II}} = S_{2n}/2$$
$$(11)\quad S_n^{\mathrm{III}} = (S_{2n+1} + 1)/2$$
$$(12)\quad S_n^{\mathrm{IV}} = S_{2n}/2$$

We may now write an expression for the total number of carboxyl groups that may be expected to be isolated in alternating sequences of all types, *viz.*

$$(13)\quad \sum_{n=1}^{\infty}(S_n^{\mathrm{I}}A_n^{\mathrm{I}} + S_n^{\mathrm{II}}A_n^{\mathrm{II}} + S_n^{\mathrm{III}}A_n^{\mathrm{III}} + S_n^{\mathrm{IV}}A_n^{\mathrm{IV}})$$

It remains to find the number of carboxyl groups that remain unlactonized because they are adjacent to other carboxyl groups. Consider such a sequence $M_1M_2M_2M_2\cdots M_2M_2M_1$. The first and last M_2 groups have already been counted in the alternating sequences flanking the sequence of M_2 groups. The remainder constitute the unlactonizable acid groups and the amount of such material is given by

$$\sum_{n=3}^{\infty}(n-2) \times [\text{total number of } M_2 \text{ sequences of length } n]$$

In view of what has been said above, the bracketed quantity may be shown to be equal to

$$Nm_1P_{12}P_{21}P_{22}^{n-1} = Nm_2P_{21}^2P_{22}^{n-1}$$

so that the total number of unlactonizable acid groups of this type is given by

$$\sum_{n=3}^{\infty}(n-2) \times Nm_2P_2^2P_{22}^{n-1}$$

Making use of the relationship $1 - P_{22} = P_{21}$, this reduces to

$$(14)\quad Nm_2P_{22}^2$$

Combining (13) and (14) we have the total number of unlactonized acid groups. Dividing by Nm_2, the total acid present initially, we have the desired quantity f, the *fraction* of the total acid that remains unlactonized.

$$(15)\quad f = \frac{1}{Nm_2}\sum_{n=1}^{\infty}(S_n^{\mathrm{I}}A_n^{\mathrm{I}} + S_n^{\mathrm{II}}A_n^{\mathrm{II}} + S_n^{\mathrm{IV}}A_n^{\mathrm{III}} + S_n^{\mathrm{IV}}A_n^{\mathrm{IV}}) + P_{22}^2$$

Substituting from equations (3), (4), (6), (7), (9), (10), (11) and (12)

$$f = \frac{1}{2}(P_{11}^2P_{21}^2 + P_{22}^2P_{12}P_{21})\sum_{n=1}^{\infty}(P_{12}P_{21})^{n-1}S_{2n+1} - \frac{1}{2}(P_{11}^2P_{21}^2 - P_{22}^2P_{12}P_{21})\sum_{n=1}^{\infty}(P_{12}P_{21})^{n-1} + (P_{11}P_{22}P_{21})\sum_{n=1}^{\infty}(P_{12}P_{21})^{n-1}S_{2n} + P_{22}^2$$

$$(16)\quad f = P_{22}^2 - \frac{P_{11}^2P_{21}^2}{2(1-P_{12}P_{21})} + \frac{P_{22}^2P_{12}P_{21}}{2(1-P_{12}P_{21})} + \frac{1}{2}(P_{11}^2P_{21}^2 + P_{22}^2P_{12}P_{21})\sum_{n=1}^{\infty}P^{n-1}S_{2n+1} + P_{11}P_{22}P_{21}\sum_{n=1}^{\infty}P^{n-1}S_{2n}$$

where we have written P for $(P_{12}P_{21})$ for simplicity in the treatment to follow.

We now have to evaluate the two summations and simplify the result. The individual constituents of the summation $\sum_{n=1}^{\infty}P^{n-1}S_{2n}$ may be expanded in a two-dimensional array

$$\left[2 + \frac{(-2)}{1!}\right]$$
$$+ P[4 + 3(-2)/1! + 2(-2)^2/2! + (-2)^3/3!]$$
$$+ P^2[6 + 5(-2)/1! + 4(-2)^2/2! + 3(-2)^3/3! + 2(-2)^4/4! + 5(-2)^5/5!]$$
$$+ P^3[8 + 7(-2)/1! + 6(-2)^2/2! + 5(-2)^3/3!\cdots\cdots]$$
$$\vdots$$

Adding the columns, we have

$$\sum_{n=1}^{\infty}P^{n-1}S_{2n} = \frac{2}{(1-P)^2} + \frac{(-2)(1+P)}{1!\,(1-P)^2} + \frac{(-2)^2 2P}{2!\,(1-P)^2} + \frac{(-2)^3P(1+P)}{3!\,(1-P)^2} + \frac{(-2)^4 2P^2}{4!\,(1-P^2)} + \cdots$$
$$= \frac{2}{(1-P)^2}\left[1 + \frac{(-2\sqrt{P})^2}{2!} + \frac{(-2\sqrt{P})^4}{4!}\cdots\right] + \frac{1+P}{\sqrt{P}(1-P)^2}\left[\frac{(-2\sqrt{P})}{1!} + \frac{(-2\sqrt{P})^3}{3!}\cdots\right]$$
$$(17)\quad = \frac{2}{(1-P)^2}\cosh 2\sqrt{P} - \frac{1+P}{\sqrt{P}(1-P)^2}\sinh 2\sqrt{P}$$

A similar treatment yields the further relationship

$$(18)\quad \sum_{n=1}^{\infty} P^{n-1} S_{2n+1} = -\frac{1}{P} - \frac{2}{\sqrt{P}(1-P)^2}\sinh 2\sqrt{P} + \frac{1+P}{P(1-P)^2}\cosh 2\sqrt{P}$$

Substituting the results of (17), and (18) in (16) and making use of the relations

$$P_{11} + P_{12} = 1$$
$$P_{21} + P_{22} = 1$$

we have

$$(19)\quad f = \frac{P_{12} - P_{21}}{2P_{12}} + \frac{P_{12} + P_{21}}{2P_{12}}\cosh 2\sqrt{P_{12}P_{21}} - \sqrt{\frac{P_{21}}{P_{12}}}\sinh 2\sqrt{P_{12}P_{21}}$$

which may be rearranged to the form

$$(20)\quad f = \left(\cosh\sqrt{P_{12}P_{21}} - \sqrt{\frac{P_{21}}{P_{12}}}\sinh\sqrt{P_{12}P_{21}}\right)^2$$

It is desirable to be able to express f as a function of the polymer composition rather than the propagation probabilities used in equation (20). This may be accomplished by making use of the relations[9]

$$\frac{P_{21}}{P_{12}} = \frac{m_1}{m_2}$$
$$\sqrt{P_{12}P_{21}} = \frac{1 - \sqrt{1 - 4m_1m_2(1 - r_1r_2)}}{2(1 - r_1r_2)\sqrt{m_1m_2}}$$

Thus we see that f is expressible in terms of the copolymer composition m_2 and the quantity $(1 - r_1r_2)$ which is a measure of the alternation tendency in copolymerization. It is possible, therefore, to plot a family of curves of f against m_2 with (r_1r_2) as parameter (see Fig. 1). In the case $r_2 = 0$ that portion of the curve for m_2 greater than 0.5 is unattainable in practice, as is that portion of the curve for m_2 less than 0.5 in the case $r_1 = 0$. The curve drawn for $r_1r_2 = 0$ may therefore be regarded as a composite of the two extreme cases.

(9) r_1 and r_2 are relative rates of propagation and are characteristic of the monomer pair used. See the references given under (8)

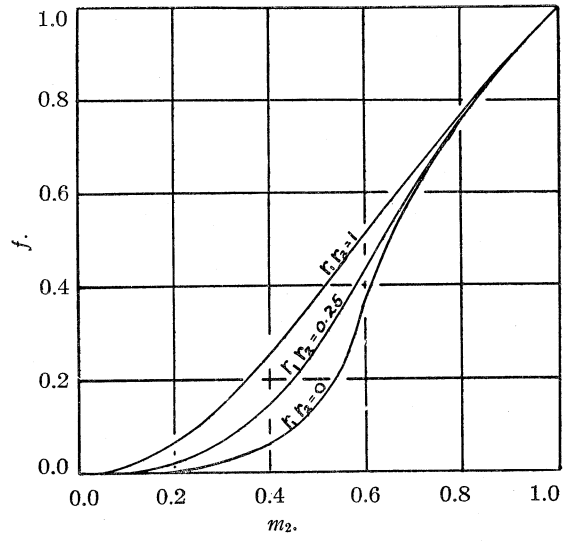


Fig. 1.—Fraction of acid remaining unlactonized as a function of mole fraction of acid in copolymer.

Summary

An expression has been derived for the amount of lactonization to be expected in a copolymer containing hydroxyl and carboxyl groups.

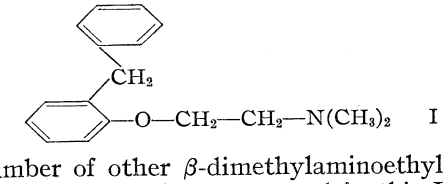
BROOKLYN, NEW YORK RECIEVED APRIL 15, 1949

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

2-Benzylphenol Derivatives. III.[1] Basic Ethers

BY WILLIAM B. WHEATLEY, LEE C. CHENEY AND S. B. BINKLEY

In previous communications the antihistaminic action of 2-benzylphenyl β-dimethylaminoethyl ether (I) and some of its analogs was reported.[1]



I

A number of other β-dimethylaminoethyl ethers related to I have been prepared in this Laboratory and submitted for pharmacological evaluation. More analogs of I are in preparation and will be the subject of a future communication.

The method of synthesis of these ethers is essentially that reported previously.[1b] The C-alkylation of phenols by halides of the benzyl type, according to the method of Claisen,[2] has been extended to heterocyclic systems. Phenol has been alkylated with 2-thenyl and 5-chloro-2-thenyl chloride to give 2-(2′-thenyl)-phenol, and 2-(5′-chloro-2′-thenyl)-phenol, respectively. In the case of alkylation of phenol with 2-thenyl chloride, the isomeric 4-(2′-thenyl)-phenol has been isolated and characterized. Alkylation of 8-hydroxyquinoline with benzyl chloride gave a compound believed to be 7-benzyl-8-hydroxyquinoline. Conversion of the various substituted phenols to the β-dimethylaminoethyl ethers proceeded smoothly via the Williamson ether synthesis.

(1) For preceding papers in this series, see (a) Cheney, Smith and Binkley, THIS JOURNAL, **71**, 60 (1949); (b) Wheatley, Cheney and Binkley, *ibid.*, **71**, 64 (1949).

(2) Claisen, *Ann.*, **420**, 210 (1925).

Experimental[3]

Several previously reported alkylated phenols were prepared: 4-bromo-2-benzylphenol,[4] 2-methoxy-6-benzylphenol,[2] 2-cinnamylphenol,[2] 1-benzyl-2-naphthol,[2] 2-benzyl-1-naphthol,[2] 1-allyl-2-naphthol,[5] and 2-allyl-1-naphthol.[6]

2-(4'-Fluorobenzyl)-phenol.—Alkylation of phenol with 4-fluorobenzyl chloride[7] in the manner described previously[1b] gave 2-(4'-fluorobenzyl)-phenol in 41% yield, b. p. 136–141° (3 mm.), $n^{26}D$ — 1.5728.

Anal. Calcd. for $C_{13}H_{11}OF$: C, 77.2; H, 5.5. Found: C, 76.5; H, 5.5.[8]

4-Fluoro-2-benzylphenol.—Alkylation of 4-fluorophenol (prepared by demethylation of 4-fluoroanisole with aluminum chloride according to the method described by Suter, Lawson and Smith[9]) with benzyl chloride gave 4-fluoro-2-benzylphenol in 41% yield, b. p. 117–123° (1 mm.), $n^{26}D$ — 1.5720.

Anal. Calcd. for $C_{13}H_{11}OF$: C, 77.2; H, 5.5. Found: C, 75.7, 75.7; H, 5.6, 5.5.

4-Dimethylamino-2-benzylphenol.—One hundred grams (0.268 mole) of 4-dimethylaminophenol sulfate was shaken with 500 ml. of saturated sodium bicarbonate solution and 200 ml. of chloroform until complete solution was attained. The lower layer was drawn off and the aqueous portion extracted twice with fresh chloroform. The combined extracts were dried with Drierite, an equal volume of toluene added and the solvent distilled until practically all of the chloroform was removed. Gradual addition of this solution to a stirred suspension of 12 g. (0.5 mole) of sodium hydride in 300 ml. of toluene gave a blue-green insoluble sodium salt. After refluxing for an hour to insure complete reaction, 62 g. (0.5 mole) of benzyl chloride was added dropwise over a period of two hours. Following one and one-half hours of additional refluxing, the mixture was hydrolyzed with water. The toluene layer was removed and filtered to remove a small amount of tarry material. The aqueous layer was extracted three times with chloroform and the extracts added to the toluene solution. This solution was dried, stripped and distilled *in vacuo*, the entire distillate boiling between 120 and 210° at 2–3 mm. being retained (69 g.). The distillate was then taken up in 200 ml. of Claisen alkali and extracted twice with Skellysolve D. Addition of sufficient concentrated hydrochloric acid to bring the *p*H of the aqueous solution down to 8 caused an oil to separate. It was taken into ether and the ether extracts dried and stripped. Distillation of the residue at 1 mm. gave three main fractions: (1) 7.9 g., b. p. 111–141°; (2) 16.4 g., b. p. 165–180°, $n^{25}D$ 1.6030; (3) 24.3 g., b. p. 180–217°, $n^{25}D$ 1.6194. Fraction (1) was mainly recovered starting material, (2) was assumed to be the desired 4-dimethylamino-2-benzylphenol and used as such immediately, and (3) was assumed to be 4-dimethylamino-2,6-dibenzylphenol.

2-(2'-Thenyl)-phenol and 4-(2'-Thenyl)-phenol.—A solution of 390 g. (4.16 moles) of phenol in 800 ml. of xylene was added to 90.9 g. (3.85 moles) of molten sodium under 1100 ml. of hot xylene at a rate such that refluxing was maintained. After the addition was complete, the mixture was refluxed for three hours. To the hot suspension of sodium phenolate was added over a period of thirty minutes 523 g. (3.95 moles) of 2-thenyl chloride.[10] The reaction mixture was refluxed for eighteen hours, acidified with concentrated hydrochloric acid and steam distilled until about four liters of distillate was collected. The two-phase residue was transferred to a separatory funnel and the aqueous layer withdrawn. It was extracted with 300 ml. of ether, the ether stripped and the residual oil added to the original organic layer. This material was taken up in one liter of Claisen alkali and washed three times with Skellysolve C. Acidification of the aqueous layer liberated the phenolic material, which was extracted into ether. The combined ether extracts were dried over anhydrous magnesium sulfate and stripped. Distillation of the residue gave 290 g. (39% yield) of mixed 2-thenylphenols, b. p. 137° (1.5 mm.)–190° (10 mm.). (Considerable decomposition occurred toward the end of the distillation.) The entire distillate was poured into a boiling solution of 365 g. of barium hydroxide octahydrate in 1.4 l. of water. After ten minutes of boiling, the solution was placed in the cold room. The following day the insoluble barium salt was removed by filtration, acidified and the crude 4-(2'-thenyl)-phenol recrystallized from carbon tetrachloride to give 36 g. of pure product (5% yield). An analytical sample melted sharply at 65°.

Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.4; H, 5.3. Found: C, 69.6; H, 5.5.

The original aqueous filtrate containing the soluble barium salt was acidified at once, and on cooling the oily 2-(2'-thenyl)-phenol crystallized. Since this compound is easily oxidized by atmospheric oxygen, it is necessary to work rapidly to avoid undue loss during manipulations. The crude phenol was collected by filtration and the wet material dissolved in 200 ml. of hot benzene. The aqueous layer was withdrawn and benzene distilled until no more water appeared in the distillate. The solution was then diluted with one liter of Skellysolve D, cooled and seeded. The crystals were collected and recrystallized from cyclohexane. There was obtained 183 g. (24% yield) of pure 2-(2'-thenyl)-phenol, m. p. 50.0–52.0°.

Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.4; H, 5.3. Found: C, 68.9; H, 5.4.

2-(5'-Chloro-2'-thenyl)-phenol.—Phenol (45.2 g., 0.482 mole) was alkylated with 85.2 g. (0.482 mole) of 5-chloro-2-thenyl chloride[11] according to the previously described procedure,[1b] giving 50.7 g. of crude product, b. p. 165–175° (5 mm.). Continued slight decomposition during distillation prevented attainment of a good vacuum, and the distillate rapidly became discolored. The distillate was therefore added to a hot solution of 53.5 g. of barium hydroxide octahydrate in 210 ml. of water and boiled ten minutes. The hot solution was cooled rapidly to 20° and filtered. Acidification of the filtrate liberated the phenol, which was removed by extraction with ether. The combined extracts were dried, stripped and the residue distilled at 1 mm. to yield 39.5 g. (39%) of 2-(5'-chloro-2'-thenyl)-phenol, b. p. 135–139°.

Anal. Calcd. for $C_{11}H_9OSCl$: C, 58.8; H, 4.0. Found: C, 58.5; H, 4.2. The phenol was immediately converted to the basic ether, which proved to be a fortunate procedure, since the next day the remainder of the analytical sample, originally a colorless liquid, had become a black solid with a strong odor of hydrogen chloride. The basic ether appeared to be perfectly stable at room temperature.

Two attempts to prepare the bromo analog from phenol and 5-bromo-2-thenyl chloride[11] were unsuccessful, as the reaction products decomposed rapidly, in one case with explosive violence.

7-Benzyl-8-hydroxyquinoline.—A solution of 100 g. (0.69 mole) of 8-hydroxyquinoline in 250 ml. of toluene was added slowly to a stirred suspension of 16.5 g. (0.69 mole) of sodium hydride in 750 ml. of toluene. A bright, yellow insoluble sodium salt formed. The reaction mixture was refluxed for thirty minutes, then, while refluxing was maintained, 79 ml. (87 g., 0.69 mole) of benzyl chloride were added dropwise over a period of five hours. The mixture was then stirred and refluxed overnight and finally hydrolyzed with dilute hydrochloric acid. Addition of sodium bicarbonate brought the *p*H of the aqueous layer up to 8. The toluene layer was removed and stripped

(3) All melting points are uncorrected.

(4) Huston, *et al.*, THIS JOURNAL, **55**, 2146 (1933).

(5) Claisen, *Ber.*, **45**, 3157 (1912).

(6) Claisen and Eisleb, *Ann.*, **401**, 61 (1913).

(7) Bennett and Jones, *J. Chem. Soc.*, 1815 (1935).

(8) The fluorine-containing phenols consistently gave low carbon analyses, but in each case the final compound gave a satisfactory analysis.

(9) Suter, Lawson and Smith, THIS JOURNAL, **61**, 161 (1939).

(10) Blicke and Leonard, *ibid.*, **68**, 1934 (1946).

(11) Clapp, *et al.*, *ibid.*, **69**, 1549 (1947).

TABLE I

R—O—CH_2—CH_2—$N(CH_3)_2$

R	Yield, %	B. p. °C.	B. p. Mm.	Hydrochlorides M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-Methoxy-6-benzylphenyl	83	144–148	1	92.5– 94.0[f]	$C_{18}H_{24}O_5N_2$[b]	62.1	61.8	6.9	7.1		
4-Bromo-2-benzylphenyl	89	164–167	1.5	179.5–181.0[f]	$C_{17}H_{21}ONBrCl$	55.1	55.7	5.7	5.7	3.8	3.8
4-Iodo-2-benzylphenyl[a]	73[a]	.....	...	167.0–170.0[g]	$C_{17}H_{21}ONICl$	48.9	49.1	5.1	5.1		
4-Fluoro-2-benzylphenyl	89	131–134	1	124.5–125.5[f]	$C_{17}H_{21}ONFCl$	65.9	65.7	6.8	6.8	4.5	4.9
4-Dimethylamino-2-benzylphenyl	73	171–186	1	154.0–156.0[h]	$C_{19}H_{27}ON_2Cl$	68.1	67.9	8.1	8.1	8.4	8.8
2-(4′-Fluorobenzyl)-phenyl	72	140–146	2	131.0–132.5[f]	$C_{17}H_{21}ONFCl$	65.9	65.7	6.8	6.9		
2-Cinnamylphenyl	82	137–141	1	154.0–156.5[f]	$C_{19}H_{24}ONCl$	71.8	71.9	7.6	7.8	4.4	4.6
2-(2′-Thenyl)-phenyl	76	159–160	1	129.0–130.0[k]	$C_{15}H_{19}ONS$[d]	68.9	68.2	7.3	6.8		
2-(5′-Chloro-2′-thenyl)-phenyl	86	149–150	1	103.0–106.0[f]	$C_{15}H_{19}ONSCl_2$	54.2	54.3	5.8	5.7	4.2	4.1
1-Benzyl-2-naphthyl	88	184–192	1.5	178.0–181.0[i]	$C_{21}H_{24}ONCl$	73.8	73.8	7.1	7.1		
2-Benzyl-1-naphthyl	79	200–207	2	183.5–185.5[f]	$C_{21}H_{24}ONCl$	73.8	73.6	7.1	7.4		
1-Allyl-2-naphthyl	87	139–143	1	151.0–152.5[f]	$C_{17}H_{22}ONCl$	70.0	70.2	7.6	7.9		
2-Allyl-1-naphthyl	79	136–145	1	.....[c]							
7-Benzyl-8-quinolyl	86	190–197	1	205.0–207.0[j]	$C_{20}H_{24}ON_2Cl_2$[e]	63.3	63.0	6.4	6.2	7.4	7.4

[a] The base was not distilled, but was directly converted to its hydrochloride. The yield is that of crude hydrochloride. [b] Melting point, formula and analysis of the nitrate. [c] A crystalline salt could not be obtained. [d] Formula and analysis of the free base. [e] Dihydrochloride. [f] Recrystallized from isopropyl alcohol–Skellysolve B. [g] Recrystallized from methyl isobutyl ketone. [h] Recrystallized from isopropyl alcohol. [i] Recrystallized from water–isopropyl alcohol. [j] Recrystallized from methanol–ether. [k] Recrystallized from acetone.

under reduced pressure. The residue was taken up in 400 ml. of Claisen alkali and extracted twice with Skellysolve D. On adjustment of the *p*H of the aqueous layer to about 7, a brown semi-solid formed. This mixture was extracted three times with ether containing a little chloroform, the extracts combined, dried and stripped. Distillation of the residue at 3 mm. gave 27 g. of recovered 8-hydroxyquinoline, followed by 93 g. (58% yield) of material boiling at 193–205°. This material solidified in the receiver, and a portion recrystallized four times from cyclohexane melted at 96.5–97.5°. By analogy with the benzylation of α-naphthol,[2] it was assumed that the product was 7-benzyl-8-hydroxyquinoline.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.7; H, 5.6. Found: C, 81.7; H, 5.6.

4-Iodo-2-benzylphenol.—Benzylation of 4-iodophenol[12] gave 4-iodo-2-benzylphenol in 44% yield, b. p. 163–167° (1 mm.). Considerable decomposition occurred during distillation, and the product was obtained as a violet oil which could not be crystallized. It was dissolved in toluene, freed of iodine by shaking with saturated sodium bisulfite solution and immediately converted to the β-dimethylaminoethyl ether.

Basic Ethers.—The basic ethers in Table I were prepared except as noted below, as described previously,[1b] using approximately a 30% excess of β-dimethylaminoethyl chloride hydrochloride. In the case of those phenols containing a basic function, 4-dimethylamino-2-benzylphenol and 7-benzyl-8-hydroxyquinoline, only the theoretical amount of β-dimethylaminoethyl chloride hydrochloride was used in order to minimize quaternary formation.

In general the basic ethers were converted to hydrochlorides by passing dry hydrogen chloride into cold ethereal solutions of the free bases. The monohydrochloride of 4-dimethylamino-2-benzylphenyl β-dimethylaminoethyl ether was obtained by dissolving the base in isopropyl alcohol, adding one equivalent of hydrogen chloride in ethanol and diluting with ether. The nitrate of 2-methoxy-6-benzylphenyl β-dimethylaminoethyl ether was prepared by adding one equivalent of concentrated nitric acid to an ethanol solution of the basic ether and precipitating the salt with ether.

Acknowledgment.—The authors are indebted to Mr. Richard M. Downing and Mrs. Neva Knight for the microanalyses reported herein. The assistance of Mrs. Sarah M. Tardy and Messrs. William E. Fitzgibbon, Lyman E. Lorensen and Richard R. Smith is gratefully acknowledged.

Summary

A number of β-dimethylaminoethyl ethers of various aralkylphenols has been synthesized. The Claisen alkylation of phenols by halides of the benzyl type has been extended to heterocyclic phenols and halides.

SYRACUSE, N. Y. RECEIVED JUNE 6, 1949

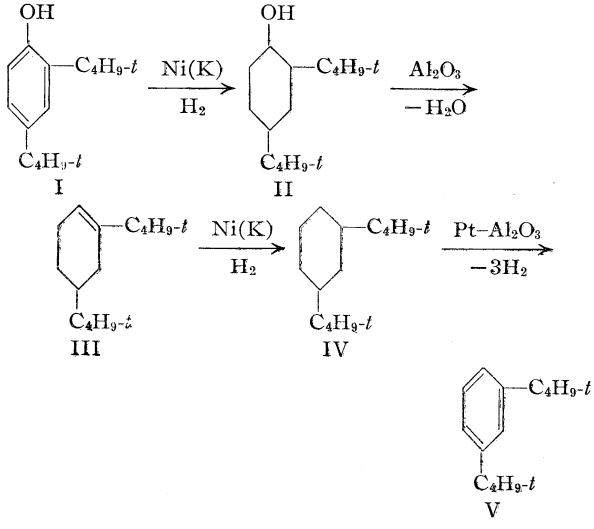
(12) Dains and Everly, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 355.

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Synthesis of 1,3-Di-*t*-butylbenzene and 1,3-Di-*t*-butylcyclohexane[1]

BY HERMAN PINES, G. J. CZAJKOWSKI AND V. N. IPATIEFF

m-Di-*t*-butylbenzene has heretofore not been synthesized; this compound cannot be prepared by the alkylation of benzene with isobutylene. The present paper describes the synthesis of this hydrocarbon from 2,4-di-*t*-butylphenol. The following steps were involved in the synthesis of *m*-di-*t*-butylbenzene.



In order to be certain that rearrangement did not occur during the dehydration of 2,4-di-*t*-butylcyclohexanol (II) nor during the dehydrogenation of 1,3-di-*t*-butylcyclohexane (IV), compound V was hydrogenated and the infrared spectrum of the product was compared with the spectra of compound IV and of 1,3-di-*t*-butylcyclohexane (Graph I) prepared by the Wolff–Kishner reduction of 2,4-di-*t*-butylcyclohexanone. It was found that all the three spectra were identical with the exception of minor outside absorptions in the spectrum of the compound obtained from hydrogenation 1,3-di-*t*-butylcyclohexene. The infrared and ultraviolet spectra of *m*-di-*t*-butylbenzene are given in Graphs 2 and 3.

Experimental Part

I. Synthesis of 1,3-Di-*t*-butylbenzene

2,4-Di-*t*-butylcyclohexanol (II).—One hundred grams of 2,4-di-*t*-butylphenol (I) (Dow Chemical Co.) was hydrogenated in a 450-cc. capacity autoclave at 115–125° in the presence of nickel–kieselguhr catalyst and under 100 atmospheres of hydrogen. Three moles of hydrogen was absorbed per one mole of compound charged. The product was in the form of white crystals; it distilled at 125° (14 mm.), m. p. 107–109°; yield 92%.

Anal. Calcd. for $C_{14}H_{28}O$: C, 79.25; H, 13.20. Found: C, 78.86; H, 13.53.

1,3-Di-*t*-butyl-x-cyclohexene (III).—Compound II (48 g.) was dissolved in 50 cc. of *t*-butyl alcohol and dehydrated by passing it over activated alumina pills at 410–420°. The olefin formed was separated, dried and distilled; b. p. 114–115° at 25 mm.; $n^{20}D$ 1.4640; d^{20}_4 0.8338; yield 66%.

Anal. Calcd. for $C_{14}H_{26}$: C, 86.51; H, 13.49. Found: C, 86.65; H, 13.30.

1,3-Di-*t*-butylcyclohexane (IV).—Compound III (29.0 g.) was hydrogenated at 50° in a 125-cc., rotating autoclave in the presence of 4 g. of nickel–kieselguhr catalyst and under an initial hydrogen pressure of 100 atmospheres. Twenty-six grams of compound IV was obtained; yield 90%. The pure compound had the following properties: boiling points, 70° at 2.4 mm., 86.4° at 6.0 mm., 93.8° at 9.4 mm., 102° at 13.5 mm., 122° at 31.5 mm.; d^{20}_4 0.8312, d^{25}_4 0.8273; $n^{20}D$ 1.45727, $n^{25}D$ 1.45527; specific dispersion, ($\delta H\beta$-Hα) = 85.2 at 20°, 84.4 at 25°.

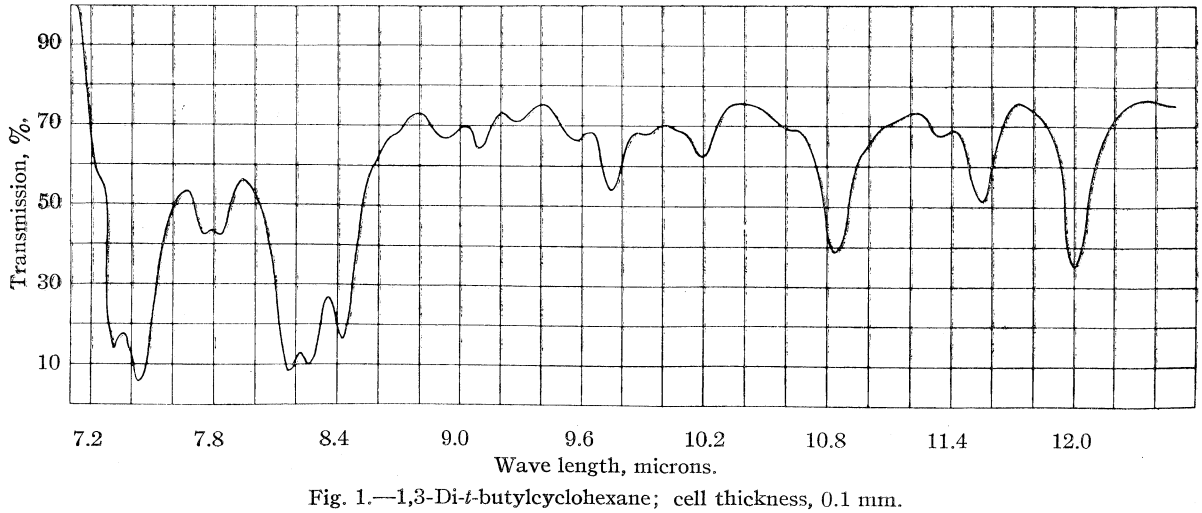


Fig. 1.—1,3-Di-*t*-butylcyclohexane; cell thickness, 0.1 mm.

(1) This work was made possible through the financial support of the Universal Oil Products Company.

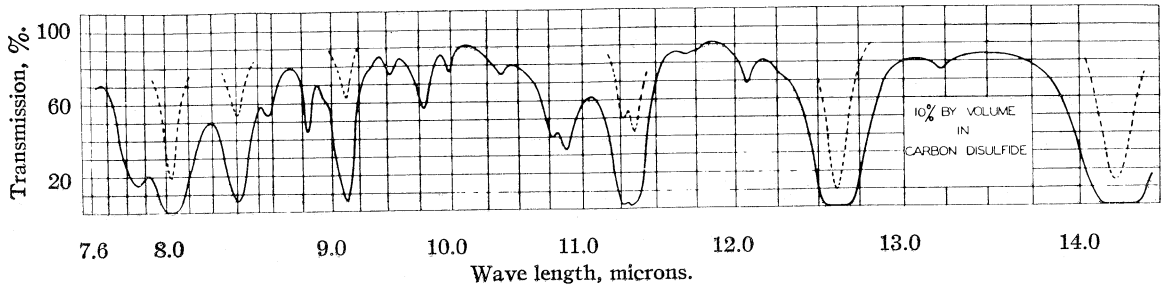


Fig. 2.—*m*-Di-*t*-butylbenzene; cell thickness, 0.1 mm.

Anal. Calcd. for $C_{14}H_{22}$: C, 85.63; H, 14.37. Found: C, 85.78; H, 14.32.

m-Di-t-butylbenzene (V).—Sixteen grams of (IV) was dehydrogenated by passing it three times over platinum–aluminum oxide catalyst at 275° according to the procedure described previously.[2] The aromatic hydrocarbon formed was purified chromatographically by dissolving it in four parts of pentane and passing the solution over a five-foot column of through-200 mesh silica gel.[3] This method enabled the separation of any unreacted 1,3-di-*t*-butylcyclohexane which might have remained. *m*-Di-*t*-butylbenzene thus purified had the following properties: boiling points, 73° at 2.5 mm.; 89.5 at 6.6 mm., 101° at 11.2 mm.; d^{20}_4 0.8589, d^{25}_4 0.8547; $n^{20}D$ 1.4879, $n^{25}D$ 1.4874; specific dispersion ($\delta H\beta$-$H\alpha$) = 126.6 at 20°, 126.7 at 25°.

Anal. Calcd. for $C_{14}H_{22}$: C, 88.42; H, 11.58. Found: C, 88.34; H, 11.73.

Compound V (2.2 g.) was acetylated according to the procedure described previously[4]; the 2,4-dinitrophenylhydrazone of the ketone melted at 208–210°. *Anal.* Calcd. for $C_{22}H_{28}N_4O_4$: C, 64.05; H, 6.84; N, 13.59. Found: C, 64.17; H, 6.82; N, 13.73.

II. Synthesis of 1,3-Di-*t*-butylcyclohexane from the Corresponding Ketone

1. **2,4-Di-t-butylcyclohexanone** (VI) was prepared in 51% yield from 50 g. of 2,4-di-*t*-butylcyclohexanol (II) dissolved in 200 ml. of acetone by means of oxidation as described previously.[5] The ketone distilled at 143° at 28 mm., $n^{20}D$ 1.4645, d^{20}_4 0.8946, MRD calculated 64.7, observed 65.1. *Anal.* Calcd. for $C_{14}H_{26}O$: C, 80.00; H, 12.34. Found: C, 79.76; H, 12.77.

The 2,4-dinitrophenylhydrazone of VI melted at 174–176°. *Anal.* Calcd. for $C_{20}H_{29}N_4O_4$: N, 14.39. Found: N, 14.37.

2. **The ketone (VI)** was reduced to the hydrocarbon by means of the modified Wolff–Kishner method[6]; 17.5 g. of 2,4-di-*t*-butylcyclohexanone, 8.5 ml. of hydrazine hydrate (85%), 85 ml. of 1,4-dioxane and 11.2 g. of potassium hydroxide were used. A 79% yield of hydrocarbon was obtained, $n^{20}D$ 1.4585, whose infrared spectrum was essentially the same as that of compound (IV).

(2) H. Pines, R. C. Olberg and V. N. Ipatieff, This Journal, **70**, 533 (1948).

(3) B. J. Mair and A. F. Forziati, *J. Research Natl. Bureau Stand.*, **32**, 151, 165 (1944).

(4) H. Pines, A. Weizmann and V. N. Ipatieff, This Journal, **70**, 3859 (1948).

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(6) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

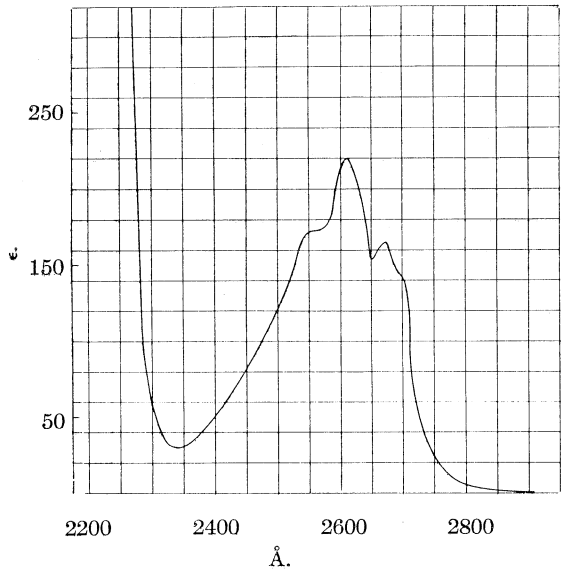


Fig. 3.—Ultraviolet absorption spectrum of 1,3-di-*t*-butylbenzene.

3. **Hydrogenation of m-Di-t-butylbenzene.**—Compound (V), 3.7 g., was hydrogenated in a 125-cc. autoclave at a temperature of 150° in the presence of a nickel–kieselguhr catalyst and 100 atmospheres of hydrogen pressure. The product gave a negative test for aromatics and its infrared spectrum showed it to be the same as that of compound (IV).

The test for aromatics was made by treating a few drops of the hydrocarbon with 1 ml. of 96% sulfuric acid solution containing 5% by weight of paraformaldehyde. The presence of traces of aromatics after two to three minutes causes a brown coloration of the sulfuric acid layer.

Summary

m-Di-*t*-butylbenzene was prepared by the dehydrogenation of 1,3-di-*t*-butylcyclohexane; the latter was obtained from 2,4-di-*t*-butylcyclohexanol by means of dehydration followed by hydrogenation.

Evanston, Illinois Received May 16, 1949

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, PHYSIOLOGICAL CHEMISTRY AND PHYSICS,[1] UNIVERSITY OF PITTSBURGH, PITTSBURGH, PENNSYLVANIA]

The Reaction of Tobacco Mosaic Virus with Formaldehyde. II. Kinetics[2]

BY MARIE A. FISCHER[3] AND MAX A. LAUFFER

Introduction

The loss of infectivity of tobacco mosaic virus in the presence of formaldehyde was studied by Ross and Stanley.[4] It appears to be a reaction of the first order. When the inactivation is carried out at room temperature in a phosphate buffer at *p*H 7, a simultaneous decrease in the amino nitrogen content of the virus occurs and the isoelectric point of the virus is shifted toward the acid side.[5] In a previous paper[6] the authors reported that the reaction products of formaldehyde inactivation appear to be electrophoretically homogeneous but to have a different mobility than untreated virus. Therefore, it seemed desirable to study simultaneously from the kinetic point of view the effects of formaldehyde treatment at *p*H 7.0 on the electrophoretic mobility, the amino nitrogen content and the infectivity of the virus to determine the possible relationship between the three changes.

Materials and Methods

Tobacco mosaic virus, isolated by the differential centrifugation method of Stanley,[7] was treated with formaldehyde by allowing a solution of 2% virus and 2% formaldehyde in 0.1 *M* phosphate buffer, *p*H 7.0, to react at 30.0°. At suitable time intervals, 15-ml. aliquots of the reacting mixture were removed and the *p*H immediately lowered to the isoelectric *p*H of the virus (*p*H 3.5) by the addition of 20 ml. of cold 1 *M* phosphate–citrate–hydrochloric acid buffer. After centrifuging for fifteen minutes at 4,000 r.p.m., the clear supernatant fluid was discarded and the virus precipitate washed by suspending the precipitate in 30 ml. of cold 0.1 *M* phosphate–citrate–hydrochloric acid buffer, *p*H 3.5, and again centrifuging and decanting the supernatant fluid. Washing was repeated and the precipitate then was dissolved in 10 ml. of phosphate buffer, *p*H 7.00 ± 0.02, 0.20 ionic strength, and dialyzed for four days against four 250-ml. portions of the same buffer. The virus protein content was determined by micro-Kjeldahl analysis, and the preparations of formaldehyde-treated virus were stored in the refrigerator. The infectivity, amino nitrogen content and the electrophoretic mobility of each sample were then determined.

Infectivity was determined by the method of Loring,[8] using *N. Glutinosa* as the test plant. So that approximately equal numbers of local lesions could be compared, two dilutions of each preparation were made and compared by using the half-leaf method and a Latin-square pattern for inoculation. The ninhydrin method described by Miller and Stanley[9] was used to determine the amino nitrogen content of each sample and electrophoretic mobilities were determined at 1° in the apparatus described by Tiselius[10] and modified by Longsworth.[11] In preparation, the virus had already been dialyzed against phosphate buffer, *p*H 7.00 ± 0.02, 0.20 ionic strength. Therefore, a portion of each sample was diluted with this buffer to a virus concentration of 0.50% just prior to electrophoresis in the same buffer. Differences in the *p*H and the specific conductances of the protein solutions and the buffer were not detectible by the precision bridge described by Luder.[12] Migration in an electric field of 4.5 volts per cm. was allowed to proceed until the essentially homogeneous boundaries had migrated a distance of 6 cm. The current was then reversed and the boundaries brought back to their original positions. The reported mobilities were calculated from the average of the distances each boundary moved away from and back to its original position.

The observation that formaldehyde-treated virus is electrophoretically homogeneous[6] justified the use of isoelectric precipitation to stop the reaction quickly. Table I shows that the method was efficient in removing excess and reversibly bound formaldehyde, for the properties of the virus treated 0-hours with formaldehyde were essentially the same as stock and control virus. Further evidence that excess formaldehyde was probably completely removed was obtained by studying the effect of the presence

TABLE I

USE OF ISOELECTRIC PRECIPITATION TO STOP THE FORMALDEHYDE-TOBACCO MOSAIC VIRUS REACTION

Treatment		Activity remaining, % stock virus	Ninhydrin color, % stock virus	Electrophoretic mobility, sq. cm./volt-sec. × 10^5
(1) Stock virus	(a)	100	100	..
	(b)	100	100	7.17
(2) Isoelectric precipitation	(a)	107	89	..
	(b)	104	100	7.16
(3) 0-hr. 2% HCHO followed by isoelectric precipitation	(a)	116	91	..
	(b)	78.6	101	7.14

TABLE II

THE EFFECT OF SMALL CONCENTRATIONS OF FORMALDEHYDE ON THE NINHYDRIN REACTION

Sample (5 mg. TMV in 1 ml.)	Water added, ml.	HCHO added, ml. of 0.36% HCHO	Concn. HCHO, %	Color[a]
1	0.10	0.00	0.000	Deep blue
2	.08	.02	.007	Deep blue
3	.06	.04	.014	Blue
4	.04	.06	.022	Light blue
5	.02	.08	.029	Faint blue
6	.00	.10	.036	Colorless

[a] Color decreased visibly according to formaldehyde concentration.

(1) Contribution no. 722 of the Department of Chemistry and 6-p-49 of the Department of Physics, University of Pittsburgh.

(2) Aided in part by a grant from the National Foundation for Infantile Paralysis, Inc.

(3) Some sections were abstracted from a thesis submitted by Marie A. Fischer to the Department of Chemistry in partial fulfillment of the requirements for the Ph.D. degree.

(4) A. F. Ross and W. M. Stanley, *J. Gen. Physiol.*, **22**, 165 (1938).

(5) W. M. Stanley, *Science*, **83**, 626 (1936).

(6) M. A. Fischer and M. A. Lauffer, *Arch. Biochem.*, **23**, 291

(7) W. M. Stanley, JOURNAL, **64**, 1804 (1942).

(8) H. S. [illegible] 637 (1937).

(9) G. L. Miller and W. M. Stanley, *ibid.*, **141**, 905 (1941).

(10) A. Tiselius, *Trans. Faraday Soc.*, **33**, 524 (1937).

(11) L. G. Longsworth, THIS JOURNAL, **61**, 529 (1939).

(12) W. F. Luder, *ibid.*, **62**, 89 (1940).

of formaldehyde on the ninhydrin reaction. To 1-ml. aliquots of stock virus, containing 5 mg. of tobacco mosaic virus, varying concentrations of formaldehyde were added, and ninhydrin determinations were carried out immediately. It is apparent from the data in Table II that small concentrations of formaldehyde inhibit the ninhydrin reaction and that the immediate reaction of excess formaldehyde affects all of the groups which are reactive to ninhydrin because color is completely absent. However, Table I shows that the immediate reaction can be reversed by the removal of the formaldehyde. This is in contrast to the Van Slyke amino nitrogen reaction which has been shown[13] to reverse partly or completely the immediate binding of formaldehyde by amino groups.

Presentation of Experimental Results

Rate of Inactivation.—Ross and Stanley[4] studied the rate at which infectivity is lost when a 2% solution of virus in 0.1 *M* phosphate buffer at *p*H 7 is allowed to react with 2% formaldehyde at room temperature. The results of similar experiments confirm the observation of Ross and Stanley that the loss of infectivity of tobacco mosaic virus in the presence of formaldehyde is a reaction of the first order. The data fit an equation of the form

$$(V) = e^{-kt} \qquad (1)$$

where (V) is virus infectivity expressed as fraction of original infectivity and t is time of contact with formaldehyde in hours. In four experiments carried out at *p*H 7 and 30°, the following values were obtained for k: 0.37, 0.44, 0.45 and 0.4 reciprocal hour.

Shift in Electrophoretic Mobility with Formaldehyde Treatment.—As was pointed out previously,[6] tobacco mosaic virus remains essentially homogeneous with respect to electrophoretic mobility after treatment with formaldehyde; however, a mobility shift occurs, because inactive virus can be separated electrophoretically from untreated virus. Since treated virus is inhomogeneous with respect to the criterion of biological activity, but homogeneous with respect to electrophoresis, it seemed desirable to study the mobility shift in more detail. In preliminary studies the kinetics of this reaction were studied by an indirect method.[14] It was first shown that a correlation could be established between the infectivity remaining, following treatment, and the electrophoretic mobility. When the logarithm of the relative activity remaining was plotted against the electrophoretic mobility of a formaldehyde-treated sample, a straight line relationship was obtained. If this proportionality is considered in relation to the logarithmic dependence of infectivity upon time, it can be deduced that the shift in electrophoretic mobility is directly proportional to the time of contact between the virus and the formaldehyde.

The experiment described in the section on materials and methods was carried out in a manner which permitted direct measurement of both time of contact with formaldehyde and electrophoretic mobility. The results are shown in Fig. 1, where electrophoretic mobility increase in a 0.1 *M* phosphate buffer at *p*H 7 is plotted as a function of time of contact with formaldehyde. The linear relationship is seen to apply only to the initial stage of the reaction. The open circles on the graph represent experimental determinations, and the smooth curve is a plot of equation (2).

$$\Delta U = 0.82(1 - e^{-0.04t}) \qquad (2)$$

ΔU in equation (2) represents the increase in anodic mobility, and t represents the time in hours during which the virus was held in contact with formaldehyde.

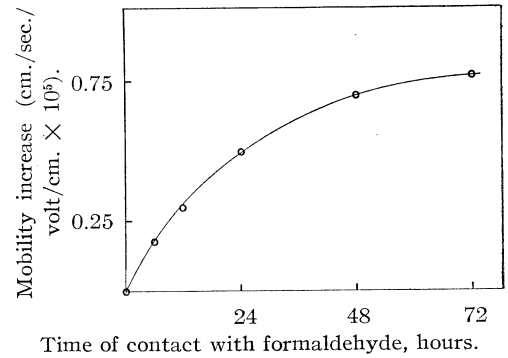


Fig. 1.—Increase in anodic electrophoretic mobility (10^5 cm.²/volt-sec.) of formaldehyde-treated tobacco-mosaic virus protein in potassium phosphate buffer, *p*H 7.00 ± 0.02, 0.2 ionic strength, plotted against time in hours of reaction at *p*H 7.0 and 30° between the protein and 2% formaldehyde.

The Decrease in Free Amino Groups.—Ross and Stanley,[4] by measuring the ninhydrin color, studied the effect of formaldehyde treatment in neutral phosphate buffer on the virus groups. In order to determine whether or not the decrease in free amino groups as shown by the ninhydrin reaction is correlated with the shift in mobility or with the decrease in infectivity, free amino groups were measured on the samples which were subjected to infectivity and electrophoretic analyses. The details of the experiment were described in the section on materials and methods. The results are presented in Fig. 2, where ninhydrin color expressed as per cent. of original is plotted against time in hours of reaction with formaldehyde. The open circles represent the experimental values obtained. If the shift in electrophoretic mobility were associated in a simple manner with the decrease in amino nitrogen, these data ought to fit the equation, $C = 100e^{-0.04t}$, where C is the color produced by ninhydrin expressed as per cent. of original, and t is the time in hours of reaction with formaldehyde. The data do not obey this equation at all. This is proof that ninhydrin does not measure exactly the

(13) H. S. Olcott and H. Fraenkel-Conrat, *Chem. Revs.*, **41**, 151 (1947).

(14) M. A. Lauffer and M. A. Fischer, preliminary report of this investigation presented to the Division of Biological Chemistry of the American Chemical Society at New York City, 1947.

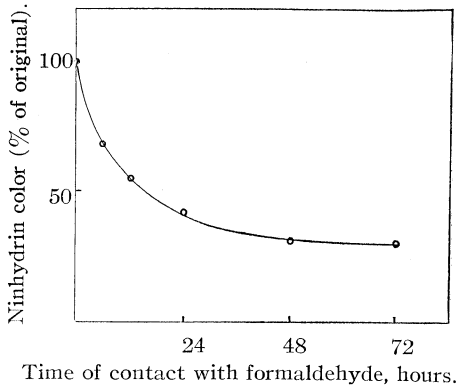


Fig. 2.—Color, expressed as per cent. of original absorption, obtained by treating formaldehyde-modified tobacco-mosaic virus protein with ninhydrin plotted against time in hours of reaction at *p*H 7.0 and 30° between the protein and 2% formaldehyde.

same thing as shift in electrophoretic mobility. The smooth curve in Fig. 2 is a plot of equation (3).

$$C = (28 + 30e^{-0.04t} + 42e^{-0.14t}) \qquad (3)$$

The parameter, 0.04, was carried over from equation (2) for reasons which will be discussed later. The other four parameters were selected to make the equation fit the data. The parameter, 28, is subject to an error of the order of magnitude of 3%. The other parameters are subject to uncertainties of the order of magnitude of 25%.

Discussion

Theoretical Considerations.—Assume that a solution contains n macromolecules per ml., each with ν groups capable of reacting with a reagent. The total concentration of groups per ml. will be $n\nu$ or N. If the reagent is present in great excess, one would expect the reaction to be first order with respect to the groups.

$$-\mathrm{d}N/\mathrm{d}t = kN \qquad (4)$$

$$N/N_0 = e^{-kt} \qquad (5)$$

N/N_0 is the fraction of groups unchanged after a time, t, of reaction with the reagent.

$$1 - N/N_0 = N'/N_0 = 1 - e^{-kt} \qquad (6)$$

N'/N_0 is the fraction of the groups which changed. The theory of probability leads to the expectation that the product should be inhomogeneous with respect to the number of groups per macromolecule reacted after time, t. The mean should be $\nu N'/N_0$. The distribution should be described by a standard deviation, σ.

$$\sigma = \sqrt{\nu NN'/N_0^2} \qquad (7)$$

Suppose that m of these ν groups on each macromolecule have some special significance. Then

$$n/n_0 = e^{-mkt} \qquad (8)$$

where n/n_0 is the fraction of macromolecules on which no one of the m special groups has reacted after time, t, in contact with reagent. The rate of disappearance of macromolecules with m intact special groups would be given by equation (9).

$$-\mathrm{d}n/\mathrm{d}t = mkt \qquad (9)$$

Types of Reaction between Formaldehyde and Proteins.—The possible reactions between formaldehyde and protein were reviewed in detail by French and Edsall[15] and by Olcott and Fraenkel-Conrat[13]. Apparently, formaldehyde is able to add reversibly to free amino groups to give groups which are weak bases and which do not produce color with ninhydrin. Further, apparently irreversible, reactions are possible by cross-linking between amino methylol groups and amide, guanidyl, imidazole, indole and phenol groups. These irreversible reactions may or may not lead to a change in charge, but do lead to change in color production with ninhydrin.

Shift in Mobility.—The negative charges on tobacco mosaic virus protein arise largely from free carboxyl groups of the dicarboxylic amino acids. These would be almost completely ionized at *p*H 7 because the pK is of the order of 4.0.[16] The negative charges are probably partially neutralized internally by positive charges originating from guanidine residues of arginine and the epsilon amino groups of lysine. At *p*H 7 the guanidine groups should be completely ionized; the free amino groups of lysine should be ionized to the extent of about 99.7%, since the pK for such groups in the polypeptide state is about 9.5, or greater.[16] Calculation from the amino acid content of tobacco mosaic virus[17] leads to the conclusion that at neutrality a tobacco mosaic virus particle should have 8,300 net charges.[18]

The mobility shift observed as a result of the reaction of the virus with formaldehyde can be interpreted as being the result of a decrease in the number of positive groups per particle, thereby increasing the net negative charge. The increase in negative charge, therefore, should be given by the quantity $\nu(N'/N_0)(\alpha_1 - \alpha_2)$, where α_1 and α_2 are the dissociation constants of the groups before and after reaction with formaldehyde, respectively. When the expression for N'/N_0 given by Equation (6) is substituted into this quantity, when it is considered that the maximum change in

(15) D. French and J. T. Edsall, *Adv. Protein Chem.*, **2**, 277 (1945).

(16) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids, and Peptides," Reinhold Publishing Corp., New York, N. Y., 1943.

(17) C. A. Knight, *J. Biol. Chem.*, **171**, 297 (1947).

(18) Unpublished acid–base binding experiments indicated that 6900 moles of acid were bound by one mole of untreated tobacco mosaic virus protein and 8200 moles of acid were bound by one mole of formaldehyde inactivated virus protein when the proteins were titrated from *p*H 3.5 (the usually accepted isoelectric point of tobacco mosaic virus protein) to *p*H 7.0. These data indicate that the theoretical valence, −8300, is of the correct order of magnitude. It should be observed that nucleic acid was omitted from consideration in arriving at the theoretical valence. This amounts to the assumption that nucleic acid does not contribute appreciably to the net charge of tobacco mosaic virus protein at *p*H 7. The reasonable agreement between the theoretical valence and that obtained by titration experiments indicates that this assumption may not be seriously in error.

charge is equal to $\nu(\alpha_1 - \alpha_2)$, and when the assumption is made that the shift in electrophoretic mobility is directly proportional to the shift in net charge, Equation (10) results.

$$\Delta U = \Delta U_{\max.} (1 - e^{-kt}) \qquad (10)$$

It is obvious that this equation is of exactly the same form as empirical Equation (2).

Experiments reported in a previous publication[6] showed that, following reaction with formaldehyde for a twenty-four-hour period, tobacco mosaic virus exhibited boundaries in the electrophoresis apparatus which were about as sharp as those exhibited by untreated virus. However, the theoretical considerations summarized by Equation (7) lead one to expect that virus treated with formaldehyde should be inhomogeneous with respect to electrophoresis. On the assumption that mobility is equal to K times the charge, Equation (11), where σ_u is the standard deviation of the distribution of mobility increments, can be derived from Equation (7).

$$\sigma_u = K \sqrt{\nu \frac{N'}{N_0} \times \frac{N}{N_0}} \qquad (11)$$

Since there are approximately 8,300 excess negative charges on a tobacco mosaic virus particle at *p*H 7, and the mobility is 7.15×10^{-5} sq. cm./volt-sec., K can be evaluated to be 0.00086×10^{-5}. Chemical analyses indicate that there are about 3,400 free amino groups on a tobacco mosaic virus particle. For reasons which will be discussed in the next section, about 30% of these can be assumed to be involved in the reaction which leads to a change in ionization. One can infer from Fig. 1 that N'/N_0 and N/N_0 are both approximately one-half for the reaction which has continued for twenty-four hours. By substituting these values into Equation (11), one can estimate that the standard deviation of the increment in mobility due to reaction of tobacco mosaic virus with formaldehyde should be of the order of magnitude of 0.014×10^{-5} cm./sec./volt/cm. Since the mobility after twenty-four hours of reaction is about 7.5×10^{-5}, the ratio of the standard deviation of the increment in mobility to the mobility is about 0.002. Inspection of electrophoresis boundary diagrams obtained with untreated tobacco mosaic virus indicates that the ratio of the standard deviation of the boundary to distance traversed is of the order of magnitude of 0.01. Therefore, the standard deviation of the boundary obtained with treated virus ought to be $\sqrt{(0.01)^2 + (0.002)^2}$, a value about 2% greater than that obtained with untreated virus. A difference of this magnitude would go undetected. Thus, the experimental observation that virus after reaction with formaldehyde is still essentially homogeneous with respect to electrophoresis is not inconsistent with the concepts used in the present case to interpret the reaction mechanism.

Decrease in Free Amino Groups.—The data presented in Fig. 2 were obtained under such conditions that they represent the irreversible change in free amino groups resulting from reaction of tobacco mosaic virus with formaldehyde. If one makes the assumption that there are three kinds of amino groups on tobacco mosaic virus particles, (a) those which do not react irreversibly with formaldehyde; (b) those which react irreversibly with formaldehyde at a relatively rapid rate; and (c) those which react with formaldehyde at a relatively slow rate, then the fraction of free amino groups remaining after time, t, would be given by a function which is the sum of a constant and two exponentials like that of Equation (5). The curved line fitting the data in Fig. 2 is a graph of Equation (3), and Equation (3) is of exactly the form described.

If the assumption is made that one of the two kinds of groups which react with formaldehyde irreversibly leads to the shift in electrophoretic mobility illustrated by the data of Fig. 1, and that the other of the two kinds of groups does not result in a shift in mobility, then it is necessary that the constant in one of the exponential terms of Equation (3) be the same as the constant in the exponential in Equation (2). Thus, the parameter, 0.04, in Equation (3) was determined from the data of Fig. 1 and not from those of Fig. 2.

It is thus evident that the results of these studies are consistent with the assumption that at least three kinds of amino groups are present on a tobacco mosaic virus particle. About 28% of the groups do not react irreversibly with formaldehyde; about 42% react irreversibly with a rate constant of about 0.14 but do not lead to a change in charge; and about 30% react irreversibly with a rate constant of 0.04 to produce a change in charge. The data of Fig. 2 are not sufficiently precise to fix these parameters with any great precision nor to rule out the possibility that more than three kinds of groups are present.

The data of Fig. 1 can be interpreted to mean that the maximum shift in mobility at *p*H 7 due to reaction of tobacco mosaic virus with formaldehyde is 0.82×10^{-5} sq. cm./volt sec. If this is divided by K, a value of 953 is obtained for the increase in net negative charge, or the decrease in positive charge per virus particle. If it is assumed that the change in charge involves free amino groups, and that $\alpha_1 = 1$ and $\alpha_2 = 0$, the shift of 953 charges would involve 953/3400 or 28% of the free amino groups. This figure agrees with the parameter, 30, in Equation (2) and constitutes evidence in favor of the reasonableness of the assumption that 30% of the amino groups react irreversibly with formaldehyde to produce a change in charge.

Kinetics of the Decrease in Infectivity.—The data of the present study and of previous studies indicate that the decrease in infectivity obtained when tobacco mosaic virus is treated with formaldehyde is a reaction of the first order. This means that the inactivation process, what-

ever it is, must be a single event phenomenon. Two possibilities exist for interpreting the decrease in infectivity. One is that the reaction is completely independent of any changes detected by chemical or electrophoretic means. The other possibility is that infectivity is lost when the first one of several particular amino groups on a virus particle has reacted irreversibly with formaldehyde. If several groups are capable of leading to inactivation, they must all be of the same sort with respect to rate of reaction with formaldehyde; otherwise, the first order law for inactivation could not be followed. If one assumes that m out of a total of ν groups of a particular sort on a virus particle can lead to loss in infectivity when irreversible reaction with formaldehyde takes place, then loss of infectivity would result when the first of these groups happened to react. Equation (9) shows that the reaction velocity constant for the loss of infectivity would be equal to m times the velocity constant for the reaction of the particular groups under study.

The reaction velocity constant for the destruction of infectivity at room temperature has been shown to be about 0.42 reciprocal hour. This is about ten times the rate constant for the change in mobility. Thus, if groups of the sort which result in shifts in mobility are responsible for the inactivation of the virus, there must be ten special groups of that sort on each virus particle. Similarly, since the rate of the reaction which leads to irreversible loss of free amino groups but not to change in charge is 0.14, there would have to be 0.42/0.14 or 3 special groups of this sort to account for the loss of infectivity.

Summary

The kinetics of the changes which take place when tobacco mosaic virus is treated with 2% formaldehyde at *p*H 7 and 30° were studied. Infectivity was found to decrease according to the law of a first order process with a rate constant of about 0.42 hour^{-1}. Electrophoretic mobility was found to increase and approach a maximum value as the time of treatment was extended indefinitely. The rate constant for this process was found to be 0.04 hour^{-1}. Free amino groups as determined by the ninhydrin color reaction were found to decrease according to a complex pattern. The results can be interpreted in terms of the assumption that 28% of the amino groups do not react irreversibly with formaldehyde; 42% react irreversibly at a rate of 0.14 reciprocal hour, and 30% react irreversibly at a rate of 0.04 reciprocal hour. These latter 30% can be assumed to be the same groups which cause shift in electrophoretic mobility. The loss of infectivity could be due either to some process entirely independent of the reactions indicated by the chemical and physical changes or to the first one of several particular amino groups of one sort reacting irreversibly with formaldehyde.

RECEIVED MAY 16, 1949

[CONTRIBUTION FROM THE RICHARDSON CHEMICAL LABORATORY, TULANE UNIVERSITY]

A New Synthesis of Tuberculostearic Acid[1a]

BY GUSTAV A. SCHMIDT[1b] AND DAVID A. SHIRLEY

Tuberculostearic acid or 10-methyloctadecanoic acid (compound V in Fig. 1) was isolated by Anderson and Chargaff[2] from the fatty envelope surrounding the tubercle bacillus and its structure later proved by Spielman[3] who prepared a synthetic sample. Recently Prout, Cason and Ingersoll[4] have reported preparation of the *dl*-form and the *d*- and *l*-enantiomorphs of 10-methyloctadecanoic acid, establishing that the naturally occurring isomer is the levorotatory form. The *dl*- and active forms have also been prepared by Ställberg-Stenhagen[5] by a still different method.

As a part of a study of derivatives of modified branched-chain fatty acids as potential antitubercular chemotherapeutic agents, we have undertaken the preparation of moderate amounts of tuberculostearic acid to be used in further synthetic work. We have developed a new method of synthesis of *dl*-tuberculostearic acid which appears to be an improvement over the one used by Spielman.[3] It is much shorter than the synthesis used by Prout, Cason and Ingersoll[4] and Ställberg-Stenhagen,[5] since these authors prepared the *d*- and *l*-forms which involved working with optically active intermediates and avoiding racemization in the transformations employed.

The steps in this synthesis are outlined in Fig. 1. Azelaic acid was converted to its half ethyl ester acid chloride and this was allowed to react with 2-decylzinc chloride (II), to give ethyl 9-keto-10-methyloctadecanoate (III). Reduction of the keto ester (III) by the Clemmensen method gave ethyl 10-methyloctadecanoate (IV) which was hydrolyzed to the corresponding acid (V). Purification of 10-methyloctadecanoic acid was effected by converting it to the amide (VI) followed by recrystallization of the amide and hydrolysis to the acid.

A distinctive feature of this synthesis is the use

(1a) Presented before the Organic Division, Atlantic City A. C. S. meeting, Sept. 21, 1949.

(1b) Frederick G. Cottrell, Research Fellow, 1948–1949.

(2) Anderson and Chargaff, *J. Biol. Chem.*, **85**, 77 (1929).

(3) Spielman, *ibid.*, **106**, 87 (1934).

(4) Prout, Cason and Ingersoll, THIS JOURNAL, **70**, 298 (1948).

(5) Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **26A**, No. 12 (1948), 28 pp.

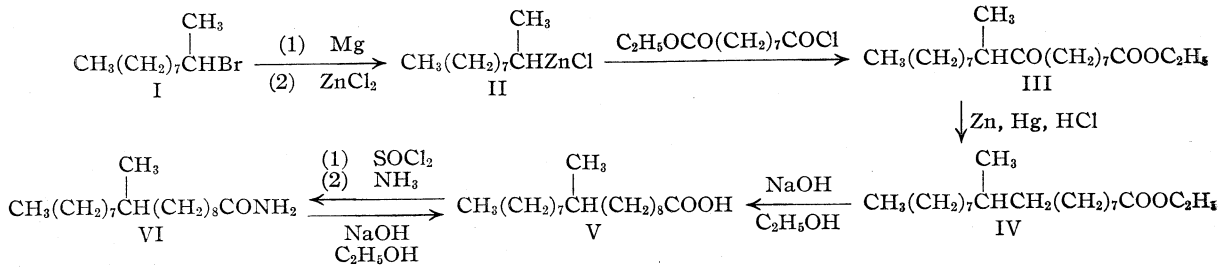


Fig. 1.—Diagram of method of synthesis of 10-methyloctadecanoic acid

of a secondary organometallic compound in its reaction with an acid chloride to form a ketone. The organocadmium compounds, usually found advantageous for ketone formation, are not satisfactory when secondary types are used.[6] The secondary organozinc compound used here allows formation of the ketone in 55% yield.

Experimental

2-Decanol.—Reaction of *n*-octylmagnesium bromide with acetaldehyde in customary fashion gave an 85% yield of 2-decanol, b. p. 123° (29 mm.), $n^{25}D$ 1.4326.

2-Bromodecane.—2-Decanol was converted to 2-bromodecane in essential accordance with the procedure of Hsueh and Marvel[7] except that the crude bromide was washed with cold concentrated sulfuric acid, then with water and dried and distilled. The yield of pure bromide was 88–92%. It boiled at 124–125° (30 mm.), $n^{25}D$ 1.4526.

Ethyl Hydrogen Azelate.—Pure azelaic acid and its diethyl ester were obtained from "Plastolein 9111," a commercial material reported to have the following composition of dicarboxylic acids; pimelic 4%, suberic 15%, azelaic 71% and undecandioic 10%.[8]

The mixed acids refluxed with excess ethanol, benzene and a small amount of sulfuric acid catalyst under conditions for continuous separation of the benzene, ethanol and water azeotrope allowed formation of the mixed diethyl esters in 96% yield. Diethyl azelate was separated from the mixed esters by two distillations through a fractionating column consisting of two 2 × 35-cm., helices packed, electrically heated sections on which was mounted a total condensation partial take-off head. Pure diethyl azelate obtained in 77% yield (based on the 71% azelaic acid present in the mixed starting acids) boiled at 140° (1 mm.),[9] $n^{25}D$ 1.4348. Saponification of diethyl azelate with alcoholic sodium hydroxide gave an essentially quantitative yield of azelaic acid, m. p. 105.5–106°, with no purification by recrystallization or other methods being necessary.

Diethyl azelate and azelaic acid were used for the preparation of the half ester, ethyl hydrogen azelate, in accordance with the procedure of Swann, Oehler and Buswell[10] for the preparation of ethyl hydrogen sebacate. The half ester was formed in 63% yield, b. p. 170° (1 mm.), m. p. 28–29°.[9]

ω-Carbethoxyoctanoyl Chloride.—Ethyl hydrogen azelate (224 g., 1.03 moles) was refluxed with excess thionyl chloride for one and one-half hours. Distillation gave the acid chloride in 84% yield, b. p. 155° (14 mm.). Ruzicka and Stoll[11] report this compound and give 155–158° at 15 mm. as its boiling point.

Anal. Calcd. for $C_{11}H_{19}ClO_3$: Cl, 15.1. Found: Cl, 15.0.

Ethyl 9-Keto-10-methyloctadecanoate (III).—The preparation of this ketone was carried out by reaction of 2-decylzinc chloride (II) with ω-carbethoxyoctanoyl chloride in essential accordance with the procedure used by Jones[12] for the synthesis of long-chain aliphatic ketoacids.

2-Decylmagnesium bromide (I) was prepared in customary manner from 280 g. (1.27 moles) of 2-bromodecane, 48 g. (2.0 g. atoms) of magnesium and 600 ml. of absolute ether. Titration of an aliquot with standard acid[13] showed an 80% yield of Grignard reagent. The solution of Grignard reagent was added to a solution of 136 g. (1.0 mole) of freshly fused anhydrous zinc chloride in 350 ml. of ether at such rate that gentle reflux was maintained. Reflux temperature was maintained for an additional one and one-half hours during which time the solvent was slowly distilled from the reaction mixture until the volume was approximately 600 ml. To the resulting mixture was added with stirring a solution of 170 g. (0.72 mole) of ω-carbethoxyoctanoyl chloride in 400 ml. of anhydrous benzene. After a three-hour reflux period, the mixture was treated with excess water containing a little hydrochloric acid and the organic layer separated and dried. The volatile organic material was removed by distillation until a head temperature of 150° (12 mm.) pressure was reached. It was found convenient at this point to treat the residue with ethanol under the esterification conditions described above until no more water was being removed from the system. In this way the ethyl hydrogen azelate (from unreacted acid chloride) present at this point was converted to its more volatile diethyl ester which increased the efficiency of its subsequent separation by distillation from the ethyl 9-keto-10-methyloctadecanoate. Distillation of the esterified material through the same column described above gave 78 g. of diethyl azelate boiling in the range 130–175° (95% boiled at 130°) at about 0.5 mm. pressure and 133 g. of ethyl 9-keto-10-methyloctadecanoate, b. p. 184–185° at about 0.5 mm., $n^{25}D$ 1.4470. The yield of ketoester was 55% based on the starting amount of ester acid chloride or 93% based on the acid chloride consumed.

9-Keto-10-methyloctadecanoic Acid.—Fifteen grams (0.044 mole) of ethyl 9-keto-10-methyloctadecanoate was refluxed for four hours with a solution of 20 g. of sodium hydroxide in 40 ml. of water and 60 ml. of ethanol. The alcohol was distilled off and the reaction mixture diluted to a volume of 500 ml. with water. The resulting solution was extracted with three portions of petroleum ether (b. p. 30–60°) and then acidified. The acid mixture was then extracted with petroleum ether and the combined extracts washed with dilute hydrochloric acid and then ten times with distilled water. The petroleum ether solution was dried and the solvent removed by distillation including a final heating period at 100° under a pressure of about 0.5 mm. to ensure complete removal of solvent. The residual light yellow oil (13 g. or 94% yield) was used for preparation of the semicarbazone described below. A small amount recrystallized three times from petroleum ether at −30° gave white platelets, m. p. 24–25°.

(6) Cason, *Chem. Revs.*, **40**, 15 (1947).

(7) Hsueh and Marvel, THIS JOURNAL, **50**, 855 (1928).

(8) We are indebted to Emery Industries, Inc., of Cincinnati for a generous supply of "Plastolein 9111" and for information on its composition.

(9) Fourneau and Sabetay, *Bull. soc. chim. France*, [4] **45**, 834 (1929).

(10) Swann, Oehler and Buswell, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 276.

(11) Ruzicka and Stoll, *Helv. Chim. Acta*, **10**, 691 (1927).

(12) Jones, THIS JOURNAL, **69**, 2350 (1947).

(13) Gilman, Wilkinson, Fishel and Meyers, *ibid.*, **45**, 150 (1923).

Anal. Calcd. for $C_{19}H_{36}O_3$: neut. equiv., 313. Found: neut. equiv., 313, 314.

A semicarbazone derivative[14] prepared in 90% yield melted at 86–86.4° after three recrystallizations from methanol, petroleum ether and acetone in that order.

Anal. Calcd. for $C_{20}H_{39}N_3O_3$: N, 11.37. Found: N, 11.42.

Ethyl 10-Methyloctadecanoate (IV).—Using the general method of Schneider and Spielman[15] for a Clemmensen reduction, 51 g. (0.15 mole) of ethyl 9-keto-10-methyloctadecanoate dissolved in 1 l. of absolute ethanol and mixed with 420 g. of amalgamated zinc[12] was saturated with dry hydrogen chloride. The mixture was refluxed for twenty-four hours, again saturated with hydrogen chloride, and then refluxed for a second twenty-four-hour period. After removal of the unreacted zinc, the volume of the solution was reduced to one-half and excess water added. The precipitated organic layer was removed by extraction with benzene and the benzene solution distilled to remove the volatile material. Distillation of the residue gave 40 g. (83%) of ester, b. p. 175–180° (2 mm.), $n^{25}D$ 1.4440. Prout, Cason and Ingersoll[4] report $n^{25}D$ 1.4447 for this compound.

Anal. Calcd. for $C_{21}H_{42}O_2$: sapon. equiv., 326. Found: sapon. equiv., 322.

10-Methyloctadecanoic Acid (V).—A mixture of 17.5 g. (0.054 mole) of ethyl 10-methyloctadecanoate, 25 ml. of 40% aqueous sodium hydroxide solution and 100 ml. of ethanol was refluxed for twelve hours and worked up as described above for the saponification of ethyl 9-keto-10-methyloctadecanoate. There was obtained 15 g. (94%) of the acid, $n^{25}D$ 1.4513 (the literature[3,4] records $n^{25}D$ 1.4512 for 10-methyloctadecanoic acid). In view of the fact that the product had a low melting point (around 5–10° compared with literature values of 20–21°[3] and 25.4–26.1°[4]), and it was difficult to recrystallize without large loss, it was decided to convert the acid to its more easily handled amide, purify the amide by recrystallization, and hydrolyze the pure amide to the acid.

10-Methyloctadecanamide (VI).—Twelve and five-tenths grams (0.042 mole) of the 10-methyloctadecanoic acid isolated above was converted to the acid chloride by refluxing with excess thionyl chloride and the excess thionyl chloride removed by distillation. The residual acid chloride dissolved in dioxane was added dropwise with rapid stirring to cold concentrated aqueous ammonia. The precipitated amide was recrystallized once from acetone and four times from petroleum ether (b. p. 30–60°) to give 8.8 g. (70%) of pure amide, m. p. 77–78° (the literature reports 76–77°[3] and 77.5–79.2°[4]).

Hydrolysis of 10-Methyloctadecanamide.—The 8.8 g. of amide prepared above was hydrolyzed by refluxing for twelve hours with 50 ml. of 10% alcoholic sodium hydroxide. The mixture was treated as described above under saponification of ethyl 9-keto-10-methyloctadecanoate to give an essentially quantitative yield of 10-methyl octadecanoic acid, m. p. 23.5–25.8° (cor.), b. p. 200–203° (1 mm.), $n^{25}D$ 1.4512.

Anal. Calcd. for $C_{19}H_{38}O_2$: neut. equiv., 299. Found: neut. equiv., 301, 303.

Table I summarizes the physical constants of 10-methyloctadecanoic acid and its derivatives found in this work in comparison with those obtained by Spielman[3] and by Prout, Cason and Ingersoll.[4]

TABLE I

PHYSICAL CONSTANTS OF 10-METHYLOCTADECANOIC ACID AND ITS DERIVATIVES

Physical constant	This work	Spielman[3]	Prout, Cason and Ingersoll[4]
Melting point of acid, °C.	23.5–25.8 (cor.)	20–21	25.4–26.1 (cor.)
Boiling point of acid, °C.	200–203 at 1 mm.	.....	.....
Index of refraction of acid $n^{25}D$	1.4512	1.4512	1.4512
Melting point of amide, °C.	77–78	76–77	77.5–79.2
Melting point of 2,4,6-tribromoanilide, °C.	93.5–94	93–94	93.4–93.9

Acknowledgment.—The authors wish to express appreciation to the Research Corporation of New York for a Frederick G. Cottrell grant which supported this work.

Summary

A new and improved method of synthesis of tuberculostearic acid (10-methyloctadecanoic acid) is reported.

NEW ORLEANS 15, LA. RECEIVED JUNE 6, 1949

(14) Shriner and Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 170.

(15) Schneider and Spielman, *J. Biol. Chem.*, **142**, 345 (1942).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

The Soluble Complex of Ferric Iron and 8-Hydroxyquinoline

BY E. B. SANDELL AND D. C. SPINDLER

In dilute mineral acid medium 8-hydroxyquinoline reacts with ferric ion to give a soluble green complex. A number of workers have made use of the formation of this green substance in the indirect colorimetric determination of magnesium by treating an acid solution of the magnesium hydroxyquinolate precipitate with a ferric salt. The present work deals with the composition of the green complex and its dissociation constant. The value of the dissociation constant is needed in calculating the solubility product of ferric hydroxyquinolate as well as in treating the problem of the extractability of ferric hydroxyquinolate by chloroform from aqueous solutions at various acidities.

The composition of the complex was established by applying the familiar method of continuous variations.[1] Solutions of ferric perchlorate and 8-hydroxyquinoline in perchloric acid were mixed in various ratios, the sum of molar concentrations of the two reactants being kept constant at 1.19×10^{-3} *M*. The transmittancy of the mixtures was determined at 645 mμ, the approximate wave length of maximum absorption by the iron–hydroxyquinoline complex; at this wave length, absorption by hydroxyquinolinium ion (in which form hydroxyquinoline is chiefly present at the acidities used) and ferric ion is negligibly small, at least in the concentrations employed. Transmit-

(1) P. Job, *Ann. chim.*, **9**, 113 (1928); **11**, 97 (1936).

tancy measurements were made with a Coleman spectrophotometer, Model 10, at a band width of 5 mμ. The mixtures were prepared at various *p*H's, ranging from 1.1 to 2.6, and a glass electrode was used to obtain the *p*H.

The results are shown in Fig. 1. At *p*H 1.9 and below, the curves exhibit a maximum at the value 0.5 for the ratio $[Fe^{+++}]/([Fe^{+++}] + [HOx \cdot H^+])$ and are symmetrical. At *p*H 2.1 to 2.6, the ratio for the maximum color intensity is shifted slightly to the left and lies between 0.45 and 0.5. It can be calculated that the solubility product of ferric 8-hydroxyquinolate is exceeded in solutions of higher *p*H in which the maximum is displaced from 0.5. These experiments demonstrate that in the more acidic solutions the colored product is an equimolecular compound of iron and 8-hydroxyquinoline and is therefore the ion $FeOx^{++}$.

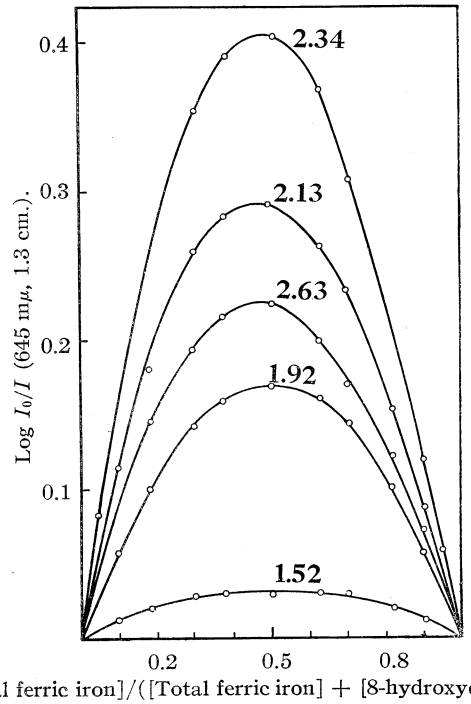


Fig. 1.—Continuous variation method applied to mixtures of ferric ion and 8-hydroxyquinoline; sum of concentrations of components 1.19 × 10^{-3} *M* except in *p*H 2.63 series where concentration is one-half of others. *p*H values are given on curves.

The same species is no doubt predominantly formed at higher *p*H's, but here the incipient formation of slightly soluble $FeOx_3$ is an obscuring factor. Even if the departure of the maximum color intensity from the ratio 0.5 is interpreted to mean formation of some $FeOx_2^+$, the amount of the latter is small compared to that of $FeOx^{++}$ if it can be assumed that the extinction coefficients of the two complex ions are similar in magnitude. Transmission curves of solutions in which ferric ion was present in excess, on the one hand, and 8-hydroxyquinoline in excess on the other, showed no significant difference in the range 450–700 mμ. In aqueous medium $FeOx_2^+$ cannot be formed in appreciable concentration because the increase in the hydroxyquinolate ion (Ox^-) concentration by addition of more 8-hydroxyquinoline or by raising the *p*H, required to shift the equilibrium toward $FeOx_2^+$, precipitates ferric hydroxyquinolate. In an alcoholic medium it may be expected that $FeOx_2^+$ can be formed in appreciable amount.

The maximum color intensity of acidic mixtures of ferric ion and 8-hydroxyquinoline is attained very rapidly, constancy being reached before the transmittancy of the solution can be measured. The color is moderately stable, but decreases in strength on long standing.

Dissociation Constant of $FeOx^{++}$

The extinctions of a series of mixtures, at three different *p*H values, of ferric perchlorate and 8-hydroxyquinoline, in which the concentration of the latter was constant and the concentration of excess iron was varied, were measured at 645 mμ and 25° (Fig. 2). The value of the extinction coefficient of $FeOx^{++}$ and of the dissociation constant

$$a_{Fe^{+++}} a_{Ox^-} / a_{FeOx^{++}} = K_1$$

were obtained from the relations indicated below. It is not feasible to obtain the extinction coefficient of the complex directly by adding a large excess of ferric ion.

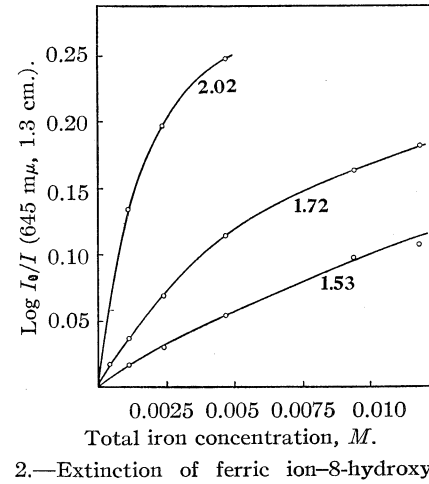


Fig. 2.—Extinction of ferric ion–8-hydroxyquinoline solutions with iron in variable excess; oxine concentration 2.38 × 10^{-4} *M*. *p*H values are given on curves.

The ionic strength of the mixtures was maintained constant at 0.073 by addition of sodium perchlorate. Buffer solutions were not used in the adjustment of the acidity because of the formation of complexes between ferric iron and anions. These experiments had to be carried out in a restricted range of acidity. If the solution is not sufficiently acidic, the hydrolysis of ferric ion becomes too extensive and introduces uncertainties; if the solution is too acidic, insufficient $FeOx^{++}$ is formed to allow measurement.

The following relations have been used to obtain the values of the constants mentioned

$E = \log I_0/I = \epsilon l[\mathrm{FeOx^{++}}]$ (1)

$K_1 = f_3[\mathrm{Fe^{+++}}]f_1[\mathrm{Ox^-}]/f_2\ [\mathrm{FeOx^{++}}]$, where f = activity coefficient, with valence of ion indicated by subscript (2)

Let b = total 8-hydroxyquinoline concentration

$$= [\mathrm{HOx{\cdot}H^+}] + [\mathrm{HOx}] + [\mathrm{Ox^-}] + [\mathrm{FeOx^{++}}]$$

where HOx represents 8 - hydroxyquinoline. When the pH is low, as in the present experiments, the concentration of undissociated 8-hydroxyquinoline and of hydroxyquinolate ion is small and can be neglected, and therefore

$$b = [\mathrm{HOx{\cdot}H^+}] + [\mathrm{FeOx^{++}}]$$

Now

$$[\mathrm{HOx{\cdot}H^+}] = \frac{(a\mathrm{H^+})^2[\mathrm{Ox^-}]}{K_{\mathrm{Ox}}}$$

where

$$K_{\mathrm{Ox}} = K_{1\mathrm{Ox}}K_{2\mathrm{Ox}} = \frac{a\mathrm{H^+}a\mathrm{HOx}}{a\mathrm{HOx{\cdot}H^+}} \times \frac{a\mathrm{H^+}a\mathrm{Ox^-}}{a\mathrm{HOx}} = \frac{(a\mathrm{H^+})^2a\mathrm{Ox^-}}{a\mathrm{HOx{\cdot}H^+}} = \frac{(a\mathrm{H^+})^2[\mathrm{Ox^-}]}{[\mathrm{HOx{\cdot}H^+}]} = 3.4 \times 10^{-16}$$

The value 3.4×10^{-16} for K_{Ox} is based on the values 1.2×10^{-5} and 2.86×10^{-11}, respectively, for $K_{1\mathrm{Ox}}$ and $K_{2\mathrm{Ox}}$ at 25°.[2]

$$\therefore [\mathrm{FeOx^{++}}] = b - [(a\mathrm{H^+})^2[\mathrm{Ox^-}]/K_{\mathrm{ox}}] \quad (3)$$

From (2) and (3)

$$[\mathrm{Ox^-}] = \frac{K_1f_2[\mathrm{FeOx^{++}}]}{f_1f_3[\mathrm{Fe^{+++}}]} = \frac{f_2K_1K_{\mathrm{ox}}b}{f_1f_3K_{\mathrm{ox}}[\mathrm{Fe^{+++}}] + f_2K_1(a\mathrm{H^+})^2} \quad (4)$$

From (1), (3) and (4)

$$E = \frac{\epsilon f_1f_3K_{\mathrm{ox}}[\mathrm{Fe^{+++}}]b}{f_1f_3K_{\mathrm{ox}}[\mathrm{Fe^{+++}}] + f_2K_1(a\mathrm{H^+})^2} \text{ when } l = 1 \quad (5)$$

Let C = sum of molar concentrations of ferric iron in all its forms in the solution

$$= [\mathrm{Fe^{+++}}] + [\mathrm{FeOH^{++}}] + [\mathrm{FeOx^{++}}]$$

Taking $a\mathrm{FeOH^{++}}a\mathrm{H^+}/a\mathrm{Fe^{+++}} = 6 \times 10^{-3}$ (Bray and Hershey[3]) we find

$$C = [\mathrm{Fe^{+++}}] + \frac{0.006f_3[\mathrm{Fe^{+++}}]}{f_2(a\mathrm{H^+})} + \frac{E}{\epsilon}$$

$$\therefore [\mathrm{Fe^{+++}}] = \frac{C - E/\epsilon}{Q}, \text{ where } Q = 1 + \frac{0.006f_3}{f_2(a\mathrm{H^+})} \quad (6)$$

Substituting (6) into (5)

$$E = \frac{\epsilon f_1f_3K_{\mathrm{ox}}b(C - E/\epsilon)}{f_1f_3K_{\mathrm{ox}}(C - E/\epsilon) + f_2K_1(a\mathrm{H^+})^2Q}$$

$$\therefore K_1 = \frac{(C - E/\epsilon)(\epsilon f_1f_3K_{\mathrm{ox}}b - Ef_1f_3K_{\mathrm{ox}})}{QEf_2(a\mathrm{H^+})^2}$$

(2) The value for K_2 is the converted concentration constant of K. G. Stone and L. Friedman, THIS JOURNAL, **69**, 209 (1947). The values for K_1 available when this work was begun were not considered reliable, and this constant was therefore determined by measuring the pH of mixtures of 8-hydroxyquinoline and hydrochloric acid. The value 1.2×10^{-5} was obtained. In the meantime, J. P. Phillips and L. L. Merritt, Jr., THIS JOURNAL, **70**, 410 (1948), reported the same value for K_1; their value was obtained spectrophotometrically.

(3) W. C. Bray and A. V. Hershey, THIS JOURNAL, **56**, 1889 (1934).

The values of K_1 and ϵ were obtained by fitting the equation to the curves. The following values were used for the activity coefficients[4]: $f_1 = 0.81$, $f_2 = 0.42$, $f_3 = 0.20$.

The following values for ϵ and K_1 were obtained at three different acidities

pH	ϵ	K_1
1.53	1120	3.2×10^{-15}
1.70	1020	3.2×10^{-15}
2.02	1120	2.0×10^{-15}

There appears to be no reason for giving greater weight to any particular set. The rounded averages are $\epsilon = 1090$ (645 mμ) and $K_1 = 3 \times 10^{-15}$. These figures cannot be regarded as very accurate, partly because of uncertainties in activity coefficients and the hydrolysis constant of ferric ion.

Solubility Product of Ferric Hydroxyquinolate

The approximate value of the solubility product of ferric hydroxyquinolate (needed to determine whether mixtures of ferric ion and 8-hydroxyquinoline were saturated in the experiments described above) was obtained by shaking dilute perchloric acid solutions with an excess of ferric 8-hydroxyquinolate and determining the amount of iron in solution. In some of these experiments, 8-hydroxyquinoline was added to the mixtures. The experimental work will not be described in detail, since the values obtained are considered preliminary, although adequate for the present purpose.

Difficulties were encountered in reaching equilibrium and the solid phase seemed to undergo aging which resulted in a decrease in solubility on long shaking. The values obtained varied from 1×10^{-48} to 6×10^{-47}. Account was taken of hydrolysis of ferric ion and the formation of $\mathrm{FeOx^{++}}$. The figure 10^{-47} will be taken as an average value for $a\mathrm{Fe^{+++}}(a\mathrm{Ox^-})^3$ in aqueous solution at 25°. Even though approximate, this value should be of use in analytical calculations, especially since the solubility products of the metal hydroxyquinolates vary over a wide range. The value of the solubility product of ferric hydroxyquinolate has not previously been reported. It is of interest that the solubility product of aluminum hydroxyquinolate has been reported as much larger (10^{-32}) than that of iron.[5]

Summary

1. 8-Hydroxyquinoline reacts with ferric ion in dilute mineral acid medium to give the green ion $\mathrm{FeOx^{++}}$.

2. The dissociation constant of this complex ion is $a\mathrm{Fe^{+++}}a\mathrm{Ox^-}/a\mathrm{FeOx^{++}} = 3 \times 10^{-15}$.

3. The approximate value of the solubility product of ferric hydroxyquinolate is 10^{-47}.

MINNEAPOLIS, MINN. RECEIVED APRIL 11, 1949

(4) Interpolated from J. Kielland, *ibid.*, **59**, 1675 (1937).

(5) S. Lacroix, *Anal. Chim. Acta*, **1**, 269 (1947).

[CONTRIBUTION NO. 1303 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

A Spectrophotometric Investigation of the Interaction between Antimony(III) and (V)[1a,b,c] in Hydrochloric Acid Solutions

BY JAMES E. WHITNEY[2] AND NORMAN DAVIDSON

Introduction.—The investigations described here are concerned with the nature of the abnormally deep and intense coloration that exists in some systems containing an element in two different oxidation states or in a "mixed" oxidation state. Hofman and Resencheck[3] first emphasized the general occurrence of this phenomenon in connection with studies of the ferri ferrocyanides. Earlier, Werner[4] had expressed his feeling that there was an analogy between the intense color of quinhydrone and the intense colors of various mixed compounds of platinum (II) and (IV), with cyanide, chloride, bromide, oxalate and ammonia as coördinating groups. Many authors have commented on the significance of this phenomenon for the theory of the color of inorganic compounds.[5,6,7,8,9,10]

The color of an ion is of course in general a function of its environment. However, the coloration referred to above that exists in some systems that can be said to contain an element in two different oxidation states is so much more intense than the color of either component in most other systems that it deserves recognition as a special phenomenon. We shall use the term "interaction absorption" for this effect. For purposes of illustration, we mention a few of the systems which exhibit this effect. In solution in hydrochloric acid, mixtures of the ions of copper(I) and (II),[11] of antimony(III) and (V),[12] of tin(II) and (IV),[13] and of iron(II) and (III),[11] are all much more intensely colored than are the components at the same concentration. In the solid state, the ferri ferrocyanides appear to be much more strongly colored than the brown ferri ferricyanides or the colorless ferro ferrocyanides. A mixed precipitate of iron(II) and iron(III) hydroxides is almost black, compared to the red-brown color of ferric hydroxide; similarly a mixed precipitate of cerium(III) and cerium(IV) hydroxides is blue, compared to the slight yellow color of hydrated ceric oxide. The bluish-black Cs_2SbCl_6[14] and black Rb_2SbCl_6[12] (formally compounds of antimony(IV)) are to be compared with the light yellow-green $RbSbCl_6$[15] and the colorless complex chlorides of antimony(III) with the alkali metal chlorides.[16] The black substance, cesium aurous auric chloride,[17,18] is similarly more colored than most of the complex chlorides of aurous or auric gold. The isomorphous salt $Cs_2AgAuCl_6$ which is believed to contain argentous silver and auric chloride is also jet black. This fact is included to emphasize that there are conditions other than the presence of an element in several oxidation states which can produce unusually intense coloration.

It is possible to continuously vary the composition of a solution, but seldom possible to do this for a solid. Furthermore it is much easier to carry out accurate spectrophotometric measurements for solutions than for solids. We have therefore chosen to study the effect of some of the concentration variables on the interaction absorption of hydrochloric acid solutions of antimony(III) and antimony(V). Exploratory measurements of the absorption spectra of mixed tin(II) and (IV) solutions, and of arsenic(III) and (V) solutions, were also made.

Experimental.—Absorption spectra of solutions were measured using a Beckman Model DU quartz spectrophotometer. The absorption cells were the usual rectangular right prism type of quartz cells with a 10-mm. light path. Quartz spacers were available to reduce the light path to one millimeter. In order to protect the spectrophotometer from acid vapors, the loosely fitting Beckman cell covers could be sealed to the cells with a molten one to one mixture of beeswax and rosin.[19]

The optical density, D, reported here is equal to $\log_{10} I_0/I$. Extinction coefficients are defined by $\epsilon = D/cl$, where l is the light path in centimeters and c is the concentration of the absorbing solution in volume molal units.

The antimony solutions were prepared by dissolving approximately known quantities of reagent grade antimony trichloride or pentachloride in measured quantities of concentrated hydrochloric acid of known titer to give solutions of known final volume.[20]

(1) (a) For a preliminary report of this work see THIS JOURNAL, **69**, 2076 (1947); (b) presented in part at the 115th meeting of the American Chemical Society, San Francisco, Calif., April, 1949; (c) a more detailed account of these investigations is contained in the thesis by James E. Whitney, submitted in partial fulfillment of the requirements for the degree of Master of Science at the California Institute of Technology, June, 1948.

(2) Present address: Kellex Corporation, New York 7, N. Y.

(3) Hofman and Resencheck, *Ann.*, **342**, 372 (1905).

(4) Werner, *Z. anorg. Chem.*, **12**, 53 (1896).

(5) Hoffman and Höschsele, *Ber.*, **48**, 20 (1915).

(6) Wells, *Am. J. Sci.*, **3**, 417 (1922).

(7) Biltz, *Z. anorg. allgem. Chem.*, **127**, 169 (1923).

(8) Stieglitz, *Proc. Nat. Acad. Sci.*, **9**, 309 (1923).

(9) Zintl and Rauch, *Ber.*, **57**, 1739 (1924).

(10) Pauling, *Chem. Eng. News*, **25**, 2970 (1947).

(11) We are unable to quote references for the original discoveries of interaction absorption in these cases. Further work on these systems has been carried out in these Laboratories. Doehlmann and Fromherz (*Z. physik. Chem.*, **A171**, 377 (1934)) have published absorption spectra of mixed Cu^{I} and Cu^{II} halide solutions.

(12) Weinland and Schmid, *Ber.*, **38**, 1080 (1905).

(13) Present research.

(14) Setterberg, *Oefversigt. Kgl. Vetenskapsakad. Förhandl.*, **6**, 22 (1882).

(15) Weinland and Feigl, *Ber.*, **36**, 244 (1903).

(16) Gmelin–Kraut, *Handbuch der anorg. Chem.*, 7th Edition, Vol. III, part 2, p. 743.

(17) Wells, *Am. J. Sci.*, **3**, 315 (1922).

(18) Elliott and Pauling, THIS JOURNAL, **60**, 1846 (1938).

(19) Strong, "Procedures in Experimental Physics," Prentice-Hall, Inc., New York, N. Y., 1938, p. 554.

(20) The concentrations quoted herein are in volume formal (*F*) or volume molal (*M*) units.

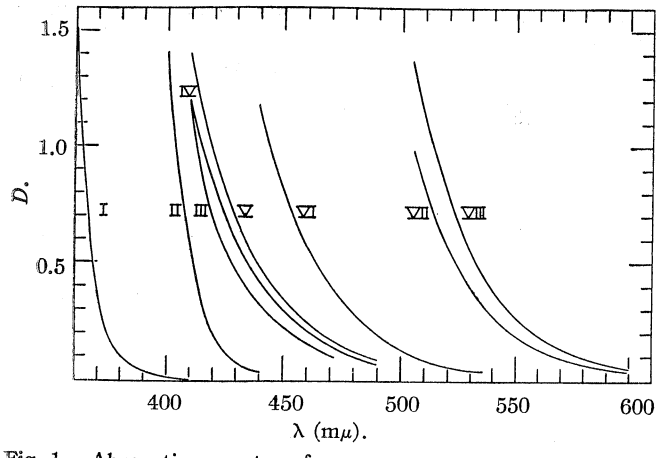


Fig. 1.—Absorption spectra of:

	I	II	III	IV	V	VI	VII	VIII
Sb(III)	0.30	0	0.068	0.22	0.16	0.03	1.17	0.745
Sb(V)	0	0.28	0.23	0.087	0.14	1.41	0.30	0.725

I–V, 11.3 *F* HCl; VI–VIII, 10.3 *F* HCl.

Aliquots (*ca.* 0.002 *F* in antimony) of the stock solutions were analyzed for antimony by a coulometric titration of antimony(III) (by means of electrolytically generated bromine).[21] Antimony(V) was determined after reduction with sulfur dioxide. Excess sulfur dioxide was removed from the solution by boiling.

For the preliminary measurements reported here, solutions of Sn(II) and Sn(IV) were obtained by dissolving reagent grade $SnCl_2 \cdot 2H_2O$ and $SnCl_4 \cdot 5H_2O$ in concentrated hydrochloric acid. Arsenic solutions were made by dissolving "primary standard" arsenious oxide, As_2O_3, in concentrated hydrochloric acid. The formal concentration of the hydrochloric acid, calculated on the assumption that the arsenious oxide was converted to the trichloride, was adjusted by the addition of weighed amounts of dry hydrogen chloride. The arsenic(V) solution was obtained from the arsenic(III) solution by oxidation with chlorine.

Spectrophotometric Results for Antimony Solutions in Concentrated Hydrochloric Acid.—Figure 1 illustrates the general nature of interaction absorption for antimony solutions in concentrated hydrochloric acid. Curves I and II are for *ca.* 0.3 *F* solutions of antimony(III) and antimony(V), respectively; curves III–V are for mixtures of these two solutions. Pure antimony(III) absorbs in the near ultraviolet and appears colorless to the eye. Antimony(V) solutions absorb on the fringe of the visible region and are a pale yellow in color. The 1:1 mixture of 0.3 *F* solutions (Curve V) is a medium yellow, and more strongly absorbing than the other mixtures for this constant total concentration. Curves VI–VIII are for antimony solutions at a total formality of 1.5. The color of the 1:1 mixture is a deep orange-brown. Comparison of Curves V and VIII reveals that for 1:1 mixtures a fivefold increase in the concentration of antimony causes a much greater increase in D at any wave length.

We define D_i, the optical density of interaction absorption, by the equation

$$D_i(\lambda, C_{III}, C_V) = D(\lambda, C_{III}, C_V) - D(\lambda, C_{III}) - D(\lambda, C_V) \quad (1)$$

In this relation, $D(\lambda, C_{III}, C_V)$ is the observed optical density (corrected to 1.00-cm. path length) of the solution containing the two oxidation states at concentrations C_{III} and C_V; $D(\lambda, C_{III})$ and $D(\lambda, C_V)$ are the absorptions due to the pure components at the same concentrations, C_{III} and C_V, in a solution of hydrochloric acid of the same concentration as the mixture.

We have found that D_i, the optical density of interaction absorption, in solutions of antimony(III) and (V) in concentrated hydrochloric acid is proportional to the product of the concentrations of the antimony(III) and (V)

$$D_i = k_i(\lambda) C_{III} C_V \quad (2)$$

In Fig. 2 it is shown that when D_i for a fixed wave length is plotted as a function of $C_{III}C_V$, a straight line going through the origin is obtained. From a survey of all the data obtained, it appeared that the values of $k_i(\lambda)$ obtained in this way are constant to better than 10% for variations of the $C_{III}C_V$ product of by a factor of 10 or more. The averaged values of $k_i(\lambda)$ obtained from all the data are plotted in Fig. 3; in obtaining these data, the $C_{III}C_V$ factor has been varied from 0.5 to 0.01. The interpretation of the result expressed by eq. (2) will be discussed in a subsequent section.

One qualitative observation that is of importance for this subsequent discussion is that when a strongly colored mixed solution of antimony(III) and (V) in concentrated hydrochloric acid is cooled to −80° it remains liquid and there is no change perceptible to the eye in the color of the system.

The extinction coefficients of antimony(V) by itself in concentrated hydrochloric acid are independent of concentration—that is, in contrast to the marked optical interaction between antimony(III) and (V) molecules, there is no interaction between antimony(V) molecules. Figure 4 is a logarithmic plot of the extinction coefficients of antimony(V) in concentrated hydrochloric acid The data in the wave-length range 380–440 mμ were obtained with 0.1 and 1.0 *F* Sb(V) solutions using 1 and 10-mm. path lengths and the observed extinction coefficients were constant to ±3%. The optical densities of 0.3 and 0.5 *F* antimony(III) solutions were also observed, and these indicate that this species also obeys Beer's law. The extinction coefficients for antimony(III) are also plotted in Fig. 4.

As reported subsequently, antimony(V) solutions in 3.5 *F* hydrochloric acid are colorless; we have examined the hypothesis that the yellow color of antimony(V) in concentrated hydrochloric acid is really interaction absorption due to the formation of some antimony(III) by the reaction

$$Sb(V) + 2Cl^- \longrightarrow Sb(III) + Cl_2 \quad (3)$$

(21) Brown and Swift, THIS JOURNAL, **71**, 2717, 2719 (1949); *cf.* Myers and Swift, *ibid.*, **70**, 1047 (1948).

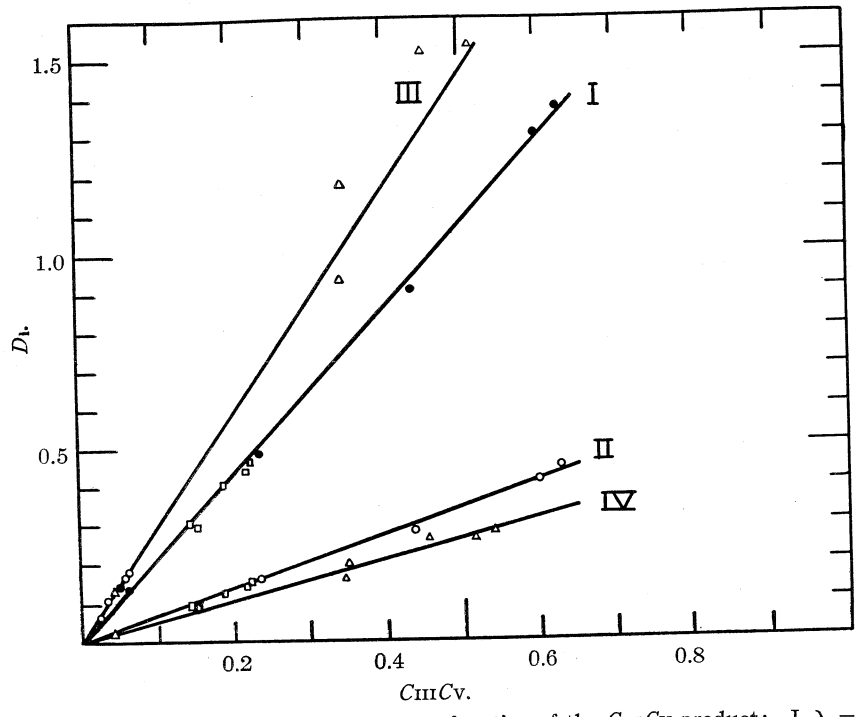


Fig. 2.—Interaction absorption, D_i, as a function of the $C_{III}C_V$ product: I, λ = 440 mμ, abscissa, 10 $C_{III}C_V$; □, total Sb = 0.3 *F*, 11.3 *F* HCl; ●, total Sb = 0.5 *F*, 10.0 *F* HCl. II, λ = 475 mμ, abscissa, 10 $C_{III}C_V$; □, total Sb = 0.3 *F*, 11.3 *F* HCl; ○, total Sb = 0.5 *F*, 10.0 *F* HCl. III, λ = 500 mμ, abscissa, $C_{III}C_V$; ○, total Sb = 0.5 *F*, 10.0 *F* HCl; △, total Sb = 1.5 *F*, 10.3 *F* HCl. IV, λ = 550 mμ, abscissa, $C_{III}C_V$; △, total Sb = 1.5 *F*, 10.3 *F* HCl.

If this were the case, the effect of the addition of chlorine would be to reverse (3), decreasing the concentration of antimony(III) and decreasing the color. Figure 5 shows that the spectrum of a 0.3 *F* antimony(V) solution saturated with chlorine is the sum of the absorption spectra of the chlorine and the antimony(V). We conclude that reaction (3) is not the cause of the color of antimony(V) in concentrated hydrochloric acid; this color is characteristic of an antimony-(V)-containing ion.

Spectrophotometric Results for Antimony Solutions in 3.5 *F* Hydrochloric Acid.—As shown in Fig. 4, the extinction coefficients of antimony(III) in 3.5 *F* hydrochloric acid are independent of the antimony concentration and the same as those observed for antimony(III) in concentrated hydrochloric acid.

The extinction coefficients of antimony(V) in 3.5 *F* hydrochloric acid are dependent on a large number of variables—the time after preparation or dilution of the solution, the concentration of the antimony(V), and the presence of other ions in the solution.

We will first present the results for antimony(V) solutions that have stood long enough so that their properties are no longer a function of time. In Fig. 6, the apparent extinction coefficients of a series of such solutions are plotted as a function of the antimony concentration. For antimony concentrations greater than 0.3 *F*, the data fit an equation of the type

$$\epsilon(\lambda) = a(\lambda)c^n \qquad (4)$$

where n has values slightly greater than 2 for the wave lengths 330, 340 and 350 mμ.

As illustrated in Fig. 6 and Table I, the extinction coefficients of antimony(V) at a concentration of 0.1–0.2 *F* are not independent of concentration but they do not change so violently with concentration as is the case at the higher concentrations.

In the same table there are presented a series of data which illustrate the effect of added ammonium perchlorate, perchloric acid and ammonium chloride. It is seen that ammonium chloride has a more marked effect on the extinction coefficients of the antimony(V) than do ammonium perchlorate or perchloric acid.

The variable extinction coefficients of antimony(V) in 3.5 *F* hydrochloric acid as a function of antimony concentration or of chloride concentration show that more than one kind of antimony(V) complex ion with water, hydroxide and chloride exists in appreciable concentration in this medium. The equilibria among the different kinds of antimony ions are established slowly.

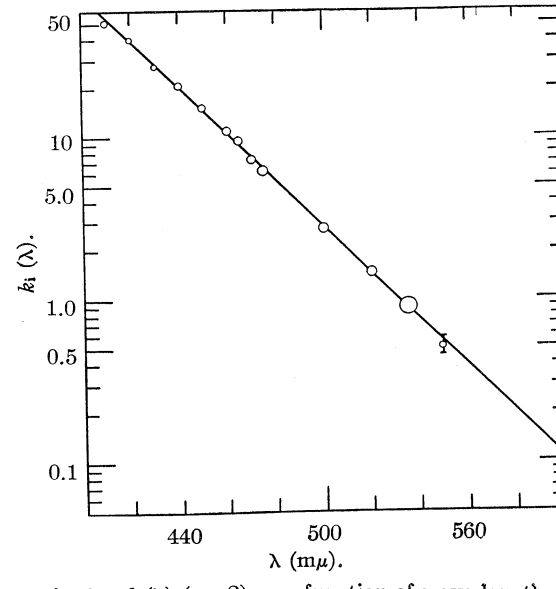


Fig. 3.—$k_i(\lambda)$ (eq. 2) as a function of wave length.

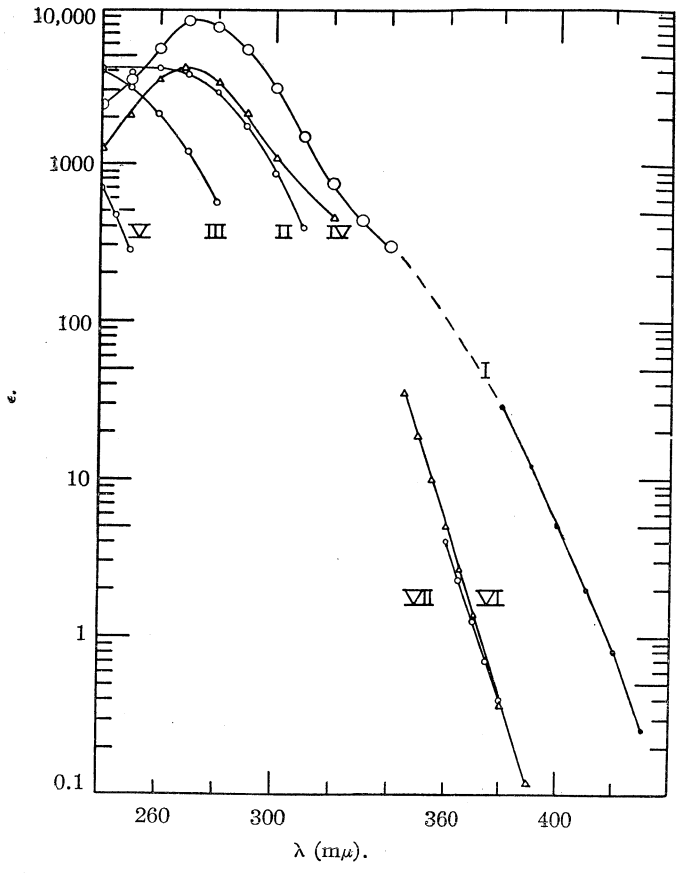


Fig. 4.—The extinction coefficients of Sb(III) and Sb(V) in various concentrations of HCl. I, Sb(V) in concentrated HCl.[a] II, 1.47×10^{-4} *F* Sb(V) in 6 *F* HCl immediately on dilution from 1.5 *F* Sb(V) in concentrated HCl. III, solution of curve II, 4 days after dilution. IV, 1.47×10^{-4} *F* Sb(V) in 3.5 *F* HCl, 3 hours after dilution from 1.5 *F* Sb(V) in concentrated HCl. V, solution of curve IV, 4 days after dilution. VI, Sb(III) in 11 *F* HCl.[b] VII, Sb(III) in 3.5 *F* HCl.[c]

[a] ○, 1.47×10^{-4} *F* Sb(V) in 11.6 *F* HCl; ●, the data were obtained for 0.10 to 1.0 *F* Sb(V) solutions in 10.5 *F* HCl, and agreed to ±3%.
[b] Data for 0.30 and 0.50 *F* Sb(III) solutions agreed to 4%.
[c] Data for 0.30 and 0.90 *F* Sb(III) solutions agreed to 10%.

When a concentrated antimony(V) solution (*ca.* 1.5 *F*) in concentrated hydrochloric acid is diluted to become a 0.5 *F* antimony solution in 3.5 *F* hydrochloric acid, the pale yellow color that is characteristic of the antimony(V) in concentrated acid slowly fades and it requires over five hours for the color to disappear completely. In Fig. 4 Curves II–V show a similar phenomenon for the dilution of antimony(V) solutions in concentrated hydrochloric acid to give *ca.* 10^{-4} *F* Sb(V) solutions in 6 and 3.5 *F* HCl. When a concentrated (1.0 *F*) antimony(V) solution in 3.5 hydrochloric acid is diluted with 3.5 *F* hydrochloric acid to an antimony formality of 0.3, the extinction coefficients observed shortly after dilution are intermediate between those of 1.0 *F* and 0.3 *F* antimony (Fig. 6). After a time of sixteen hours equilibrium apparently has been reached. We have not attempted to follow the behavior with time of these systems more closely.

Mixed solutions of antimony(V) and antimony(III) in 3.5 *F* hydrochloric acid that have stood for a while do not show the pronounced interaction absorption that occurs in concentrated acid. Table II lists some optical densities for a mixture containing 0.4 *F* antimony(V) and (III). These values are somewhat (but not spectacularly) greater than the sums of the optical densities of separate 0.4 *F* antimony(V) and (III) solutions. However, the extinction coefficients of antimony(V) are a function of the antimony(V) concentration, due perhaps to polymerization, to ionic strength effects, or to chloride supplied by hydrolysis of antimony pentachloride. In Table II, the special interaction between antimony(V) and (III) in 3.5 hydrochloric acid has been evaluated by assuming that the extinction coefficients of 0.4 *F* antimony(V) in the presence of 0.4 *F* antimony(III) are the same as the extinction coefficients of a 0.8 *F* antimony(V) solution. The resulting D_i's are quite small. We may therefore conclude that there may be weak "interaction absorption" of mixtures of antimony(V) and (III) in 3.5 *F* hydrochloric acid, but that this is of the same order of magnitude as the effect of other perturbations, such as ionic strength, added chloride, or other antimony(V)-containing molecules, on the absorption spectrum of antimony(V).

TABLE I

THE EXTINCTION COEFFICIENTS OF 0.1–0.2 *F* Sb(V) IN 3.5 *F* HCl IN THE PRESENCE OF VARIOUS OTHER IONS

λ, mμ	0.2 *F* Sb(V)	0.1 *F* Sb(V) 0.65 *F* NH_4Cl	0.1 *F* Sb(V) 0.5 *F* $HClO_4$	0.1 *F* Sb(V) 0.5 *F* NH_4ClO_4	0.1 *F* Sb(V)
280		109	95	88	77
290	54	53	46	43	36
300	23.6	24.2	19.8	20.2	15.9
310		10.8	8.0	9.8	4.45
320	3.45				2.3
330	1.36				1.12

TABLE II

THE ABSORPTION SPECTRUM OF A MIXED Sb(III) AND Sb(V) SOLUTION IN 3.5 *F* HCl

λ, mμ	D(III + V) / 0.4 *F* Sb(III) 0.4 *F* Sb(V)	D(III) 0.4 *F* Sb(III)	D(V)[a]	D_i[b]
370	1.02	0.49	0.57	−0.05
375	0.66	.28	.37	+ .01
380	.45	.16	.24	+ .05
390	.228	.072	.099	+ .057
400	.133	.040	.045	+ .048

[a] D(V) are the calculated optical densities for 0.4 *F* Sb(V) using the extinction coefficients observed for 0.8 *F* Sb(V). [b] $D_i = D(\text{III} + \text{V}) - D(\text{III}) - D(\text{V})$.

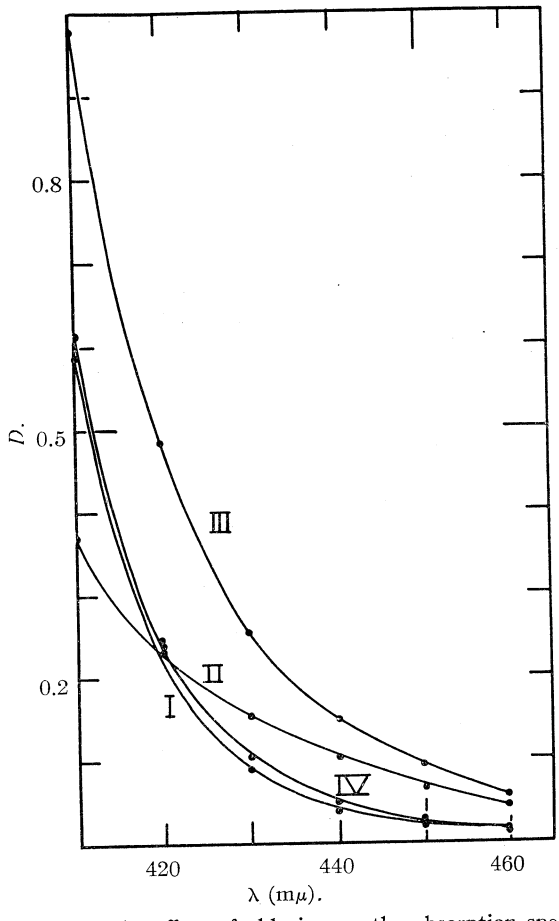


Fig. 5.—The effect of chlorine on the absorption spectrum of Sb(V) in concentrated HCl. I, 0.28 *F* Sb(V) in 11 *F* HCl; II, 11 *F* HCl saturated with Cl_2; III, 0.28 *F* Sb(V) in 11 *F* HCl, saturated with Cl_2; IV, III–II.

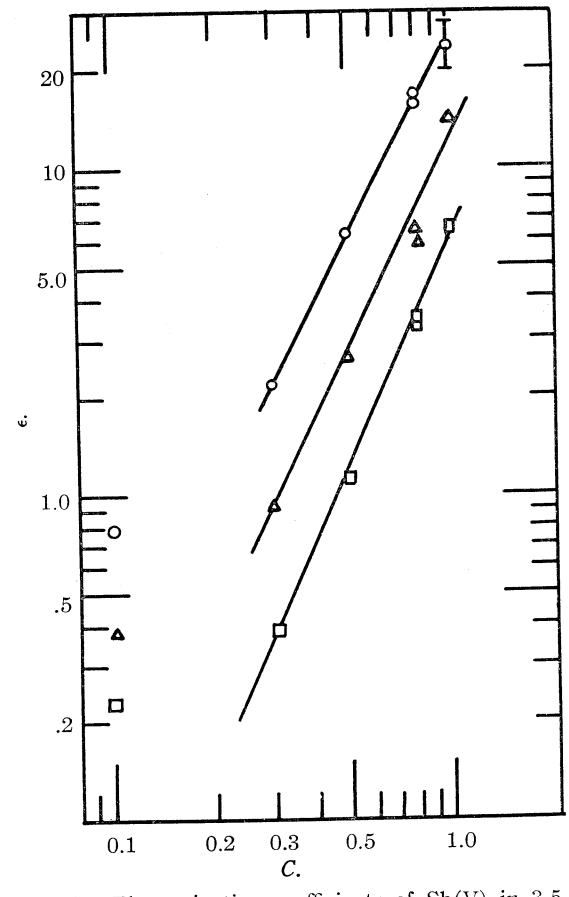


Fig. 6.—The extinction coefficients of Sb(V) in 3.5 *F* HCl as a function of antimony concentration: O, λ = 330; △, λ = 340; □, λ = 350. The slopes of the three straight lines are: 2.06 (λ = 330), 2.16 (λ = 340), 2.28 (λ = 350).

When a 1:1 mixture of antimony(III) and (V) in concentrated hydrochloric acid at a total antimony concentration of *ca.* 1.5 *F* is diluted to become *ca.* 0.5 *F* in antimony and 3.5 *F* in hydrochloric acid, the interaction absorption color (which is much more intense than that of antimony(V) itself) does not fade immediately but loses its color in a period of about an hour. This indicates that the kind or kinds of antimony(V) molecules which exist in concentrated hydrochloric acid and which interact with the antimony(III) molecules to give rise to interaction absorption are slowly converted into "non-interacting" kinds of antimony(V) molecules in 3.5 *F* hydrochloric acid. The rate of disappearance of the intense "interaction absorption" color was greater than the rate of disappearance of the pale yellow color of antimony(V) in concentrated acid upon dilution.

Brown and Swift,[21] in these Laboratories have reported that when an antimony(III) solution in 3.5 *F* hydrochloric acid is partially oxidized with chlorine, the yellow "interaction absorption" color results but fades upon standing. This indicates that the kind of antimony(V) molecule first formed by reaction of chlorine with antimony(III) is like the antimony(V) present in concentrated hydrochloric acid in that it can give rise to "interaction absorption" and in that it is slowly hydrolyzed to a non-interacting form.

When a solution of antimony(V) in 3.5 *F* acid is warmed, a pale yellow color develops, and slowly disappears again when the solution has cooled. The more intense interaction absorption may also be reversibly generated by heating a mixed solution of antimony(III) and (V) in dilute acid.

Spectrophotometry of Tin and Arsenic Solutions.—We have investigated the absorption spectra of mixed tin(II) and (IV) and mixed arsenic(III) and (IV) solutions in concentrated hydrochloric acid. Figure 7 shows that there is marked interaction absorption for the tin mixture,[22] but that there is no marked interaction absorption for the mixed arsenic solution.

The interaction absorption for the mixed tin solution occurs in the near ultraviolet and is barely perceptible to the eye. This is presumably

(22) A more detailed study of this case has been made by Mr. C. I. Browne of these Laboratories, and will be reported shortly.

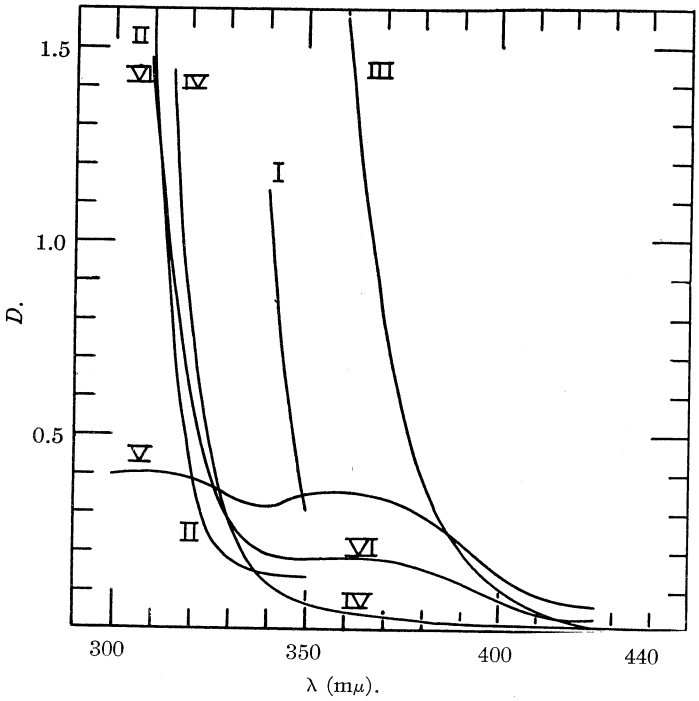


Fig. 7.—The absorption spectra of mixed As(III) and As(V), and of mixed Sn(II) and Sn(IV) solutions in concentrated HCl: I, 0.84 *F* Sn (II); II, 0.84 *F* Sn(IV); III, 0.42 *F* Sn(II), 0.42 *F* Sn(IV); I, II, III in 11.6 *F* HCl. IV, 0.76 *F* As(III); V, 0.76 *F* As(V)[a]; VI, 0.38 *F* As(III), 0.38 *F* As(V); IV, V, VI in 11.3 *F* HCl.

[a] Additional data not plotted for the As(V) solution are:

λ (mμ)	250	260	270	275
D	1.56	1.01	0.700	0.596

the reason why it has not been previously reported.

Discussion and Interpretation.—The fact expressed by equation (2) that in concentrated hydrochloric acid the optical density of interaction absorption is proportional to the product of the concentrations of the antimony(III) and (V) implies that the absorbing species is a dimeric complex containing one antimony(III) and one antimony(V). That is, the equilibrium involved in the formation of the absorbing species is of the type

$$Sb(III)Cl_4^- + Sb(V)Cl_6^- \rightleftarrows Sb_2Cl_{10}^= \quad (5)$$

$$C(Sb_2Cl_{10}^=) = KC_{III}C_V \quad (6)$$

rather than the type

$$2Cl^- + Sb(III)Cl_4^- + Sb(V)Cl_6^- \rightleftarrows 2Sb(IV)Cl_6^= \quad (7)$$

$$C(Sb(IV)Cl_6^=) = \sqrt{K'C_{III}C_V} \quad (8)$$

The equilibrium equations (6) and (8) should of course be written with activities instead of concentrations. That equation (2) fits the data so well indicates that in concentrated hydrochloric acid the appropriate activity coefficient product involving the activity coefficients of antimony(III) and (V) and of the dimer are to a good approximation independent of the total antimony concentration even when this is as high as 1.5 *F*.

The similarity of the absorption spectra of antimony(III) in 3.5 *F* and 11 *F* hydrochloric acid indicates that this component exists mainly in the same form at both acidities; this is usually assumed to be the $SbCl_4^-$ ion.

We assume that the pale yellow form of antimony(V) in concentrated hydrochloric acid is the $SbCl_6^-$ ion. The spectrophotometric data indicate that in 3.5 *F* hydrochloric acid, the $SbCl_6^-$ ion undergoes a slow hydrolysis to a less colored ion

$$SbCl_6^- + xH_2O = SbCl_{6-x}(OH)_x^- + xH^+ + xCl^- \quad (9)$$

The qualitative observation of the effect of temperature on the color of antimony(V) in 3.5 *F* hydrochloric acid suggests that reaction (9) is exothermic. As noted below, the hydrolyzed ion, $SbCl_{6-x}(OH)_x$, may be in part polymerized. It may of course also be neutralized by attachment of H^+.

The qualitative observation that on dilution from concentrated acid, interaction absorption in a mixture of antimony(III) and (V) fades more rapidly than does the pale yellow color of the $SbCl_6^-$ ion suggests that reaction (9) proceeds in several steps and that in the first of these the antimony(V) is converted to a form which is itself still colored but which is incapable of interacting with the antimony(III) to give interaction absorption; in a later step, the non-interacting but colored form of antimony(V) is further hydrolyzed to a colorless form. Because the relative rates of fading of "interaction" color and "antimony(V)" color have only been casually observed and not carefully studied, this interpretation must be regarded as a suggestion rather than a conclusion.

Brown and Swift[21] have also suggested equilibria of the type embodied in equations (5) and (9) in order to interpret their results on the electrochemical properties of the antimony(III)–(V) couple.

The variation of the optical density of antimony(V) solutions in 3.5 *F* hydrochloric acid with antimony concentration described by eq. (4) could be explained by a polymerization of the type

$$3Sb(OH)_6Cl_{6-x}^- \rightleftarrows (Sb(OH)_6Cl_{6-x})_3^{-3} \quad (10)$$

It is unlikely that this simple explanation is valid in view of the marked effect of other variables, chloride concentration, acidity, and ionic strength on the spectrum of antimony(V) in 3.5 *F* acid. It may even be that the variation with antimony concentration of the extinction coefficients of antimony(V) in 3.5 *F* hydrochloric acid is due simply to a shift in the equilibrium of eq. (9) due to changes in the free chloride concentration, the

acidity, and the ionic strength associated with changes in the antimony concentration.

The explanation of interaction absorption in terms of eq. (5) is in accordance with the properties of the intensely black solids, Rb_2SbCl_6, Cs_2SbCl_6, and $(NH_4)_2SbBr_6$.[23,24,25] These substances are formally compounds of antimony(IV). X-Ray analysis shows that they have the K_2SnCl_6 structure, and therefore contain crystallographically equivalent $SbX_6^=$ octahedra, in which each antimony atom is separated from neighboring antimony atoms by two non-bonded halogen atoms. However, these substances are diamagnetic; they do not contain independent $Sb(IV)Cl_6^=$ groups each having an odd electron and being paramagnetic. In the crystal, a $SbCl_6$ octahedron can interact with 12 equivalent neighboring octahedra. In solution, two antimonys must interact in a similar way; by analogy with the solids, we need not suppose that there is any halogen bridging involved in the dimerization in solution.

The fact that the data are satisfied by eq. (2) and do not require an equation of the type $C_D = K(C_{III} - C_D)(C_V - C_D)$ (where C_D is the concentration of interaction dimer) indicates that even in 1:1 mixed solutions that are 1.5 F in total antimony, the dimeric complex does not contain over 10–20% of the antimony. The comparatively weak color of the mixed solutions as compared to the intense black of the crystals suggests that the concentration of the dimeric "interaction" complex in solution is quite low.

It is probable that resonance between structures of the type ($Sb(V)X_6^-$, $Sb(III)X_6^=$) and ($Sb(III)X_6^=$, $Sb(V)X_6^-$) is of importance for the structure of solid M_2SbX_6 compounds and for the structure of the dimer in solution. Jensen has discussed in more detail the kinds of structure which will allow electrons to be passed back and forth between antimony atoms.[25] It is evident from the results in 3.5 F acid, that substitution of halogen coördination by oxygen coördination (of water or hydroxide) decreases the tendency for colored complexes of this type to form. This may be the reason why no interaction absorption was observed for the arsenic case—since it is generally believed that arsenic acid, H_3AsO_4, like phosphoric acid, is not converted to a chloroarsenic acid in concentrated hydrochloric acid. It is reasonable to assume that the positive effect observed for the tin solutions is due to interaction between chloro complexes of tin(II) and (IV).

The observation that cooling to −80° had no perceptible effect on the interaction absorption of a solution of antimony(III) and (V) in concentrated hydrochloric acid implies that there is very little heat for reaction (5). Since the entropy change in a dimerization reaction is usually negative, one would therefore expect the dimeric interaction complex not to be very stable. The M_2SbX_6 compounds are not very stable either and often decompose on attempted recrystallization. It may be that the interaction dimer is not at all a stable complex in solution but that it is "collision complex" which is formed for a very short period of time whenever an $Sb(V)Cl_6^-$ ion and an $Sb(III)Cl_4^-$ (or $Sb(III)Cl_6^=$??) ion come close to each other in solution.

The following calculation is intended to indicate the plausibility of this suggestion. In the crystal of Rb_2SbCl_6, the Sb–Sb distance for neighboring $SbCl_6$ octahedra is 7.25 Å.[25] This corresponds to the closest possible distance of approach of 2 $SbCl_6$ octahedra, because in the crystal the Cl–Cl distance for chlorine atoms of neighboring octahedra is 3.6 Å., which is twice the ionic or Van der Waals radius of chlorine. If now we consider that for a given $Sb(V)Cl_6^-$ in solution, any $Sb(III)Cl_4^-$ (or $Sb(III)Cl_6^=$) ion that approaches within 7.25 to 7.35 Å. will have formed a "collision complex" with the $Sb(V)Cl_6^-$ ion, the volume of solution that could be occupied by the antimony(III) molecule while interacting with the antimony(V) molecule is $4\pi \times 7.30^2 \times 0.10 = 67$ Å.^{3} The total available volume per molecule in a 1 mole/liter solution is 1660 cu. Å. (neglecting the molal volume of the solute for this rough calculation). Therefore if there were no attractive or repulsive forces between the Sb(III) and Sb(V) molecules (other than a repulsive force on contact) the fraction of 67/1660 = 0.04 of the Sb(V) molecules in a 1 F Sb(III) solution would have Sb(III) molecules within 0.1 Å. of the distance of approach of SbX_6 octahedra in the crystal. A concentration of this order of magnitude for a strongly colored dimer could account for the observed color of the mixed solutions.

If there is no marked energy of interaction in the ground state between $Sb(V)X_6^-$ and $Sb(III)X_6^=$ in the crystal or in the solution, then the marked effect on the absorption spectrum of the system can be explained as being due to a strong interaction in the optically excited states of the system. A further discussion of this idea will be contained in subsequent contributions on this general subject.

Acknowledgment.—This research has been supported in part by the Office of Naval Research. Mr. A. E. Larsh, Jr., is responsible for many of the measurements on solutions in 3.5 F acid and has assisted us in other ways. Mr. W. Wooster has generously carried out the antimony analyses. We have profited from discussions on this subject with Mr. R. Brown, Mr. H. McConnell, Professor L. Pauling and Professor E. H. Swift, all of this Laboratory. We are indebted to Professor Dan H. Campbell for many kindnesses in connection with the use of the spectrophotometer.

Summary

The absorption spectra of mixed antimony(III)

(23) Elliott, *J. Chem. Phys.*, **2**, 298 (1934).

(24) Asmussen, *Z. Elektrochem.*, **45**, 698 (1939).

(25) Jensen, *Z. anorg. allgem. Chem.*, **232**, 193 (1937); **252**, 317 (1944).

and antimony(V) solutions, of mixed tin(II) and tin(IV) solutions, and of mixed arsenic(III) and arsenic(V) solutions, all in hydrochloric acid, have been studied. The first two systems in solution in concentrated hydrochloric acid exhibit the phenomenon of "interaction absorption."

The optical density of interaction absorption for the mixed antimony solutions is proportional to the product of the concentrations of the antimony(III) and antimony(V) implying that the absorbing species is a dimeric complex containing one Sb(III) and one Sb(V). In 3.5 *F* hydrochloric acid, there is no marked interaction absorption.

The spectroscopic results indicate that Sb(III) exists as the same ion or molecule in concentrated and 3.5 *F* hydrochloric acid but that Sb(V) undergoes hydrolysis from an ion like $SbCl_6^-$ to an ion of the type $SbCl_x(OH)_{6-x}^-$ as the hydrochloric acid concentration is decreased from *ca.* 11 *F* to 3.5 *F*.

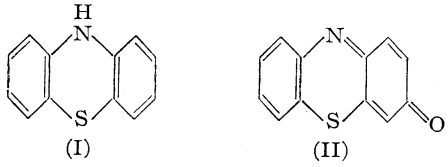
PASADENA, CALIF. RECEIVED MAY 31, 1949

[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY[1]]

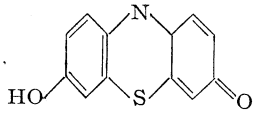
Phenothiazine Derivatives: Mono-oxygenated Compounds

BY DAVID F. HOUSTON, E. B. KESTER AND FLOYD DEEDS

Phenothiazine (I) has been shown[2] to have *in vitro* tuberculostatic action which is somewhat diminished in the presence of serum. The oxidized derivatives known as phenothiazone (II) and thionol (III) also showed a moderate inhibiting effect, and it was postulated that their lesser effectiveness might be connected with their decreased solubility in lipids. Compounds having



(I) (II)



(III)

substituents on the nitrogen were relatively ineffective, suggesting that the nitrogen should be free to take part in oxidation–reduction effects.

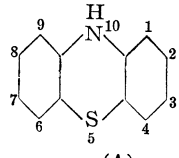
The indications are, therefore, that compounds related to phenothiazine and thionol which have unsubstituted nitrogen atoms and increased lipid solubilities might show greater tuberculostatic action. A number of compounds meeting these requirements have been synthesized, and this paper reports a series of ethers related to phenothiazone.[3]

Phenothiazone-3 was first prepared as a noncrystalline compound by Bernthsen[4] by fusion of *p*-hydroxydiphenylamine with two atoms of sulfur, recovery as 3-hydroxyphenothiazine, and oxidation with ferric chloride. Kehrmann[5] later obtained it as a crystalline product, melting at 165–166°, by ferric chloride oxidation of phenothiazine in hot aqueous alcohol. A convenient modification of this method by Pummerer and Gassner[6] gave a product melting at 162–163°. A reported improvement of this process is the subject of a recent patent.[7] The crude product is recrystallized and 45% of phenothiazone-3 melting at 163–164° is obtained. Similarly, Granick, Michaelis and Schubert[8] recrystallized the product from the reaction and found a melting point of 161°. Small-scale experiments in this Laboratory have given yields up to 62.5%, though the reaction was very susceptible to changes in process conditions.

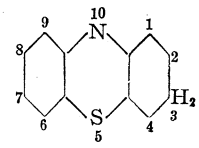
(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted. Presented at A. C. S. meeting, San Francisco, California, March 27–April 1, 1949.

(2) B. L. Friedlander, *Proc. Soc. Exptl. Biol. Med.*, **57**, 106–107 (1944).

(3) The awkwardness in naming derivatives of phenothiazine and related compounds has been pointed out by Michaelis and co-workers [THIS JOURNAL, **62**, 1802 (1940), and **63**, 351 (1941)], who also emphasized that the difficulties were greater with the quinonimine or oxidized form than with the hydroxyamine or reduced form. This trouble is largely overcome, however, by basing names of reduced-from compounds on the phenothiazine skeleton A (Ring Index No. 1860) and those of oxidized-form compounds on the theoretical 3-isophenothiazine skeleton B (Ring Index No. 1859).



(A)



(B)

Although this has the disadvantage of naming the reduced and oxidized forms of a compound on the basis of two isomeric ring skeletons, it offers a systematic nomenclature for phenothiazine derivatives that conforms with the present usage of *Chemical Abstracts*. The disadvantage has been avoided, at least in part, in this paper by the common use of the term phenothiazine (Skeleton A) to denote the parent compound of derivatives of the reduced form, and phenothiazone-3 instead of 3-isophenothiazine-3-one (from Skeleton B) as the parent compound for derivatives of the oxidized form.

(4) A. Bernthsen, *Ann.*, **230**, 182 (1885); *Ber.*, **17**, 2860 (1884).

(5) F. Kehrmann, *Ann.*, **322**, 54 (1902).

(6) R. Pummerer and S. Gassner, *Ber.*, **46**, 2324 (1913).

(7) Nederlandische Centrale Organisatie voor Toegepast Natuurwetenschappelijk Orderzoek, Dutch Patent 59,559, June 16, 1947, *C. A.*, **41**, 5557 (1947).

(8) S. Granick, L. Michaelis and M. P. Schubert, THIS JOURNAL, **62**, 1802 (1940).

For the preparation of larger quantities, attention was turned to fusion experiments. Preliminary fusions of aniline, hydroquinone and sulfur[9] were unpromising. The preparation according to Bernthsen[4] proceeded rapidly and smoothly at 185–195° when catalyzed with iodine. Reaction was complete within a half hour, and phenothiazone-3 was consistently recovered in 41–47% yield. Recovery consisted in aeration of a suspension of the ground product in dilute aqueous alkali, and extraction of the phenothiazone-3 from the dried insoluble solids with hexane. Methods of recovery have been incompletely explored, and higher yields may be possible.

The isopropyl, octyl, dodecyl and hexadecyl ethers of 3-hydroxyphenothiazine were similarly prepared from the corresponding *p*-alkoxydiphenylamines, which were readily formed by etherification of *p*-hydroxydiphenylamine.[10] The methyl ether has previously been prepared by this fusion process by Baltzly, Harfenist and Webb[11] and by Gilman and Shirley.[12] Agreement between properties of the compounds so prepared with those of the product from methylation of 3-hydroxyphenothiazine by dimethyl sulfate[6] confirms the position of the ether group.

Sulfur fusions proceeded more smoothly with the ethers than with the free hydroxyl compound, and gave the *n*-alkoxyphenothiazines as light yellow solids in 80–84% yields. The 3-isopropoxy ether was obtained in 60% yields; more vigorous fusion conditions led to some decomposition.

The 3-alkoxyphenothiazines are insoluble in water and appreciably more soluble in organic solvents than is phenothiazone-3. They are readily susceptible to oxidation and tend to discolor when exposed to light and air. Their similarity in structure to that of phenothiazine is indicated from the similarity of the ultraviolet absorption curves.

Ultraviolet and visible absorptions of a number of compounds have been measured for control and comparison purposes. The differences between the absorption curves for phenothiazine (maxima at 254 and 318 mμ, inflection at 285), phenothiazine-5-oxide (228, 272, 302, 337 mμ) and phenothiazone-3 (236, 273, 357, 505 mμ)—all in methanol—are shown in Fig. 1. Substitution of a hydrocarbon or ether group for the hydrogen at the 3-position of phenothiazine caused only slight changes in the absorption in the range covered (maxima for 3-methylphenothiazine at 255 and 320 mμ; see also Table I). However, indications point to differences at lower wave lengths.

(9) Gesellschaft für Chemische Industry in Basel, Swiss Patent 204,521, Aug. 1, 1939.

(10) D. F. Houston, THIS JOURNAL, **71**, 395 (1949).

(11) R. Baltzly, M. Harfenist and F. Webb, *ibid.*, **68**, 2673 (1946).

(12) H. Gilman and D. Shirley, *ibid.*, **66**, 888 (1944). Professor Gilman kindly supplied samples of 3-methyl- and 3-methoxyphenothiazine.

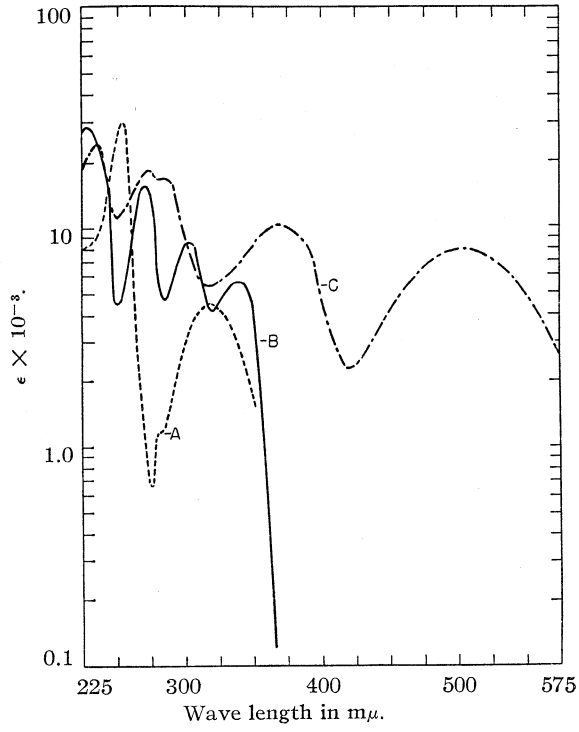


Fig. 1.—Molar extinction curves in absolute methanol (measured on solutions containing 3 to 10γ of solute per ml. of solution): (A) phenothiazine; (B) phenothiazine-5-oxide; (C) phenothiazone-3.

Phenothiazine had essentially the same maxima in isoöctane (254, 315 mμ) as in methanol. Phenothiazone-3, however, showed considerable shift with change in solvents as measured in the visible range.[13] The main absorption peak for a series of solvents was located as follows: Skellysolve B[14] (478), ether (482), benzene (490), chloroform (502), methanol (505) and water (533). The absorption of phenothiazone-3 is in agreement with the results of previous investigators.[4,8,15] The tuberculostatic properties of these compounds are the subject of other investigations, and the findings will be reported elsewhere.

Experimental[16]

A. Materials.—Phenothiazine was recrystallized from benzene and washed with commercial hexane before use.

***p*-Hydroxydiphenylamine,**[17] purified by distillation with superheated steam, followed by recrystallization from benzene–hexane,[10] consisted of pearly flakes melting at 69–70° in agreement with the reported[18] value of 70°.

(13) Measurements were made with a Hardy–General Electric Recording Spectrophotometer.

(14) Skellysolve B is named as part of the experimental conditions. Its use does not imply recommendation over other solvents having the same properties.

(15) (a) F. Eckert and R. Pummerer, *Z. physik. Chem.*, **87**, 612 (1914); (b) R. Pummerer, F. Eckert and S. Gassner, *Ber.*, **47**, 1498 (1914).

(16) All melting points are corrected unless otherwise indicated. Nitrogen analyses were made by the Kjeldahl procedure of White and Secor, *Ind. Eng. Chem. Anal. Ed.*, **18**, 457 (1946).

(17) Furnished by courtesy of the B. F. Goodrich Chemical Company.

(18) A. Calm, *Ber.*, **16**, 3799 (1883).

TABLE I

3-ALKOXYPHENOTHIAZINES

R in formula $C_{12}H_8NOSR$[a]	M. p., °C.	Empirical formula	Analytical data, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Absorption maxima mμ
Isopropyl	123.0–123.7	$C_{15}H_{15}NOS$	70.00	70.2	5.88	5.88	5.44	5.46	255, 320
n-Octyl	110.1–111.5	$C_{20}H_{25}NOS$	73.35	73.1	7.70	7.52	4.28	4.31	255, 320
n-Dodecyl	101–103	$C_{24}H_{33}NOS$	75.15	75.1	8.67	8.61	3.65	3.65	.....
n-Hexadecyl	101.5–103	$C_{28}H_{41}NOS$	76.48	76.4	9.40	9.30	3.19	3.21	.....

[a] The methoxy compound, $C_{13}H_{11}NOS$, has previously been reported as melting at 158–159,[12] 159,[20] 160–161[11] and 163°.[6] It shows absorption maxima at 254 and 322 mμ in methanol.

p-**Alkoxydiphenylamines** were prepared and purified by methods previously described.[10]

Phenothiazine-5-oxide (sulfoxide) was made according to Pummerer and Gassner.[6]

B. Preparation of Phenothiazone-3 by Oxidation of Phenothiazine.—The best preparation by the method of Pummerer and Gassner[6] confirmed their results; 1.0 g. of phenothiazine yielded 0.67 g. (62.5%) of coppery granular solids that melted at 160.5–162°. The filtrate was digested for one hour on the steam-bath, cooled and filtered. Rusty purple solids weighing 0.29 g. remained.

In other experiments, differing in slight details, the purplish solids formed the main precipitate in yields of 62–96%. A composite sample (2.46 g., 76% yield) was treated by extraction with and precipitation from alcohol (210 cc.) then similarly with water (3000 cc.) according to the purification scheme of Granick, Michaelis and Schubert.[8] The yield was 0.77 g. of phenothiazone-3 (25% based on phenothiazine) melting at 160–161°.

Anal. Calcd. for $C_{12}H_7ONS$: N, 6.57. Found: N, 6.52.

C. Phenothiazone-3 by Sulfur Fusion of *p*-Hydroxydiphenylamine.—Fusion was essentially according to Bernthsen[4] except that iodine was added as catalyst. A mixture of 3.7 g. (0.02 mole) of *p*-hydroxydiphenylamine and 1.4 g. (0.044 g. atom) of sulfur was ground in a mortar and placed in a 50-cc. distilling flask carrying a bubbler tube on the side-arm. Then 0.04 g. of iodine was added, and the flask was stoppered and placed in a metal-bath preheated to 180°. Bath temperature was held at 185–195° during the fifteen to twenty minutes that gas evolution continued, and for an added ten minutes. The reaction mixture was poured into a porcelain dish and allowed to cool. It crystallized in a cake of dark greenish-brown solid which melted at 170–175° (rapid heating in capillary tube, uncorrected). DeEds and Thomas[19] reported a melting point of 172–174° for 3-hydroxyphenothiazine.

The fusion product was ground with 200 cc. of 0.5% potassium hydroxide per gram, aerated for thirty to forty-five minutes, filtered and washed with cold water. The dried solids were extracted with commercial hexane until the extracts were no longer orange. Evaporation of the solvent left a rust-red crystalline residue of phenothiazone-3. Further purification was achieved by crystallization from aqueous alcohol or—for small amounts—from water. The product melted at 161°, and was identical with the phenothiazone from the oxidation reaction. Yields varied from 40–45%.

Anal. Calcd. for $C_{12}H_7ONS$: N, 6.57. Found: N, 6.53.

Use of this recovery process has shown that the reaction is relatively insensitive to a small excess of either reactant.

Phenothiazone-3 can be separated from congeners by adsorption from hexane or benzene solutions on alumina, followed by elution with benzene containing 20% of chloroform. The phenothiazone-3 is collected in the eluate and recrystallized by concentration of the solution. It may be sublimed slowly at boiling xylene temperatures in the vacuum of a mechanical pump.

D. 3-Isopropoxyphenothiazine.—A ground mixture of 4.55 g. (0.02 mole) of *p*-isopropoxydiphenylamine[10] and 1.30 g. (0.041 g. atom) of sulfur was fused with 0.1 g. iodine at 160–170° as for phenothiazone-3. After forty-five minutes the odor of the evolving gases changed from that of hydrogen sulfide to one suggesting organic sulfides, and heating was stopped. The cooled reaction mass was an olive-brown resin which partially crystallized on mechanical working. Extraction of the solids with hexane until extracts were nearly colorless (eleven hours) left 10.5% of insoluble residue. From the solution was obtained 58.5% of clusters of yellow crystals. Evaporation left 26% of reddish oil. The crystals were purified by solution in hot benzene (5 cc./g.), addition of hexane (200 cc./g.) and cooling to 0°. The faintly tan crystalline powder melted at 123.0–123.7°. On exposure to the atmosphere it gradually becomes discolored. Vacuum sublimation at 110° first removes the colored portion. The 3-isopropoxyphenothiazine sublimes very slowly under these conditions.

Aeration for thirty minutes of a suspension of 0.5 g. of the ether in 100 cc. of 0.5% potassium hydroxide, and extraction of the dried insoluble solids with hexane, yielded 0.39 g. composed of phenothiazone-3 and the original ester.

E. 3-*n*-Alkoxyphenothiazines.—These were also prepared by iodine-catalyzed fusion of the appropriate amine with two atom-equivalents of sulfur. At temperatures of 160–170° gas evolution ended in fifty to sixty minutes. No sulfide odors developed. Extraction with and crystallization from hexane gave 80–84% of nearly white powders, and left residues of yellow oil. Melting points and analytical data are collected in Table I.

Acknowledgment.—The authors are indebted to Dr. E. J. Eastmond, Mrs. Bernice Williams and Mr. G. F. Bailey for the measurement of spectral absorptions, to Mr. L. M. White and Miss Geraldine Secor for microchemical analyses, and to Dr. F. T. Jones for microscopical examinations of numerous products.

Summary

Phenothiazone-3 has been prepared by the oxidation of phenothiazine with ferric chloride and by the iodine-catalyzed condensation of *p*-hydroxydiphenylamine with sulfur. Similar condensations of *p*-alkoxydiphenylamines and sulfur have given the isopropyl and the normal octyl, dodecyl and hexadecyl ethers of 3-hydroxyphenothiazine.

ALBANY, CALIFORNIA RECEIVED APRIL 11, 1949

(19) F. DeEds and J. O. Thomas, *J. Parasitol.*, **28**, 363 (1942).

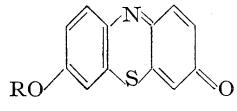
(20) F. Kehrmann, and L. Diserens, *Ber.*, **48**, 327, footnote 4 (1915).

[CONTRIBUTION FROM WESTERN REGIONAL RESEARCH LABORATORY[1]]

Phenothiazine Derivatives: Di-oxygenated Compounds

BY DAVID F. HOUSTON, E. B. KESTER AND FLOYD DEEDS

The synthesis of phenothiazine derivatives with possible tuberculostatic action[2] has been extended to the preparation of a series of ethers of 7-hydroxyphenothiazone-3[3] or "thionol" (I, R = H), which—from structural considerations—might have improved lipid solubility over the parent compound, and yet retain its oxidation–reduction characteristics. The investigation has been closed with the achievement of a minimum objective and the results are presented in this



I

report, although some experimental procedures are incompletely developed.

Bernthsen[4] prepared 7-hydroxyphenothiazone-3 as early as 1885 by digestion of phenothiazine with sulfuric acid. Oxidation of phenothiazine with hydrogen peroxide and hydrochloric acid[5] gave 7-hydroxyphenothiazone-3 which was found to contain difficullty removable chlorine compounds. In 1940, Granick, Michaelis and Schubert[6] called attention to the difficulty of consistently obtaining this product in suitable yields with satisfactory purity. The original Bernthsen method is exceedingly tedious, and the yields are low and variable. A recent modification[7] in which the desired product is isolated as the sparingly soluble lithium salt (I, R = Li) makes the process much more convenient.

The synthesis of 7-hydroxyphenothiazone-3 by fusion of hydroquinone, *p*-aminophenol and sulfur was patented by Vidal[8] as a dye intermediate, but practically no data on properties were recorded. A product obtained[9] by fusing sulfur with *p,p'*-dihydroxydiphenylamine at 180° did not have the properties of 7-hydroxyphenothiazone-3. The recovery of thionol from the urine of animals dosed with phenothiazine has been summarized by Collier[10] and co-workers.

In general, the high melting point (>360°) and the low solubility of thionol have hindered its purification and characterization.

Published information on ethers of 7-hydroxyphenothiazone-3 appears to be limited to the reported formation[11] of the methyl and ethyl leuco compounds by the fusion of 1:1 molar mixtures of hydroquinone and the appropriate *p*-alkoxyaniline with an excess of sulfur. The compounds were converted directly to sulfur dyestuffs.

In the present investigation, 7-hydroxyphenothiazone-3 was prepared by two methods. The first was a modification of Schneider's[9] process, in which iodine was used as a catalyst. The *p,p'*-dihydroxydiphenylamine was prepared according to Knoevenagel and Berlin[12] by condensing two molecules of *p*-aminophenol in the presence of iodine. The purified amine was then fused with sulfur, using an iodine catalyst, to form 3,7-dihydroxyphenothiazine (leucothionol). Solution of the reaction product in dilute alkali afforded the oxidized form, which was precipitated as the lithium salt and subjected to recrystallization. This material represented a 36% yield, and gave chloroform extracts having the visible absorption spectrum characteristic of 7-hydroxyphenothiazone-3. There was still present, however, a congener that was obstinately retained with the desired product. Further investigation may provide a way of capitalizing on this apparently good yield.

The second method of preparation was the lithium salt procedure of Granick and Michaelis.[7] Application of the process in this Laboratory gave somewhat lower yields of the lithium salt than the reported 8%, likely because of differences in experimental details. Further investigation showed that the yield increased as the reaction time at 160–165° was shortened, until a six-hour sulfuric acid digestion of phenothiazine gave 15% of the lithium salt. Shorter digestion periods gave very low yields. Sulfuric acid digestions at 155° with acid of various concentrations gave low yields and poor separations. At temperatures of 172–175° yields were again lower than at 160–165°, and decreased as acid concentration increased. Acid concentrations of 75 to 90% were most favorable at 160–165°, and 80% acid was generally used. The use of commercial phenothiazine melting at 174–178° gave apparently as good yields as did purified phenothiazine melting at 182.5–183.5°. However, lower yields of purified alkyl ethers resulted from the lower-melting phenothiazine. Recrystallizations of the

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted. Presented at the A. C. S. Meeting, San Francisco, Calif., March 27–April 1, 1949.

(2) D. F. Houston, E. B. Kester and Floyd DeEds, THIS JOURNAL, **71**, 3816 (1949).

(3) A discussion of nomenclature occurs in ref. 2.

(4) A. Bernthsen, *Ann.*, **230**, 187 (1885).

(5) F. DeEds and C. W. Eddy, THIS JOURNAL, **60**, 1446 (1938).

(6) S. Granick, L. Michaelis and M. Schubert, *ibid.*, **62**, 1802 (1940).

(7) S. Granick and L. Michaelis, *ibid.*, **69**, 2982 (1947), and personal communications.

(8) H. R. Vidal, German Patent 103,301; March, 1897.

(9) F. Schneider, *Ber.*, **32**, 689 (1899).

(10) H. B. Collier, D. E. Allen and W. E. Swales, *Can. J. Research*, Sect. D., **21**, 151 (1943).

(11) Gesellschaft für Chemische Industrie in Basel, Swiss Patents 209,501 (methyl) and 209,502 (ethyl); July, 1940.

(12) E. Knoevenagel and H. J. Berlin, *J. prakt. Chem.*, **197**, 24 (1914).

product from boiling glacial acetic acid yielded crystalline 7-hydroxyphenothiazone-3 which had optical and crystallographic properties in agreement with those of Granick and Michaelis' product.[13] This method was used to provide the needed amounts of 7-hydroxyphenothiazone-3 and its lithium salt.

The ethyl, amyl, octyl, dodecyl and hexadecyl ethers have been prepared by the reaction between the silver salt of thionol and the proper *n*-alkyl iodides in refluxing benzene. Bromides proved unsatisfactory. In most cases, the silver salt was made directly from the precipitated lithium salt by treatment with silver nitrate solution. Purification was achieved by chromatographing the benzene solution of the ether on alumina, eluting with benzene–chloroform mixtures, removing all volatile material (finally in vacuum), and crystallizing from hexane–benzene or acetone.

Absorption spectra of solutions of the ethers were nearly identical, though the orange-to-rust-red colors of the crystals changed appreciably with size and shape. Some evidence points toward polymorphism, although this may be induced by residual impurities. For example, crystallization of the octyl ether in one case yielded both chunky garnet-red crystals and spherulitic clusters of orange needles. Microscopical examination showed the two forms were very similar optically and crystallized from melts in apparently identical forms. The orange needles seemed to change to the darker form below the melting point.

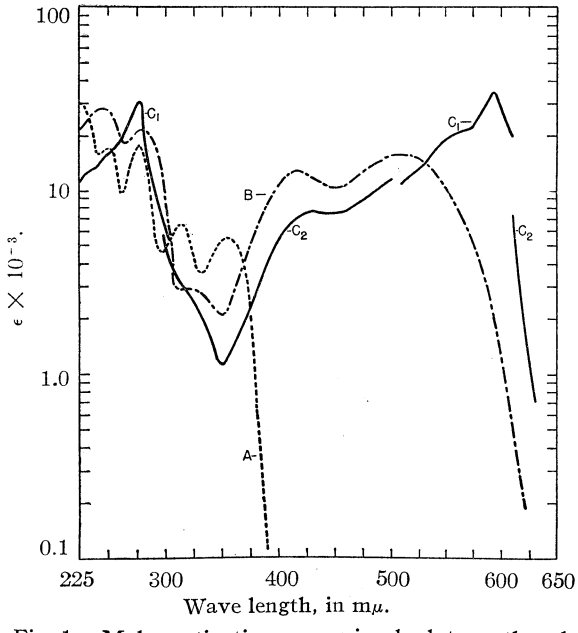


Fig. 1.—Molar extinction curves in absolute methanol: (A) 3-*n*-octoxyphenothiazine-5-oxide (2.33γ/ml.); (B) 7-*n*-octoxyphenothiazone-3 (4.33γ/ml.); ($C_1 - C_2$) 7-hydroxyphenothiazone-3 (C_1 = 0.588γ/ml.; C_2 = 2.94γ/ml.).

(13) A sample for comparison was kindly supplied by Dr. Granick.

An attempted formation of 7-*n*-octoxyphenothiazone-3 by ferric chloride oxidation of 3-*n*-octoxyphenothiazine[2] according to the method of preparing phenothiazone-3 from phenothiazine[14] caused hydrolysis of the ether linkage and yielded chiefly phenothiazone-3. Traces of 7-hydroxyphenothiazone-3 were noted, but no octoxy compound. Reaction of 3-octoxyphenothiazine with alkaline solutions of hydrogen peroxide effectively oxidized the sulfur atom, yielding 3-octoxyphenothiazine-5-oxide. This type of di-oxygenated derivative shows sensitivity to light and air similar to that of 3-alkoxyphenothiazines.

Spectral Absorptions.[15]—Granick and Michaelis[7] have recently published data on the spectral absorption of 7-hydroxyphenothiazone-3 and its semiquinone form. Lipson[16] has recorded absorption peaks at 552 and 500–510 mμ for an ethanol solution of 7-hydroxyphenothiazone-3, recovered from the urine of sheep treated with phenothiazine. Collier and co-workers,[10] discussing the spectrometry of phenothiazine derivatives in animal experimentation, pointed out that the peak at 552 mμ was due to the semiquinone form of phenothiazone-3.

The spectral absorption of thionol prepared in this work is in agreement with the results of Granick and Michaelis. This was conclusively shown by the identity of absorption curves obtained on methanol solutions of the two preparations. It is of further interest to note that the sharp peak at 590 mμ for these preparations in 0.01 *N* alkali is concordant with the predicted peak at 587 ± 3 mμ calculated by the rules of Lewis.[17] The visible absorption maxima of 7-hydroxyphenothiazone-3 shift with solvent (411, 502 mμ in chloroform and 424, 518 in methanol), and the absorption shows some deviation from Beer's law. This deviation is consistent with the similar characteristics of methylene blue and thionine,[18,19] amino analogs of thionol. Absorption curves for representative di-oxygenated compounds are shown in Fig. 1.

Tuberculostatic properties are being investigated by other workers and will be reported in a separate publication.

Experimental[20]

Materials.—Phenothiazine was purified by crystallization from toluene, followed by washing with hexane.

(14) R. Pummerer and S. Gassner, *Ber.*, **46**, 2324 (1913).

(15) Visible absorption was usually measured on a Hardy-General Electric Recording Spectrophotometer; ultraviolet (and some visible) absorption was determined with a Beckman Model DU quartz spectrophotometer.

(16) M. Lipson, *Australian J. Exptl. Biol. Med. Sci.*, **18**, 269 (1940).

(17) G. N. Lewis, THIS JOURNAL, **67**, 770 (1945).

(18) L. Michaelis, M. P. Schubert and S. Granick, *ibid.*, **62**, footnote p. 210 (1940).

(19) L. F. Epstein, F. Karush and E. Rabinowitch, *J. Opt. Soc. Am.*, **31**, 80 (1941).

(20) All melting points are corrected unless otherwise indicated. Nitrogen analyses were made by the Kjeldahl procedure of White and Secor, *Ind. Eng. Chem., Anal. Ed.*, **18**, 457 (1946).

TABLE I

PROPERTIES OF ETHERS OF 7-HYDROXYPHENOTHIAZONE-3

Alkyl group of ether	Color	Yield (crude), %	Empirical formula	Melting point, °C.	Analytical data, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Ethyl	Orange	58, 71	$C_{14}H_{11}NO_2S$	208–209	65.35	65.4	4.31	4.27	5.44	5.45
n-Amyl (1)	Deep rust	38, 41	$C_{17}H_{17}NO_2S$	124.5–126	68.20	68.2	5.73	5.63	4.68	4.66
n-Amyl (2)	Deep rust		$C_{17}H_{17}NO_2S$	131–132	68.20	68.3	5.73	5.69	4.68	4.68
n-Octyl	Garnet-red	53	$C_{20}H_{23}NO_2S$	115.5–116	70.35	70.8	6.79	6.88	4.10	4.02
n-Dodecyl	Garnet-red	52	$C_{24}H_{31}NO_2S$	121–122.5	72.50	72.9	7.86	7.88	3.52	3.47
n-Hexadecyl	Orange-red	44	$C_{28}H_{39}NO_2S$	120.5–121.5	74.13	74.0	8.66	8.65	3.09	3.04

Sublimed sulfur (U. S. P.) was used in fusions. *p,p'*-Dihydroxydiphenylamine prepared according to Knoevenagel[12] melted at 167.5–168.5° in agreement with 169° reported by him. Ethyl and amyl iodides, amyl, octyl, dodecyl and hexadecyl bromides were reagent grade chemicals boiling within two-degree ranges, and were used as received. Octyl, dodecyl and hexadecyl iodides were prepared by treating the corresponding bromides with sodium iodide in refluxing acetone. The octyl and dodecyl iodides were distilled at reduced pressures, and hexadecyl iodide was recrystallized at 0° from alcohol–benzene to a melting point of 22°.

Oxidation of 3-Alkoxyphenothiazines.—(a) A 0.5-g. portion of 3-isopropoxyphenothiazine[2] was suspended in 100 cc. of 0.5% potassium hydroxide and aerated for thirty minutes. Filtration yielded rust-brown solids. A chloroform extract showed the absorption spectrum of phenothiazone-3, and recrystallization gave brick-red crystals, m. p. 158–161° (uncor.). Phenothiazone-3 melts at 161–162°. The original purple alkali solution suggested 7-hydroxyphenothiazone-3, but none was found.

(b) Oxidation of 0.5 g. of 3-*n*-octoxyphenothiazine[2] by the ferric chloride–hydrogen peroxide procedure of Pummerer and Gassner[14] resulted in a marked odor of *n*-octanol and yielded 0.34 g. of crude phenothiazone-3. Extraction with hexane gave 0.24 g. (75% on original ether) melting at 157.5–160.5° (uncor.). Chromatographing a benzene solution of this material on Alorco F-20 alumina and eluting with benzene–chloroform provided 0.2 g. of phenothiazone-3, m. p. 160–161°. Indications were obtained of a trace of 7-hydroxyphenothiazone-3.

(c) A solution of 0.5 g. of 3-octoxyphenothiazine in 20 cc. of 1% alcoholic potassium hydroxide was treated on the steam-bath with 0.5 cc. of 30% hydrogen peroxide, and with a further 0.5 cc. after one-half hour. During the two-hour heating, the original brown color changed gradually to a pale yellow with a green fluorescence. Crystallization at 0° from the reaction solution yielded 0.42 g. of light yellow solid, m. p. 166° (uncor.). Recrystallization from acetone gave 0.28 g. (53.5%) of platelets, m. p. 168.2–168.7° (dec.). This type of oxidation is common in converting sulfides to sulfoxides; the analysis corresponds to 3-*n*-octoxyphenothiazine-5-oxide.

Anal. Calcd. for $C_{20}H_{25}NO_2S$: C, 69.93; H, 7.34; N, 4.08. Found: C, 69.6; H, 7.25; N, 4.06.

7-Hydroxyphenothiazone-3. (a) Bernthsen Synthesis.[4]—The digestion of 50.0 g. of phenothiazine according to Bernthsen's original procedure provided 1.15 g. of crude 7-hydroxyphenothiazone-3. The leuco compound was extracted with ether in a carbon dioxide atmosphere, reoxidized by air in ammonia solution, and crystallized from acetic acid. The product required intensive drying, because of strong retention of moisture, before analyses approximating the theoretical were obtained.

(b) **Lithium Salt Process.**—Application of the method of Granick and Michaelis[7] to 22.0 g. of phenothiazine gave 0.98 g. of lithium thionol (3.8%) instead of the 2.01 g. reported. Liquid temperatures of 160–165° were maintained for twenty-six hours without stirring in a one-liter flask heated with a glass-cloth electric heater. These conditions may have varied from those used by Granick and Michaelis. Their recommended rapid filtration of the sodium carbonate extracts of the product was not achieved.

The lithium salt was extracted with two 100-cc. portions of boiling glacial acetic acid, which on cooling and filtration gave 0.43 g. of crystalline 7-hydroxyphenothiazone-3. Recrystallization provided rosettes of fine brownish-red needles that did not melt at 360°. Drying *in vacuo* over Anhydrone at 78° for ninety hours gave an analytical sample.

Anal. Calcd. for $C_{12}H_7NO_2S$: C, 62.87; H, 3.08; N, 6.11. Found: C, 62.7; H, 2.99; N, 6.07.

In view of the differences in yield, further exploration of reaction conditions was made. The optimum reaction conditions of digestion for about six hours at 160–165° with 75–90% acid gave 15–16% of lithium salt. Separation of hot sodium carbonate extracts with a basket centrifuge was much more convenient than filtration, though the yields were reduced slightly. Mechanical stirring did not increase the yield. The effect of changing the 4% concentration of phenothiazine in the reaction mixture was not investigated.

(c) **Sulfur Fusion Process.**—Equivalent amounts of sulfur (1.28 g., 0.04 atom) and *p,p'*-dihydroxydiphenylamine (4.06 g., 0.02 mole) ground together were placed in a long-necked flask with 0.1 g. of iodine. The flask was immersed in a metal-bath preheated to 190° and held at 195–200° until evolution of hydrogen sulfide was practically complete. This required forty-five to sixty minutes, during which time the dark reaction mixture solidified. Some ammonia and phenol were generated during the reaction. The coke-like residue, readily broken out of the flask, was digested with successive one-liter portions of 0.7 and 0.6% boiling sodium carbonate solution and filtered. The combined heated filtrates were treated with 20 g. of lithium chloride and chilled to 0°. Filtration left 0.65 g. of dark solids. Treatment of the reheated filtrate with a further 25 g. of lithium chloride gave 1.70 g. (36.3%) of lithium salt of 7-hydroxyphenothiazone-3. Recrystallizations from glacial acetic acid eventually yielded the crystalline product, though removal of persistent congeners was difficult and gave low final yields.

Anal. Calcd. for $C_{12}H_7NO_2S$: C, 62.87; H, 3.08; N, 6.11. Found: C, 62.2; H, 3.01; N, 6.18.

Ethers of 7-Hydroxyphenothiazone-3.—Preparations of the individual ethers were closely similar, and are illustrated by the details of synthesis for the amyl ether. Data on the products are collected in Table I. Excesses of alkyl iodide varied from 2.5 to 5 equivalents, but smaller amounts would likely be suitable. The vacuum treatment can be omitted in larger-scale preparations.

7-*n*-Amyloxyphenothiazone-3.—The silver salt was prepared from 2.35 g. (0.01 mole) of crude lithium salt by solution in one liter of water on the steam-bath, treatment with 2.5 g. (0.015 mole) of silver nitrate in 100 cc. of water, digestion for one hour, filtration, exhaustive washing, and drying at 105°.

The silver salt was dispersed in 500 cc. of refluxing benzene and treated with 9.9 g. of *n*-amyl iodide (5 equivalents). After seven hours reflux the liquid was cooled and filtered. The solids were washed with 200 cc. of hot benzene. Duplicate experiments showed 38 and 41% of

crude product at this point. The combined solutions were chromatographed on Alorco F-20 alumina (3.3 cm. diam., 15 cm. long), then developed and eluted with 250 cc. of benzene, 1000 cc. of 9:1 and 2500 cc. of 4:1 benzene–chloroform. The ether traveled through the column as a deep-red band, and was saved in a separate eluate. Unetherified 7-hydroxyphenothiazone-3 and some dark impurities remained strongly adsorbed at the top of the column. Evaporation of the eluate left the ethers as a partially crystalline solid. Vacuum treatment at 78° removed some volatile material, and recrystallization from hexane–benzene and from acetone provided garnet-red lath-like crystals (1) m. p. 124.5–126°. The substitution of amyl bromide for the iodide resulted in only 7% yield of the desired ether.

Repetition of this preparation with a larger amount of crude material (31.5 g.), eliminating the vacuum heating step, gave material (2) melting at 131–132°.

Acknowledgment.—The writers are indebted to Dr. E. J. Eastmond, Mrs. Bernice Williams and Mr. G. L. Bailey for the measurements of spectral absorption, to Mr. L. M. White and Miss Geraldine Secor for microchemical analyses, and to Dr. F. T. Jones for microscopical investigation of numerous products.

Summary

Thionol (7-hydroxyphenothiazone-3) has been prepared by condensation of *p,p'*-dihydroxydiphenylamine with sulfur, and by sulfuric acid oxidation of phenothiazine followed by isolation as the lithium salt. The yield from the previously reported latter process has been increased by shortening the reaction time.

The ethyl, amyl, octyl, dodecyl and hexadecyl ethers of 7-hydroxyphenothiazone-3 have been prepared by treating the silver salt with the appropriate alkyl iodides.

3-Octoxyphenothiazine-5-oxide has been made by alkaline peroxide treatment of 3-octoxyphenothiazine.

ALBANY, CALIFORNIA RECEIVED APRIL 11, 1949

[CONTRIBUTION FROM THE BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH, UNIVERSITY OF TORONTO]

Synthesis of Inositol-5-monophosphoric Acid and Scyllitol Monophosphoric Acid[1]

BY BEAT M. ISELIN[2]

The widespread occurrence of inositol phosphoric acids in plants has long been recognized.[3] For many years inositol hexaphosphoric acid, or phytic acid was the only inositol phosphate known until Anderson,[4] in 1914, succeeded in isolating inositol monophosphoric acid from wheat bran. The same substance has been obtained by the action of the enzyme phytase on phytic acid[5,6] or by partial hydrolysis of phytic acid with dilute sulfuric acid.[7] More recent investigations have shown that inositol monophosphoric acid is a constituent of many phosphatides. Anderson has found this substance as a polysaccharide in the phosphatide fraction of tubercle bacilli.[8,9] Klenk and Sakai have described a preparation of inositol monophosphoric acid from soy bean lipositol[10] in which, as has been demonstrated by Woolley,[11] it is combined with galactose in glycosidic linkage.

The inositol monophosphoric acids isolated from natural sources are optically inactive. Their structure has not been investigated as yet. However, in the light of the present knowledge of the configuration of meso-inositol it is evident that only those mono-substituted derivatives are optically inactive in which the substituent is in position 2 or 5[12]; substitution in other positions is expected to yield products with optical activity. Assuming that the natural inositol monophosphates are not resolvable it may be concluded that the phosphoric acid residue is attached to carbon atom 2 or 5.

The synthesis of an inositol monophosphoric acid carrying the substituent on carbon atom 5 was effected by taking advantage of the known fact that *Acetobacter suboxydans* oxidizes meso-inositol specifically in position 5 yielding scyllo-meso-inosose. This substance, by acetylation and subsequent catalytic hydrogenation of the keto group with platinum oxide in glacial acetic acid, is converted to 1,2,3,4,6-pentaacetyl-meso-inositol as has been described by Posternak.[13] When the directions for the hydrogenation of scyllo-meso-inosose pentaacetate given by this author were closely followed, a product was obtained that had the recorded melting point (161–162°); acetylation to the hexaacetate and the bioassay of the hydrolyzed material with *Saccharomyces cerevisiae* revealed, however, that the product contained approximately 25% of the scyllitol isomer. It was found impossible to achieve a satisfactory separation of the two isomers by fractional crystallization. If the hydrogenation of scyllo-meso-inosose pentaacetate was carried out using methanol in-

(1) Presented at the 115th meeting of the American Chemical Society, San Francisco, March, 1949.

(2) Present address: Squibb Institute for Medical Research, New Brunswick, N. J.

(3) *E. g.*, E. Winterstein, *Ber.*, **30**, 2299 (1897).

(4) R. J. Anderson, *J. Biol. Chem.*, **18**, 441 (1914).

(5) R. J. Anderson, *ibid.*, **20**, 475 (1915).

(6) S. Posternak and Th. Posternak, *Helv. Chim. Acta*, **12**, 1165 (1929).

(7) R. J. Anderson, Ph.D. Dissertation, Cornell University, 1919.

(8) J. Cason and R. J. Anderson, *J. Biol. Chem.*, **126**, 527 (1938).

(9) G. I. de Sütö-Nagy and R. J. Anderson, *ibid.*, **171**, 749, 761 (1947).

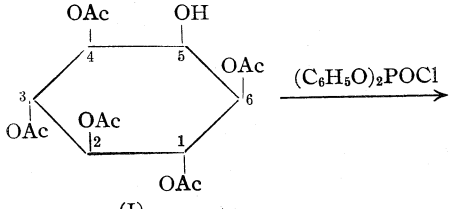
(10) E. Klenk and R. Sakai, *Z. physiol. Chem.*, **258**, 33 (1939).

(11) D. W. Woolley, *J. Biol. Chem.*, **147**, 581 (1943).

(12) Numbering according to H. O. L. Fischer, "Harvey Lectures," Ser. **40**, 156 (1945), and H. G. Fletcher, "Advances in Carbohydrate Chemistry," **3**, 45 (1948).

(13) Th. Posternak, *Helv. Chim. Acta*, **24**, 1045 (1941).

stead of acetic acid as a solvent, 1,2,3,4,6-pentaacetyl-meso-inositol (I) melting at 177–179° was obtained that contained no detectable amount of the scyllitol isomer.



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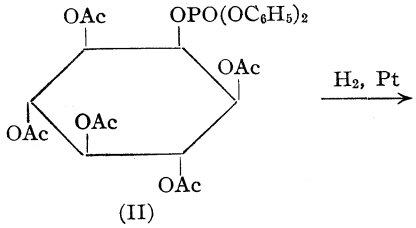

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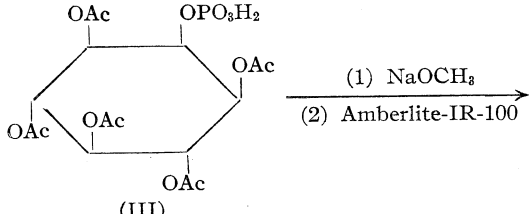

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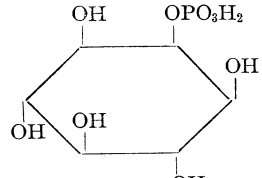


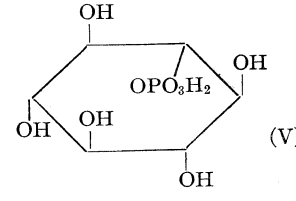
(IV)

Attempts to phosphorylate this substance by treatment with phosphorus oxychloride were unsuccessful. Quite unexpectedly the substance also proved to be rather resistant to phosphorylation with diphenylchlorophosphonate at low temperatures though this phosphorylating agent has been shown to react very rapidly with primary or secondary hydroxyl groups of carbohydrates.[14,15,16] By increasing the reaction temperature to 80° and by the use of an excess of diphenylchlorophosphonate it was possible to obtain 1,2,3,4,6-pentaacetyl-inositol-5-diphenylphosphate (II) in 64% yield. Removal of the phenyl groups by reductive cleavage with hydrogen in the presence of platinum oxide yielded 1,2,3,4,6-pentaacetyl-inositol-5-phosphoric acid (III) (80%).

The hydrolysis of the acetyl groups could be effected by various methods. Best results were obtained by catalytic saponification with sodium methylate in methanol. The sodium salt of inositol-5-phosphoric acid formed in the course of this reaction in quantitative yield is of sufficient purity for biological purposes. Removal of the cation by means of ion exchange gave inositol-5-phosphoric acid (IV) that crystallized from aqueous ethanol in hexagonal plates melting at 198–200° with decomposition. Both the free acid and the sodium salt were optically inactive. All the salts of inositol-5-phosphoric acid, with the exception of the lead salt, were easily soluble in water. The barium salt was precipitated as a white amorphous powder from an aqueous solution by addition of ethanol. Hydrolysis of inositol-5-phosphoric acid with hydrochloric acid gave meso-inositol which, after acetylation, proved to be identical with the hexaacetate of natural meso-inositol.

Inositol-5-phosphate was not attacked by *Acetobacter suboxydans* as was to be expected since the point of attack by the bacterial enzyme, the hydroxyl group on carbon atom 5, is blocked by a substituent. In bioassays with *Saccharomyces cerevisiae* the substance had approximately 4% of the activity shown by free meso-inositol whereas in assays with *Neurospora crassa* it was about 10% as effective as inositol. This is in agreement with the finding of Woolley[17] who demonstrated that inositol monophosphate isolated from soy bean lipositol had an activity of the same order. On hydrolysis of inositol-5-phosphoric acid the calculated amount of meso-inositol was liberated as could be shown in tests with *Neurospora crassa*.

The preparation of scyllitol monophosphoric acid[18] started from the mixture of inositol- and scyllitol-pentaacetates as obtained by catalytic reduction of scyllo-meso-inosose pentaacetate in glacial acetic acid.[13] Phosphorylation with diphenylchlorophosphonate gave a mixture of pentaacetylinositol-5-diphenylphosphate and of pentaacetylscyllitol-diphenylphosphate. The two components could not be separated at this stage, but after reductive cleavage of the phenyl groups the pentaacetyl-scyllitol-phosphoric acid could be separated easily from the corresponding derivative of meso-inositol by fractional crystallization. Catalytic saponification of the acetyl groups with sodium methylate yielded the sodium salt of scyllitol phosphoric acid. Removal of the cation by means of ion exchange gave scyllitol monophosphoric acid (V) that melted at 212–214°. The acid and its salts have characteristics similar to those of inositol-5-phosphoric acid. Hydroly-



(V)

(14) P. Brigl and H. Müller, *Ber.*, **72**, 2121 (1939).
(15) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **150**, 213 (1943).
(16) H. A. Lardy and H. O. L. Fischer, *ibid.*, **164**, 513 (1946).
(17) D. W. Woolley, *J. Biol. Chem.*, **140**, 461 (1941).
(18) Not numbered since all mono-substituted derivatives of scyllitol are identical due to the symmetric structure of the molecule.

sis with hydrochloric acid gave scyllitol in nearly quantitative yield.

Scyllitol monophosphoric acid was completely inactive in the bioassay with *Neurospora crassa* before and after hydrolysis of the phosphoric acid residue.

Experimental[19]

1,2,3,4,6-Pentaacetyl-inositol (I).—A suspension of 4 g. of scyllo-meso-inosose pentaacetate,[13] m. p. 147°, in 80 ml. of dry methanol was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 0.8 g. of platinum oxide (Adams catalyst). In the course of the reduction the starting material gradually dissolved. The absorption of hydrogen stopped after five hours when 1.1 moles of hydrogen had been consumed. After removing the catalyst by filtration the solution was concentrated at reduced pressure to 25 ml. On cooling, the 1,2,3,4,6-pentaacetyl-inositol crystallized in fine needles that were filtered after standing at 0° overnight; yield 2.73 g., m. p. 174–178°. From the mother liquor, after concentration to 5 ml., an additional 0.64 g. of the product with a slightly lower melting point was obtained (total yield, 84%). After recrystallization from anhydrous ethanol the substance melted at 177–179°.

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.22; H, 5.69. Found: C, 49.03; H, 5.95.

170 mg. of the substance was acetylated to the hexaacetate by treatment with 1 ml. of a mixture of 95% acetic anhydride and 5% concd. sulfuric acid; yield 180 mg. The hexaacetate, after recrystallization from ethanol, melted at 214–215°; admixture of inositol hexaacetate prepared from meso-inositol produced no depression of the melting point.

1,2,3,4,6-Pentaacetyl-inositol-5-diphenylphosphate (II).—To a solution of 5 g. of 1,2,3,4,6-pentaacetyl-inositol in 15 ml. of anhydrous pyridine, 10.35 g. (3 moles) of diphenylchlorophosphonate[14] was added. The mixture was kept at 80° for twenty hours with careful exclusion of moisture. On cooling in an ice-bath crystals of pyridine hydrochloride separated from the yellow colored solution. After dilution with 15 ml. of pyridine and addition of 0.2 ml. of ice-water to hydrolyze the excess of acid chloride the mixture was added to 1000 ml. of ice-water with vigorous stirring. From the emulsion, after about ten minutes, crystals appeared that were filtered after standing at 0° for two hours, washed with ice-water and cold ethanol, and dried *in vacuo* over sulfuric acid. Recrystallization of the crude product (5.95 g.) from 100 ml. of anhydrous ethanol gave 5.15 g. (64%) of pure 1,2,3,4,6-pentaacetyl-inositol-5-diphenylphosphate which crystallized in fine needles melting at 192–193°.

Anal. Calcd. for $C_{28}H_{31}O_{14}P$: C, 54.02; H, 5.02; P, 4.97. Found: C, 53.96; H, 5.15; P, 5.01.

The substance is easily soluble in acetone, ethyl acetate and chloroform, less soluble in methanol and ethanol, and only sparingly soluble in ether.

1,2,3,4,6-Pentaacetyl-inositol-5-phosphoric Acid (III).—A suspension of 4.5 g. of 1,2,3,4,6-pentaacetyl-inositol-5-diphenylphosphate in 90 ml. of anhydrous ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 0.2 g. of platinum oxide. The starting material went into solution as the reduction proceeded. The absorption of hydrogen stopped abruptly after ninety minutes when the theoretical quantity (8 moles) had been consumed. The catalyst was removed by filtration and the filtrate was concentrated at reduced pressure to 20 ml. On standing at 0° rapid crystallization occurred (prisms). After gradual addition of 20 ml. of petroleum ether (b. p. 50–60°) and standing at 0° for two hours the crystals were filtered and washed with a mixture of equal parts of ethanol and petroleum ether; yield 2.76 g. (80%). The substance melted at 233–234°; recrystallization did not change this melting point.

(19) All melting points are corrected.

Anal. Calcd. for $C_{16}H_{23}O_{14}P$: C, 40.85; H, 4.93; P, 6.59. Found: C, 40.99; H, 5.01; P, 6.53.

The substance is soluble in water, methanol, ethanol and acetone, insoluble in chloroform and ether. An aqueous solution reacts strongly acid.

Sodium Inositol-5-phosphate.—To 2.5 g. of 1,2,3,4,6-pentaacetyl-inositol-5-phosphoric acid dissolved in 25 ml. of cold anhydrous methanol 13.3 ml. of a 1 *N* solution of sodium methoxide in dry methanol (2.5 moles, 2 moles required for neutralization of the free acid groups) was added. After five minutes an amorphous precipitate of sodium inositol-5-phosphate appeared. The mixture was allowed to stand at 0° overnight. The product was separated by centrifuging and was washed on the centrifuge with dry methanol until the supernatant reacted neutral (four to five washings). After two additional washings with dry ether the substance was dried *in vacuo*. It weighed 1.59 g. (97%).

Anal. Calcd. for $C_6H_{11}O_9PNa_2$: P, 10.19. Found: P, 10.09.

The fine white powder is slightly hygroscopic. A 5% solution in water has a *p*H of 8.0.

Inositol-5-phosphoric Acid (IV).—This substance was prepared by passing a solution of 1 g. of the sodium salt of inositol-5-phosphoric acid in 10 ml. of water through a column containing 15 g. of moist Amberlite-IR-100-AG. The effluent was concentrated at reduced pressure to 3 ml. On addition of ethanol to incipient turbidity spontaneous crystallization occurred. After standing overnight at room temperature the crystals were collected on the filter and washed with ethanol; yield 0.70 g. (82%). For recrystallization the substance was dissolved in 2 ml. of water and 10 ml. of ethanol was added gradually. The colorless hexagonal plates melted with decomposition at 198–200° when rapidly heated and at 195–197° on slow heating.

Anal. Calcd. for $C_6H_{13}O_9P$: C, 27.69; H, 5.04; P, 11.92. Found: C, 27.63; H, 5.06; P, 11.96.

The substance showed no optical activity in concentrations up to 10%. It was very soluble in water, but insoluble in all organic solvents. A 0.2 molar aqueous solution had a *p*H value of 1.4. The salts of inositol-5-phosphoric acid were soluble in water, with the exception of the lead salt, which was formed by addition of lead acetate in excess to an aqueous solution of the free acid or its sodium salt. The barium salt was prepared by neutralizing a solution of the inositol-5-phosphoric acid with barium hydroxide (phenolphthalein) and adding an equal volume of ethanol. The amorphous precipitate was centrifuged, washed with several portions of 50% ethanol and finally with anhydrous ethanol, and dried *in vacuo*. The product contained water of crystallization which was removed only by heating at 120° and 0.1 mm. pressure for three hours.

Anal. Calcd. for $C_6H_{11}O_9PBa$: Ba, 34.7. Found: Ba, 34.6.

Cleavage of the phosphoric acid ester was effected by heating 0.25 g. of inositol-5-phosphoric acid in a sealed tube with 20 ml. of 2 *N* hydrochloric acid at 130° for twenty-four hours. After this period of time the solution was evaporated to dryness and the partly crystalline residue was dissolved in 3 ml. of water. On addition of ethanol to incipient turbidity meso-inositol crystallized spontaneously; yield 158 mg. (91%). The crude product (m. p. 222–226°), on acetylation with 1.2 ml. of a mixture of acetic anhydride (95%) and concd. sulfuric acid (5%), gave 345 mg. (91%) of inositol hexaacetate which, after recrystallization from ethanol, melted at 214–216°. Admixture of hexaacetate prepared from meso-inositol produced no depression of the melting point.

Biological Experiments

The action of *Acetobacter suboxydans* upon inositol-5-phosphoric acid was studied manometrically. Sodium inositol-5-phosphate, in quantities varying from 10 to 100 micromoles and adjusted to *p*H 6 with 1/15 molar phosphate buffer, was not attacked by a suspension of resting

bacteria (about 10 mg. dry weight) while in experiments with meso-inositol (20 micromoles) the calculated amount of oxygen was consumed within thirty minutes.

In the bioassay with *Saccharomyces cerevisiae* the method of Jurist and Foy[20] was used. The activity of inositol-5-phosphoric acid was 4 ± 2% of that shown by free meso-inositol. In bioassays with *Neurospora crassa*, carried out according to Beadle,[21] the substance was about 10% as active as inositol. All comparisons were made on the basis of the molecular weight. Hydrolysates of inositol-5-phosphoric acid, prepared by heating the sample with 2 *N* hydrochloric acid at 130° for twenty-four hours and subsequent concentration to dryness and neutralization with dilute sodium hydroxide, showed a 100 ± 3% activity for the inositol calculated to be present in such solutions.

Pentaacetyl-scyllitol Phosphoric Acid.—The synthesis of this substance started from the mixture of inositol- and scyllitol-pentaacetates as obtained by carrying out the hydrogenation of scyllo-meso-inosose pentaacetate in acetic acid instead of methanol. The product crystallized in apparently homogeneous needles melting at 161–163°.

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.22; H, 5.69. Found: C, 49.23; H, 5.52.

Acetylation of 300 mg. of this substance with 1.5 ml. of a mixture of 95% acetic anhydride and 5% concd. sulfuric acid gave 200 mg. of inositol hexaacetate which, after recrystallization from ethanol, melted at 215–216°, and 50 mg. of scyllitol hexaacetate melting at 299–300° after recrystallization from acetic anhydride. In the bioassay with *Saccharomyces cerevisiae* the mixture of meso-inositol- and scyllitol-pentaacetates, after hydrolysis with 2*N* hydrochloric acid, had only 74% of the activity shown by a hydrolysate of pure 1,2,3,4,6-pentaacetyl-inositol. These results indicate that the mixture contained about 25% scyllitol-pentaacetate. All attempts to separate scyllitol-pentaacetate from the inositol isomer failed.

Phosphorylation with diphenylchlorophosphonate, as described before, gave a mixture of pentaacetyl-inositol-diphenylphosphate and the corresponding scyllitol derivative in 65% yield. After recrystallization from ethanol the product melted at 173–181°.

Anal. Calcd. for $C_{28}H_{31}O_{14}P$: C, 54.02; H, 5.02; P, 4.97. Found: C, 53.81; H, 5.21; P, 4.96.

Attempts to separate the two isomers at this stage by fractional crystallization from ethanol or acetone–water and by fractional extraction with ether were unsuccessful.

3.1 g. of this product was hydrogenated as has been described for the pure pentaacetyl-inositol-diphenylphosphate. When the reduction neared completion fine crystals of pentaacetyl-scyllitol phosphoric acid separated. After warming to dissolve the product the catalyst was removed by filtration and the solution was concentrated at reduced pressure to 20 ml. On standing at room temperature pentaacetyl-scyllitol phosphoric acid separated in extremely fine needles; yield 0.43 g. (18%). From the mother liquor, after further concentration and standing at 0°, 1.60 g. (68%) of 1,2,3,4,6-pentaacetyl-inositol-5-phosphoric acid was obtained which was converted to free inositol-5-phosphoric acid as described before. Pentaacetyl-scyllitol phosphoric acid, after recrystallization from dry methanol, melted at 252–253° with decomposition.

Anal. Calcd. for $C_{16}H_{23}O_{14}P$: C, 40.85; H, 4.93; P, 6.59. Found: C, 41.03; H, 5.14; P, 6.50.

This substance, after removal of the substituents by hydrolysis with hydrochloric acid, was inactive in the bioassay with *Saccharomyces cerevisiae*.

Scyllitol Phosphoric Acid (V).—From 0.80 g. of pentaacetyl-scyllitol phosphoric acid, by catalytic saponification with 2.5 moles of sodium methoxide, 0.51 g. (98%) of sodium scyllitol phosphate was obtained as a white slightly hygroscopic powder.

Anal. Calcd. for $C_6H_{11}O_9PNa_2$: P, 10.19. Found: P, 9.88.

The free scyllitol-phosphoric acid was prepared from 0.4 g. of the sodium salt by removal of the cation with Amberlite-IR-100-AG. From the concentrated aqueous solution, on gradual addition of five volumes of ethanol, the free acid separated in fine crystals; yield 0.28 g. (82%). After recrystallization from water–ethanol the substance melted at 212–214° with decomposition.

Anal. Calcd. for $C_6H_{13}O_9P$: C, 27.69; H, 5.04; P, 11.92. Found: C, 27.61; H, 5.02; P, 11.89.

The substance is insoluble in all organic solvents. An aqueous solution reacts strongly acid (in 1 per cent. solution, *p*H 1.8). The lead salt is the only salt of scyllitol phosphoric acid that is insoluble in water. The barium salt is precipitated from an aqueous solution as a white amorphous powder by addition of 1 volume of ethanol.

Hydrolysis of 50 mg. of scyllitol-phosphoric acid by heating with 10 ml. of 2 *N* hydrochloric acid at 130° for twenty-four hours yielded 33 mg. (95%) of scyllitol, m. p. 345–350°. The crude product, on acetylation, gave 65 mg. (82%) of scyllitol hexaacetate that melted at 298–300°.

Acknowledgment.—The author wishes to express his gratitude to Professor H. O. L. Fischer who has made it possible for him to work on this problem. He is indebted to Dr. H. K. Mitchell, California Institute of Technology, for carrying out the bioassays with *Neurospora crassa*, and to Mr. H. C. Stancer, University of Toronto, for the bioassays with *Saccharomyces cerevisiae*.

Summary

Inositol-5-monophosphoric acid and scyllitol monophosphoric acid have been prepared in good yields by a method involving relatively few steps. Inositol-5-phosphoric acid is resistant to the attack by *Acetobacter suboxydans* and shows only a low activity in the bioassay with *Saccharomyces cerevisiae* and *Neurospora crassa*.

TORONTO, CANADA RECEIVED MAY 21, 1949

(20) V. Jurist and J. R. Foy, *J. Bacter.*, **47**, 434 (1944).

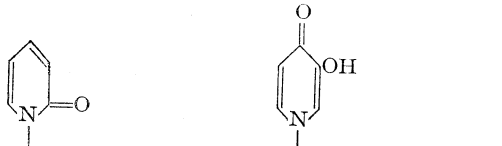
(21) G. W. Beadle, *J. Biol. Chem.*, **156**, 683 (1944).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Addition and Condensation Reactions of 2-Pyridone

BY ROGER ADAMS AND VIRON V. JONES[1]

2-Pyridone was used as a model compound for the study of reactions leading to structure I, which is analogous to the proposed structure for leucenol (II). Taking advantage of the ease with which 2-pyridone adds to acrylonitrile,[2] the reaction between 2-pyridone and α-acetamidoacrylic acid was studied. The adduct was obtained and by



hydrolysis the desired product (I) resulted. By substitution of 3-methoxy-4-pyridone for 2-pyridone and using a similar series of reactions, the successful synthesis of leucenol was attained.[3]

Many reactions of 2-pyridone which might lead to structure I were explored, before a satisfactory method was discovered. Some new chemistry of 2-pyridone was uncovered which is described in this communication.

2-Pyridone and acrylonitrile react readily to form β-(N-2-pyridone)-propionitrile[2] and by hydrolysis β-(N-2-pyridone)-propionic acid results. In an attempt to prepare the corresponding α-bromo compound from which the amino compound I could be made by the action of ammonia, β-(N-2-pyridone)-propionic acid was treated with bromine and red phosphorus. The isolated product contained two unreactive atoms of bromine from which it was deduced that two bromine atoms had probably been substituted in the 3,5-positions of the pyridone ring. 2-Pyridone has been shown by Koenigs and Geigy[4] to react very readily with bromine with formation of 3,5-dibromo-2-pyridone.

2-Pyridone and chloroacetaldehyde condense to the hydrochloride of N-2-pyridone acetaldehyde. The free base could not be obtained crystalline but a crystalline oxime and semicarbazone were prepared. The methods ordinarily successful for converting an aldehyde into the corresponding amino acid, which would permit the synthesis of I, failed.

2-Pyridone and bromopyruvic acid gave a product which appeared to be the 2-pyridonium salt of N-2-pyridone pyruvic acid hydrobromide since 2-pyridone was readily removed in the cold by means of picric acid and an immediate precipitate of silver bromide with silver nitrate suggested a hydrobromide. Since the reduction of the pyridone ring in the conversion of the keto to the primary amino group seemed likely from other experiments, this possible route to I was abandoned.

2-Pyridone adds to butadienesulfone with potassium hydroxide as catalyst to give the one-to-one addition product. It does not add under similar conditions to mesityl oxide.

The reaction of sodium 2-pyridone with α,β-dibromopropionic acid in an attempt to prepare α-bromo-β-(N-2-pyridone)-propionic acid was unsuccessful. Instead, a water soluble product ($C_8H_8NO_3Br$) resulted, the constitution of which was thoroughly investigated. Its aqueous solution was acid to congo red and gave an immediate precipitate of silver bromide with aqueous silver nitrate. The same product resulted from sodium 2-pyridone and ethyl α,β-dibromopropionate, followed by hydrolysis. After some knowledge of the structure was obtained, it was discovered that it could be more conveniently prepared from 2-pyridone and α-bromoacrylic acid. α-Bromoacrylic acid was probably an intermediate in the formation of the compound when α,β-dibromopropionic acid was used as a starting material. Ethyl α-bromoacrylate also reacted with 2-pyridone and the product upon heating in aqueous solution on the steam-bath gave the 2-pyridone α-bromoacrylic acid compound.

The structure of this adduct was determined through a study of its reactions. By treatment with ammonia the halogen atom was replaced by an amino group and the product was an amino acid which was isomeric but different from I and gave no color with ninhydrin. It was, therefore, assumed to be α-(N-2-pyridone)-β-aminopropionic acid (III). Upon treatment with dry hydrogen bromide, water was eliminated and the hydrobromide of a β-lactam (IV) was formed which by means of aqueous ammonia reverted to the amino acid. The amino acid upon treatment with dilute alkali was transformed with loss of ammonia to the corresponding hydroxy acid (V), which could be obtained directly from the 2-pyridone α-bromoacrylic acid adduct by the action of dilute aqueous alkali. It was also synthesized from 2-pyridone and glycidic acid. By the action of acetic anhydride, merely acetylation of the hydroxyl group took place, and no dehydration to the corresponding acrylic acid could be detected. The hydroxy acid was stable to and unchanged by boiling with 48% hydrobromic acid.

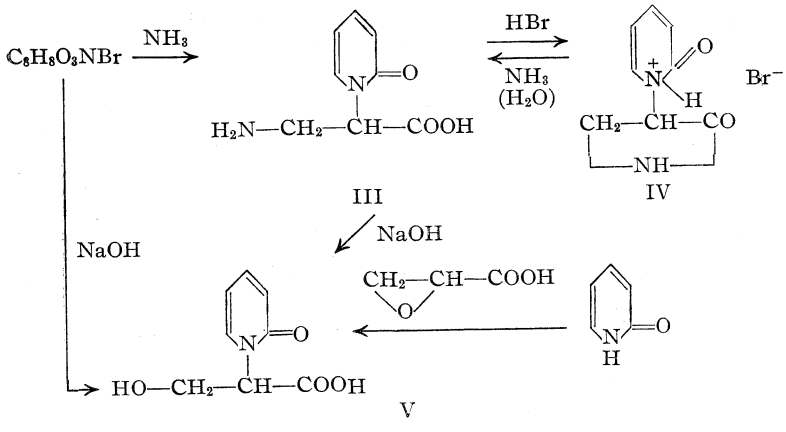
Electrometric titration of the 2-pyridone α-

(1) From a thesis presented by Viron V. Jones to the Graduate College of the University of Illinois, May, 1949, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. He held the Cincinnati Chemical Works Fellowship, 1946–1949.

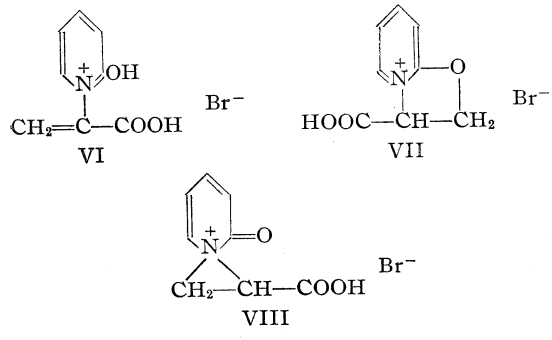
(2) Adams and Jones, THIS JOURNAL, **69**, 1803 (1947).

(3) Adams and Johnson, *ibid.*, **71**, 705 (1949).

(4) Koenigs and Geigy, *Ber.*, **17**, 591 (1884).



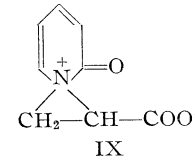
bromoacrylic acid adduct with sodium hydroxide exhibited a curve having but one end-point and typical for that of a strong monobasic acid. The strength of the acid and high activity of the halogen is comparable to that of a betaine hydrobromide $(R_3NCH_2COOH)^+(Br)^-$. Three possible structures, (VI, VII, VIII), which will serve to explain the electrometric titration, water solubility and the ionizable bromine, can be postulated for the adduct.



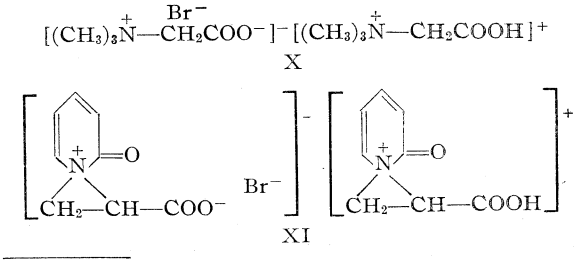
The infrared absorption showed two bands in the carbonyl region, one at 1760 cm.$^{-1}$, attributed to a carboxyl, and one at 1649 cm.$^{-1}$, to a pyridone carbonyl (Fig. 1). The absorption coincides well with that of β-(N-2-pyridone)-propionic acid. These data are presented as evidence against formula VI and VII. Moreover, 2-propoxypyridine has no absorption in the carbonyl region, while N-*n*-propylpyridone has a strong band at 1660 cm.$^{-1}$ (Fig. 1).

Formula VIII is in accord with the structure of similar compounds proposed by Cromwell[5] as intermediates in the reaction of amines with α-bromo-α,β-unsaturated ketones. The formation of a β-amino or β-hydroxy acid by the action of ammonia or aqueous alkali on the 2-pyridone α-bromoacrylic acid adduct may be explained on the basis of this formula by assuming cleavage in the β-position to the carboxyl group, thus leaving the pyridone residue in the α-position.

When VIII reacted in the cold with silver oxide or sodium bicarbonate, a halogen-free product resulted, insoluble in non-polar solvents, soluble in water and lower alcohols. A molecular weight determined by the freezing point depression of water showed it to be monomeric. Infrared data indicated a free carboxyl ion which must exist as an internal salt. A comparison of the infrared spectrum of a betaine hydrobromide with that of the corresponding betaine was made. A carbonyl band at 1740 cm.$^{-1}$ in the former and a carbonyl band at 1625 cm.$^{-1}$ in the latter was found, a difference of 115 cm.$^{-1}$. The absorption of the 2-pyridone α-bromoacrylic acid adduct shows a carbonyl band at 1760 cm.$^{-1}$ and that of the hydrobromide free product, a carbonyl band at 1630 cm.$^{-1}$, a difference of 130 cm.$^{-1}$. It has been shown that the carboxyl group in compounds containing zwitterions absorbs at a lower wave number than compounds containing normal carboxyl groups.[6] These results support the postulation that the hydrobromide-free product has structure IX. Another similarity to the betaines is found in the formation of a hemihydrobromide.



Stoltzenberg[7] prepared a hemihydrochloride and hemihydrobromide of the betaine of N-trimethylglycine. The 2-pyridone α-bromoacrylic acid adduct reacts with one-half mole of silver oxide to give a compound containing one atom of bromine for two pyridone residues. The same product resulted from mixing equimolar quantities of the 2-pyridone α-bromoacrylic acid adduct and the hydrohalide-free product. Structures for such hemihalides can be formulated on the basis of the assumption that a proton from the carboxyl of the betaine hydrobromide is accepted by a molecule of the betaine base with a crystalline salt resulting (X and XI).



(5) Cromwell and Cram, THIS JOURNAL, **65**, 301 (1943); Cromwell and Witt. *ibid.*, **65**, 308 (1943).

(6) Wright, *J. Biol. Chem.*, **127**, 137 (1939).

(7) Stoltzenberg, *Z. physiol. Chem.*, **92**, 470 (1914).

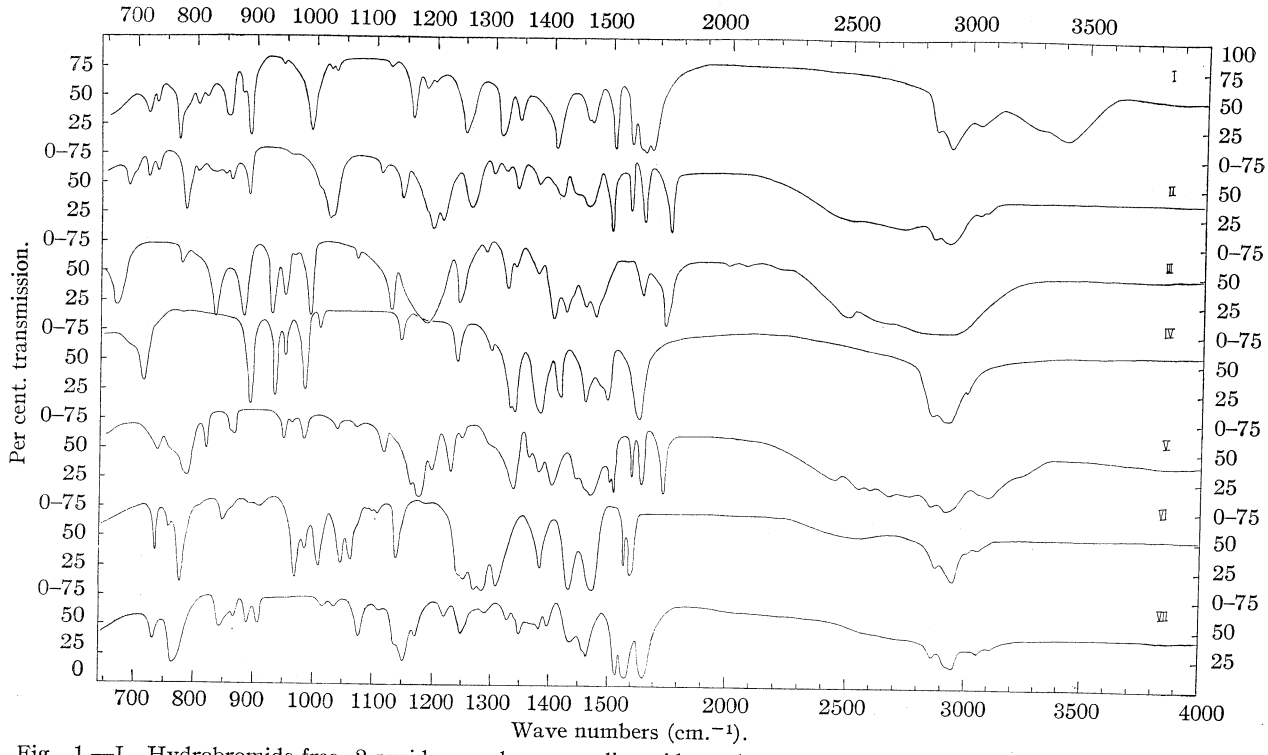


Fig. 1.—I, Hydrobromide-free 2-pyridone α-bromoacrylic acid product; II, 2-pyridone α-bromoacrylic acid adduct; III, betaine hydrobromide; IV, betaine; V, N-2-pyridonepropionic acid hydrobromide; VI, 2-propoxypyridine; VII, N-*n*-propyl-2-pyridone. Compounds I–V (inc.) were run as nujol mulls; compounds V and VI, which were liquids, were run in a 0.025 mm. cell.

The reduction products of the 2-pyridone α-bromoacrylic acid adduct were also investigated. With palladium on charcoal as catalyst, two moles of hydrogen were absorbed and a sirup resulted which would not crystallize. It contained an ionizable bromine since a copious precipitate of silver bromide formed upon treatment with silver nitrate. By the action of ammonia, an amino acid resulted, identical with the hydrogenation product of α-(N-2-pyridone)-β-aminopropionic acid (III) in which the pyridone residue had been reduced to piperidone. The intermediate sirup is probably the piperidone analog of VIII.

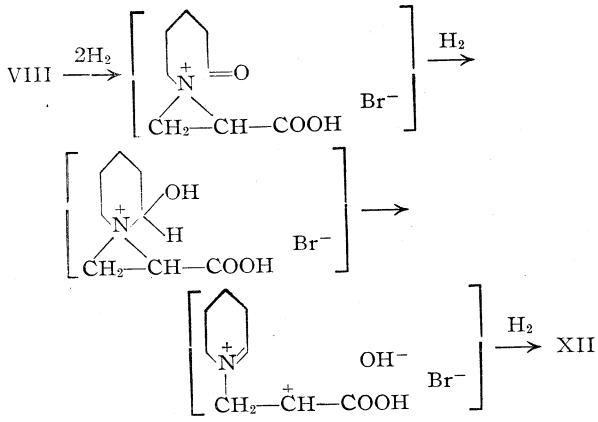
On the other hand, when platinum oxide was used as a catalyst, four moles of hydrogen were absorbed and a crystalline compound, $C_8H_{15}NO_3$·HBr, was obtained. A free base resulted upon treatment with silver oxide. Esterification to a methyl ester hydrobromide occurred when boiled in methanol but not by treatment with diazomethane. The free base was not identical with β-(N-2-piperidone)-propionic acid or α-(N-2-piperidone)-propionic acid formed by the reduction with hydrogen and platinum oxide of the corresponding pyridones. Moreover, the corresponding hydrobromide of β-(N-2-pyridone)-propionic acid absorbed only two moles of hydrogen.

A clue to the structure of this reduction product was obtained by its pyrolysis at 185° (1 mm.) in a sublimation apparatus. Piperidine hydrobromide was obtained, indicating that the oxygen in the pyridone ring in the starting compound had migrated to the propionic acid residue. The infrared spectrum of the reduction product showed no carbonyl group other than the carboxyl and a band at 3400 cm.$^{-1}$ indicative of a hydroxyl. The product proved to be α-hydroxy-β-piperidinopropionic acid (XII). It was synthesized from α-hydroxy-β-chloropropionic acid and piperidine or from piperidino-acetaldehyde hydrochloride by treatment with sodium cyanide followed by hydrolysis.



XII

The mechanism of the formation of XII probably involves first reduction of the pyridone nucleus to the piperidone since by hydrogenation of the 2-pyridone α-bromoacrylic acid adduct with palladium on charcoal as catalyst, followed by treatment with ammonia, a piperidone derivative resulted. If the piperidone carbonyl is next reduced, a pseudo base will be formed which may rearrange to a carbonium hydroxide. The latter upon reduction could yield the hydrobromide of the hydroxy acid (XII).



Ethyl α-bromo-β-ethoxypropionate and sodium 2-pyridone yielded a compound with the composition $C_{15}H_{16}O_4N_2$. The product was assumed to be ethyl α,β-di-(N-2-pyridone)-propionate. Both the ethoxy group and bromine atom appear to have been replaced by pyridone residues.

Experimental

α-Acetamido-β-(N-2-pyridone)-propionic Acid.—A mixture of 0.5 g. of α-acetamidoacrylic acid[8] and 0.5 g. of 2-pyridone[2] was heated on a metal-bath at 140° for one hour. The thick sirup which formed was dissolved in 5 ml. of chloroform and allowed to evaporate overnight. A small amount of solid separated in the sirup. This product was stirred with 5 ml. of acetone and left in the refrigerator for one day. A small amount of colorless granules was obtained. After recrystallization from methanol, the product melted at 199° (cor.) with decomposition.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.40. Found: C, 53.20; H, 5.50.

α-Amino-β-(N-2-pyridone)-propionic Acid.—A mixture of 0.3 g. of α-acetamido-β-(N-2-pyridone)-propionic acid and 5 ml. of 48% hydrobromic acid was refluxed for six hours. The excess acid was removed by distillation on the steam-cone under reduced pressure. The sirup which remained was made just basic to litmus paper with concentrated ammonia, and evaporated to dryness. The residue was crystallized from the minimum amount of water. The yield was 0.17 g. (72%) of a product melting at 236° (cor.) with decomposition. It gave a blue color with ninhydrin solution.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.75; H, 5.53. Found: C, 52.75; H, 5.79.

Bromination of β-(N-2-Pyridone)-propionic Acid; β-(3,5-Dibromo-N-2-pyridone)-propionic Acid.—A mixture of 15 g. of β-(N-2-pyridone)-propionic acid,[2] 3.6 g. of red phosphorus and 30 ml. of carbon tetrachloride contained in a three-necked round-bottom flask was cooled in an ice-bath and equipped with dropping funnel, stirrer and reflux condenser. To this was added dropwise with stirring 60 g. of bromine. After completion of the addition, the mixture was gradually heated until nearly all the hydrogen bromide had been removed. The carbon tetrachloride was distilled on the steam-cone leaving a dark semi-solid material which was then boiled with a little water and diluted to 400 ml. with water. After cooling in an ice-bath, fine white granules precipitated. The yield was 10 g. (32%). The product was recrystallized from 50% ethanol and melted at 182° (cor.). It gave a negative test with boiling silver nitrate solution.

Anal. Calcd. for $C_8H_7NO_3Br_2$: C, 29.44; H, 2.22; N, 4.31. Found: C, 29.63; H, 2.23; N, 4.40.

(8) Bergmann and Grafe, *Z. physiol. Chem.*, **187**, 187 (1930).

N-2-Pyridone Acetaldehyde Hydrochloride.—A mixture of 20 g. of methyl chloroacetal and 10 g. of water containing ten drops of concentrated hydrochloric acid was refluxed until the two phases disappeared. To this hot solution was added 10 g. of 2-pyridone and the refluxing continued for one hour. All the volatile materials were distilled on a steam-cone at 20 mm. After addition of 50 ml. of acetone to the resulting sirup, it was placed in a refrigerator overnight. A solid crystalline mass resulted which upon filtration gave 12 g. (66%) of product. After recrystallization from absolute ethanol, the melting point was 139–140° (cor.).

This product upon treatment with aqueous sodium bicarbonate or sodium hydroxide yielded a sirup which would not crystallize. The sirup was soluble in ethanol and ether, but insoluble in water. It gave a positive reaction to Tollens reagent.

Anal. Calcd. for $C_7H_8NO_2Cl$: C, 48.48; H, 4.62; N, 8.17; Cl, 20.42. Found: C, 48.53; H, 4.58; N, 7.97; Cl, 20.25.

After neutralization of the hydrochloride with solid sodium bicarbonate and extraction with ether, the N-2-pyridone acetaldehyde was treated with pyridine and hydrogen cyanide and a trace of solid potassium hydroxide. After standing and subsequent treatment with ammonia, followed by hydrobromic acid hydrolysis, no amino acid could be isolated.

Similarly, ammonium carbonate and sodium cyanide did not give the desired condensation product.

N-2-Pyridone Acetaldoxime.—A solution of 20 ml. of 95% ethanol containing 1.0 g. of 2-pyridone acetaldehyde hydrochloride and 1.0 g. of hydroxylamine hydrochloride was made just basic to moist litmus paper with 10% aqueous sodium hydroxide, and evaporated to dryness on a steam-cone. The residue was extracted with 20 ml. of ether and yielded 0.75 g. (85%) of a light yellow solid upon evaporation. Recrystallization from carbon tetrachloride resulted in a product melting at 78–79° (cor.).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.33; N, 18.41. Found: C, 55.41; H, 5.14; N, 18.32.

N-2-Pyridone Acetaldehyde Semicarbazone.—A mixture of 1.0 g. of 2-pyridone acetaldehyde hydrochloride, 1.5 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate was dissolved in 20 ml. of water and heated on a steam-cone for five minutes. A white precipitate formed after cooling in an ice-bath. The yield of product was 1.1 g. (100%). After crystallization from methanol, the product melted at 155–156° (cor.).

Anal. Calcd. for $C_8H_{10}O_2N_4$: C, 49.49; H, 5.16; N, 28.87. Found: C, 49.46; H, 5.14; N, 28.80.

Reaction of 2-Pyridone and Bromopyruvic Acid.—To 75 ml. of chloroform containing 3.4 g. of bromopyruvic acid,[9] 4 g. of 2-pyridone was added and the mixture held at 55° for ten hours. After evaporation to a thick sirup, 50 ml. of acetone was added and then five drops of 48% hydrobromic acid. Upon standing in a refrigerator for twenty-four hours, a granular solid formed weighing 5.8 g. (78%). After recrystallization from 95% ethanol, the melting point was 143–145° (cor.) with decomposition.

Anal. Calcd. for $C_{13}H_{13}O_5N_2Br$: C, 43.72; H, 3.67. Found: C, 43.65; H, 3.49.

This product gave a 2-pyridone picrate from ethanol and a positive test with Tollens reagent.

Reaction of 2-Pyridone and Butadiene Sulfone.—A mixture of 5.0 g. of 2-pyridone and 7.0 g. of butadiene sulfone was refluxed for two hours in 50 ml. of absolute ethanol containing two pellets of potassium hydroxide. The ethanol was distilled off on a steam-cone using vacuum toward the end. The resulting thick sirup was stirred up with 25 ml. of acetone and placed in a refrigerator overnight. A mass of fine white crystals formed. The filtrate yielded upon evaporation a second crop of crystals, making the total yield of 8.2 g. (73%). The product was purified by recrystallization from acetone, m. p. 136–137°.

(9) Sprinson and Chargaff, *J. Biol. Chem.*, **164**, 411 (1946).

Anal. Calcd. for $C_9H_{11}NO_3S$: C, 50.70; H, 5.17; N, 6.57. Found: C, 51.00; H, 5.08; N, 6.64.

Under analogous conditions, no condensation product of 2-pyridone and mesityl oxide resulted.

Reaction of α,β-Dibromopropionic Acid and the Sodium Salt of 2-Pyridone.—A mixture of 20 g. of the dihydrate of the sodium salt of 2-pyridone and 30 g. of α,β-dibromopropionic[10] acid in 50 ml. of acetone was heated on a steam-cone until bumping became too severe. The solvent was then allowed to evaporate aided by a stream of air. The resulting thick pasty mass was extracted once with 50 ml. of hot nitromethane and filtered from the sodium bromide. Ether was added to the filtrate until faint cloudiness appeared and then placed in a refrigerator overnight. The yield of almost white granular material was 22 g. (64%). After recrystallization once from 95% ethanol and once from water, the melting point was 122–123° (cor.).

The product was soluble in water forming a solution acid to congo red paper. The very pure material was insoluble in all organic solvents, but when crude was soluble in ethanol. The aqueous solution formed instantly a voluminous precipitate with aqueous silver nitrate solution.

Anal. Calcd. for $C_8H_8O_3NBr \cdot H_2O$: C, 36.41; H, 3.79; N, 5.30. Found: C, 36.76; H, 3.81; N, 5.19.

The sample was dried in an Abderhalden at 100° and 1 mm. to constant weight.

Anal. Calcd. for $C_8H_8O_3NBr$: C, 39.04; H, 3.27; N, 5.69. Found: C, 39.18; H, 3.01; N, 5.64.

Electrometric Titration.—A solution of 0.242 g. of the adduct hydrate in 25 ml. of water was titrated electrometrically with 0.0895 *N* sodium hydroxide. The initial *p*H was 2.0 and readings were taken at regular intervals to the phenolphthalein end-point. The resulting curve was typical of that for strong acids such as hydrobromic acid, and there was but one end-point. Calcd. for $C_8H_{10}NO_4Br$: mol. wt., 264. Found: mol. wt., 267.

Reaction of Sodium 2-Pyridone and Ethyl α,β-Dibromopropionate.—To a mixture of 12 g. of anhydrous sodium 2-pyridone in 100 ml. of absolute ethanol was added 28 g. of ethyl α,β-dibromopropionate.[10] A reaction occurred with the evolution of heat. The mixture was refluxed until bumping became severe (about fifteen minutes), and filtered from an inorganic residue. The filtrate was evaporated to a sirup and after taking up in 50 ml. of isopropyl alcohol was filtered from more of the inorganic material. The isopropyl alcohol was evaporated leaving a sirup which was soluble in water and ethanol but insoluble in ether and benzene. The aqueous solution was acid to congo red paper and yielded instantly a heavy precipitate of silver bromide with cold silver nitrate solution. The sirup did not crystallize after standing in a warm place for one week, but after mixing with acetone and allowing to stand in the refrigerator for two days, 6 g. of a crystalline product, m. p. 122°, was isolated. The melting point of this mixed with a 2-pyridone bromoacrylic acid adduct showed no depression.

Reaction of 2-Pyridone and α-Bromoacrylic Acid.—A mixture of 10 g. of 2-pyridone and 16 g. of α-bromoacrylic acid[10] and 0.2 g. of water containing 0.5 g. of *t*-butylcatechol was heated on the steam-cone with occasional stirring for one hour. The resulting thick sirup was dissolved in 50 ml. of boiling isoamyl alcohol and allowed to stand at room temperature for twenty-four hours then transferred to a refrigerator overnight. The fine white crystalline solid weighed 19 g. (70%). After recrystallization from a small volume of water it melted at 122–123° (cor.). This is the preferred method of synthesis.

Reaction of 2-Pyridone and Ethyl α-Bromoacrylate.—A mixture consisting of 9.5 g. of 2-pyridone and 18 g. of ethyl α-bromoacrylate[10] was heated for four hours on the steam-cone. A thick sirup resulted which was acid to moist congo red paper, and which yielded instantly a heavy precipitate of silver bromide with silver nitrate solution. The sirup was soluble in water and ethanol, but insoluble in ether and benzene. No crystallization occurred after standing in a warm place for three days, but when stirred with 25 ml. of acetone and allowed to stand in the refrigerator twenty-four hours, a granular precipitate formed. The yield was 4.5 g. and after recrystallization from ethanol melted at 120°.

Reaction of the 2-Pyridone Bromoacrylic Adduct with Ammonia; α-(N-2-Pyridone)-β-aminopropionic Acid.—A mixture of 2.0 g. of the adduct hydrate and 20 ml. of concentrated aqueous ammonia was refluxed for one hour. The resulting solution was evaporated to a solid and a sirup on the steam-cone aided by a stream of air. It was then dissolved in 25 ml. of methanol and allowed to stand twenty-four hours in the refrigerator, after which the granular crystals were filtered. An additional amount of material was obtained by evaporating the filtrate to dryness and recrystallizing from the minimum amount of boiling methanol. The total yield was 1.0 g. (71%) and after recrystallization from 50% methanol it melted at 213–215° (cor.) with decomposition. The pure product was soluble in water, insoluble in ethanol and non-polar solvents, and gave a negative test with ninhydrin and with Nessler reagent.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.54; N, 15.40. Found: C, 52.89; H, 5.41; N, 15.33.

Reaction of α-(N-2-Pyridone)-β-aminopropionic Acid and Hydrobromic Acid; α-(N-2-Pyridone)-β-aminopropiolactam Hydrobromide.—Dry hydrogen bromide was passed into a suspension of 0.35 g. of the amino acid in 2 ml. of absolute ethanol until a clear solution resulted. This solution, after standing in a refrigerator overnight, yielded 0.45 g. (89%) of fine colorless crystals. After recrystallization from 95% ethanol the product melted at 298–299° (cor.) with decomposition.

Anal. Calcd. for $C_8H_9N_2O_2Br$: C, 39.20; H, 3.72; N, 11.43; Br, 32.60. Found: C, 39.36; H, 3.75; N, 11.63; Br, 32.72.

A little of this material was dissolved in 0.5 ml. of water and made basic to litmus with aqueous ammonia. After evaporating to dryness, the residue was dissolved in the minimum amount of methanol and set in an ice-bath. The white granular crystals melted at 211–213° (cor.) with decomposition and the melting point of a mixture with α-(N-2-pyridone)-β-aminopropionic acid showed no depression.

Reaction of α-(N-2-Pyridone)-β-aminopropionic Acid and Sodium Hydroxide; α-(N-2-Pyridone)-β-hydroxypropionic Acid.—A solution of 0.5 g. of sodium hydroxide in 5 ml. of water and 0.8 g. of the amino acid was refluxed for one-half hour. Ammonia was liberated. The resulting solution was made acid to congo red paper with concentrated hydrochloric acid and allowed to remain in the refrigerator overnight. The granular crystals weighed 0.42 g. (52%) and melted at 168–172°. This proved to be identical with the hydroxy acid prepared by treating the 2-pyridone-α-bromoacrylic acid adduct with alkali.

Reaction of the 2-Pyridone Bromoacrylic Adduct with Sodium Hydroxide; α-(N-2-Pyridone)-β-hydroxypropionic Acid.—A solution of 6.8 g. of the adduct hydrate and 2.0 g. of sodium hydroxide in 25 ml. of water was refluxed for one hour. After cooling somewhat, 2.5 g. of concentrated sulfuric acid was added carefully and the mixture allowed to remain in the refrigerator overnight. The yield of fine granular crystals was 3.8 g. (79%). After recrystallization from methanol, the melting point was 173–175° (cor.).

Anal. Calcd. for $C_8H_9NO_4$: C, 52.45; H, 4.97. Found: C, 52.72; H, 5.18.

A mixture of 1.5 g. of the hydroxy acid and 10 ml. of 48% hydrobromic acid was refluxed for four hours. The excess acid was distilled *in vacuo* and the semicrystalline residue was taken up in 5 ml. of water. After neutralizing with sodium carbonate to congo red, a crystalline precipitate formed which was unchanged hydroxy acid.

α-(N-2-Pyridone)-β-acetoxypropionic Acid.—Upon refluxing 1 g. of this compound with 5 ml. of acetic an-

(10) Marvel, Cook and Cowan, THIS JOURNAL, **62**, 3495 (1940).

hydride for fifteen minutes and distilling the excess anhydride *in vacuo*, a thick sirup was obtained which solidified on standing. It was washed with acetone and recrystallized from methanol. The yield of colorless flakes was 0.47 g. (39%). The pure product melts at 224–225° (cor.).

Anal. Calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.93; N, 6.23. Found: C, 53.11; H, 4.99; N, 6.07.

Reaction of 2-Pyridone and Glycidic Acid; α-(N-2-Pyridone)-β-hydroxypropionic Acid.—A mixture of 1.3 g. of the potassium salt of glycidic acid[11] and 0.95 g. of 2-pyridone in 2 ml. of ethanol was heated on the steam-cone for one hour. The sirup was taken up in 10 ml. of absolute ethanol and made just acid to congo red paper with hydrochloric acid and evaporated to dryness. The residue was extracted with 1.0 ml. of glacial acetic acid to remove the inorganic residue. The acetic acid was distilled on the steam-cone using vacuum. The sirup was transferred to a vacuum desiccator containing moist sodium hydroxide and allowed to stand overnight. The material solidified and after recrystallizing from 10 ml. of absolute ethanol yielded 1.0 g. (55%) of a tan-colored solid. After recrystallizing from methanol, the product melted at 173° (cor.) and the melting point of this mixed with the product obtained from the alkali treatment of the 2-pyridone α-bromoacrylic acid adduct showed no depression.

Reaction of the 2-Pyridone α-Bromoacrylic Acid Adduct and One Mole of Silver oxide.—A solution of 2.6 g. of the very pure adduct hydrate in 20 ml. of methanol was poured into a mortar and macerated for two minutes with the silver oxide prepared from 1.7 g. of silver nitrate. The silver bromide was removed by filtration and the filtrate evaporated at room temperature aided by a stream of filtered air. The crystalline residue was stirred with 10 ml. of *n*-propyl alcohol and filtered. The yield was 1.0 g. (56%). The melting point was elevated to 105–107° (cor.) by dissolving in the minimum amount of cold methanol and repeating the evaporation and *n*-propyl alcohol treatment. The product which is merely the adduct with a molecule of hydrogen bromide eliminated was insoluble in acetone, ether and benzene. It was soluble in hot *n*-propyl alcohol but no crystalline product could be obtained by cooling.

Anal. Calcd. for $C_8H_7NO_3.H_2O$: C, 52.45; H, 4.97. Found: C, 52.98; H, 5.13.

Upon drying in an Abderhalden, the melting point was 159–165° (cor.).

Anal. Calcd. for $C_8H_7NO_3$: C, 58.17; H, 4.28. Found: C, 58.45; H, 4.41.

Upon dissolving the product in concentrated hydrobromic acid and evaporating, a sirup resulted which on standing crystallized. It proved to be the 2-pyridone α-bromoacrylic acid adduct.

Reaction of the 2-Pyridone α-Bromoacrylic Acid Adduct and One-Half Mole of Silver Oxide.—A solution of 0.2 g. of the adduct hydrate in 25 ml. of methanol was macerated in a mortar for several minutes with the silver oxide prepared from 0.67 g. of silver nitrate. After removing the silver bromide by filtration, the filtrate was evaporated at room temperature to a crystalline residue aided by a stream of air. The solid was dissolved in the minimum amount of boiling absolute ethanol and allowed to stand for forty-eight hours in a refrigerator. The yield of granular crystals was 0.8 g. (50%). Recrystallization from methanol yielded a product melting at 156° (cor.) with decomposition. This product is a hemihydrobromide. An aqueous solution gave a heavy precipitate of silver bromide with silver nitrate solution.

Anal. Calcd. for $C_{16}H_{15}N_2O_6Br$: C, 46.72; H, 3.69. Found: C, 46.49; H, 3.54.

This product was also prepared by mixing 0.45 g. of the 2-pyridone α-bromoacrylic acid adduct hydrate and 0.25 g. of the hydrobromide-free compound in 2 ml. of 50% methanol and evaporating to dryness. The residue upon recrystallizing from ethanol yielded 0.37 g. of crystals melting at 156° (cor.) with decomposition. No depression in melting point was observed when mixed with the hemihydrobromide prepared by the silver oxide method.

Hydrogenation of the 2-Pyridone α-Bromoacrylic Acid Adduct with Palladium on Charcoal and Treatment of the Product with Ammonia; α-(N-2-Piperidone)-β-aminopropionic Acid.—A solution of 2 g. of the adduct hydrate in 100 ml. of hot 95% ethanol was hydrogenated at 50° and 50 lb. hydrogen pressure using 1.0 g. of palladium–charcoal catalyst. Two moles of hydrogen were absorbed. The solution was filtered and evaporated to a sirup. A solution of 50 ml. of methanol saturated with ammonia was added to the sirup and allowed to evaporate in a warm place. The resulting sirup was placed in a vacuum desiccator for two days. A small amount of granular material formed. This was washed with acetone and recrystallized from methanol. The yield of product was 0.5 g. melting at 177–179° (cor.) with decomposition.

Anal. Calcd. for $C_8H_{14}N_2O_3 \cdot H_2O$: C, 47.04; H, 7.93; N, 13.73. Found: C, 47.10; H, 7.63; N, 13.38.

α-(N-2-Pyridone)-β-aminopropionic Acid.—A solution of 1 g. of the amino acid in 50 ml. of 50% ethanol was hydrogenated at 50-lb. pressure and at 50° using 50 mg. of platinum oxide catalyst. Twelve hours was required for complete hydrogenation during which two moles of hydrogen was absorbed. The solution was filtered to remove the catalyst and evaporated at room temperature to a thick sirup. After drying in a vacuum desiccator for one day, a hard glass formed which from isoamyl alcohol yielded 0.65 g. (59%) of a white powder. Purification was effected by recrystallization from methanol, m. p. 177–179° (cor.) with decomposition. A melting point of a mixture with the product prepared in the previous experiment showed no depression.

Hydrogenation of the 2-Pyridone α-Bromoacrylic Acid Adduct with Platinum Oxide Catalyst.—A solution of 100 ml. of 95% ethanol containing 4.0 g. of the adduct hydrate and 50 mg. of platinum oxide was hydrogenated at 50° and 50 lb. pressure. In three hours four moles of hydrogen had been taken up and no further absorption occurred. The platinum was filtered off and the filtrate evaporated at room temperature aided by a stream of air. The crystalline solid which remained was washed with acetone. The yield was 3.2 g. (83%). The melting point of the sample purified by recrystallizing from nitromethane was 173–174° (cor.).

Anal. Calcd. for $C_8H_{16}NO_3Br$: C, 37.80; H, 6.36; N, 5.52. Found: C, 38.10; H, 6.36; N, 5.45.

Maceration in a mortar of 0.9 g. of the product in 10 ml. of methanol with silver oxide prepared from 0.61 g. of silver nitrate, was continued until the brown color disappeared. The filtrate from this slurry was evaporated at room temperature aided by a stream of air. The residual solid was crystallized from methanol and weighed 0.5 g. (82%). After further purification, the product melted at 219–220° (cor.) with decomposition.

This product was soluble in water and methanol, insoluble in the higher alcohols and all non-polar solvents. When refluxed with 48% hydrobromic acid for four hours, the original hydrobromide was obtained in 86% yields.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.46; H, 8.75; N, 8.09. Found: C, 55.33; H, 8.83; N, 8.07.

Esterification of the Hydrogenated 2-Pyridone α-Bromoacrylic Acid Adduct.—A solution of 5 g. of the hydrogenated adduct in 50 ml. of methanol and 1 ml. of 48% hydrobromic acid was refluxed for twelve hours. The volatile materials were removed by distillation on a steam-cone using vacuum toward the end. A thick sirup remained which solidified upon cooling. The yield of material, after recrystallization from isopropyl alcohol, was 4.5 g. (86%). The melting point after further recrystallization from the same solvent was 141° (cor.).

Anal. Calcd. for $C_9H_{18}NO_3Br$: C, 40.31; H, 6.79. Found: C, 40.14; H, 6.78.

(11) Freudenberg, *Ber.*, **47**, 2027, 2034 (1914).

Attempts to obtain the free ester by treatment with silver oxide and methanol resulted in hydrolysis and only the free acid could be isolated. Diazomethane in methanol failed to methylate the free acid.

Pyrolysis of the Platinum Oxide Hydrogenated 2-Pyridone α-Bromoacrylic Acid Adduct.—The pyrolysis was conducted by heating 0.62 g. of the four mole hydrogenated 2-pyridone α-bromoacrylic acid adduct in a sublimation apparatus at 175–185° (1 mm.). At first considerable bubbling occurred, but after about one hour the mass became solid, and the temperature was elevated to 205–210°. A white product sublimed onto the cold finger weighing 0.35 g. (88%). After recrystallization from nitromethane, the product melted at 236° which was identified as piperidine hydrobromide.

The same product was obtained by allowing the pyrolysis temperature to remain at 185°, and the solid mass taken up in nitromethane. Upon cooling and adding an equal volume of dioxane, the piperidine hydrobromide separated.

Reaction of Piperidine and α-Hydroxy-β-chloropropionic Acid.—A mixture of 2.0 g. of α-hydroxy-β-chloropropionic acid and 4.0 g. of piperidine was heated on a steam-cone for one hour. Upon cooling, a solid and a sirup remained. This was stirred with 15 ml. of dioxane and chilled in an ice-bath. The piperidine hydrochloride which separated was removed by filtration, and the filtrate allowed to evaporate. The resulting sirup was left in a vacuum desiccator overnight. A crystalline product was obtained after allowing to stand under 25 ml. of ether in a warm place and replacing the colored ether with fresh ether every two hours over a period of one day. The solid was washed with dioxane and weighed 1.6 g. (55%). The product was purified by recrystallizing from methanol, m. p. 219° (cor.) with decomposition. The melting point when mixed with the four mole hydrogenated 2-pyridone α-bromoacrylic acid adduct base showed no depression.

Piperidinoacetaldehyde Hydrochloride.—A mixture of 22 g. of piperidinoacetaldehyde methyl acetal[12] and 20 ml. of concentrated hydrochloric acid was refluxed for one hour. The aqueous acid was distilled on a steam-cone *in vacuo* leaving a thick sirup. After standing in a vacuum desiccator containing sodium hydroxide for twenty-four hours, the sirup became hard without crystallizing. The sirup was dissolved in 25 ml. of nitromethane and allowed to evaporate aided by a stream of air. A crystalline solid and sirup remained. About 50 ml. of acetone was stirred into the mixture and a flocculent precipitate formed. After filtering from the solution, the gummy solid was dissolved in 15 ml. of nitromethane and allowed to remain in the refrigerator overnight. The solid mass was washed with ice-cold nitromethane leaving 5 g. of an almost white material melting at 106–107°. This product checks with that prepared by Stoermer who reported a melting point of 106°. Upon evaporation, the filtrate yielded a gummy sirup which could not be induced to crystallize.

α-Hydroxy-β-piperidinopropionitrile.—A solution of 5 g. of the aldehyde hydrochloride prepared in the previous experiment in 15 ml. of water was added slowly to an ice-cold solution consisting of 1.5 g. of sodium cyanide in 25 ml. of water. A solid product precipitated immediately weighing 4.5 g. (95%). After recrystallizing from benzene, the product melted at 97–98° (cor.).

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.35; H, 9.09. Found: C, 62.50; H, 9.28.

This product could be advantageously prepared in 73% yield directly from the crude piperidinoacetaldehyde hydrochloride sirup.

α-Hydroxy-β-N-piperidinopropionic Acid.—The hydrolysis was carried out by refluxing 2.4 g. of the nitrile for four hours with 10 ml. of concentrated hydrobromic acid. The excess acid was removed by distillation at atmospheric pressure until a solid separated, then further concentration was accomplished by evaporation on the steam-cone aided by a stream of air. The solid which remained was extracted with four 15-ml. portions of boiling *n*-propyl alcohol. This solution was evaporated to a solid and recrystallized from the minimum amount of boiling-hot isopropyl alcohol. The yield was 3.7 g. (92%) and after recrystallizing melted at 173–175° (cor.) with decomposition. The melting point when mixed with the four mole hydrogenated 2-pyridone α-bromoacrylic acid adduct showed no depression.

β-(N-2-Piperidone)-propionic Acid.—A solution of 2 g. of β-(N-2-pyridone)-propionic acid in 100 ml. of 95% ethanol was hydrogenated at 40 lb. pressure and room temperature using 1.0 g. of palladium on charcoal catalyst. After eighteen hours, two moles of hydrogen were absorbed. The catalyst was filtered from the solution which was then evaporated to dryness at room temperature aided by a stream of air. The white crystalline solid was recrystallized from acetone, yielding 1.4 g. (70%) of fine white flakes. After recrystallization the melting point was 148° (cor.).

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.68; N, 8.18. Found: C, 56.48; H, 7.80; N, 8.28.

An excess of dry hydrogen bromide was passed into a solution of 0.47 g. of this product contained in 10 ml. of chloroform. Upon cooling in an ice-bath, a white crystalline product separated. The yield of hydrobromide was 0.6 g. (95%). The sample was purified by recrystallizing from nitromethane, m. p. 179° (cor.), with decomposition.

Anal. Calcd. for $C_8H_{14}NO_3Br$: C, 38.11; H, 5.60; N, 5.56. Found: C, 38.25; H, 5.37; N, 5.42.

Reaction of Methyl α-Bromopropionate and the Sodium Salt of 2-Pyridone; α-(N-2-Pyridone)-propionic Acid.—A mixture of 5.8 g. of the anhydrous sodium salt of 2-pyridone, and 8.8 g. of methyl α-bromopropionate in 25 ml. of absolute ethanol was refluxed for one hour and filtered hot. The solution was distilled on the steam-cone using vacuum toward the end. The sirup remaining was soluble in water and chloroform but insoluble in ether. No crystalline product could be obtained from the sirup so it was saponified by heating for an hour on the steam-cone with a solution of 4.0 g. of sodium hydroxide in 10 ml. of water. This solution was then made acid with 25 ml. of ethanol containing 2.5 g. of concentrated sulfuric acid. An inorganic precipitate was filtered off and the filtrate evaporated to dryness. The residue was washed with 50 ml. of hot chloroform. The granular crystals remaining weighed 7.0 g. (84%). After recrystallizing from absolute ethanol, the melting point was 215–217° (cor.) with decomposition.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.52; H, 5.43; N, 8.38. Found: C, 57.39; H, 5.18; N, 8.51.

α-(N-2-Piperidone)-propionic Acid.—A suspension of 2.0 g. of α-(N-2-pyridone)-propionic acid and 50 mg. of platinum oxide in 50 ml. of absolute ethanol was hydrogenated at 50-lb. pressure and 50°. Two moles of hydrogen were absorbed in two hours. After filtering from the catalyst, the filtrate was evaporated at room temperature aided by a stream of air. The crystalline solid which remained was recrystallized from benzene. The yield was 1.9 g. (93%). The melting point was elevated to 144° (cor.) after further recrystallization from the same solvent.

Anal. Calcd. for $C_8H_{12}NO_3$: C, 56.13; H, 7.67; N, 8.18. Found: C, 56.27; H, 7.41; N, 8.25.

Reaction of Sodium 2-Pyridone and Ethyl α-Bromo-β-ethoxypropionate; α,β-Di-(N-2-pyridone)-propionic Acid.—A solution of 5.0 g. of the anhydrous sodium salt of 2-pyridone and 8.0 g. of ethyl α-bromo-β-ethoxypropionate[13] in 25 ml. of absolute ethanol was refluxed for four hours. The solvent was evaporated on the steam-cone aided by a stream of air until only a sirup and a solid remained. The sirup was extracted with 25 ml. of chloroform and the solvent distilled on the steam-cone using vacuum to remove the last trace of solvent. The sirup was allowed

(12) Stoermer, *Ber.*, **31**, 2542 (1898).

(13) Wood and DuVigneaud, *J. Biol. Chem.*, **134**, 413 (1940).

to remain in a vacuum desiccator overnight then extracted with 25 ml. of boiling xylene. The resulting solution was set in a warm place and evaporated. A crystalline residue resulted weighing 1.5 g. (12%). It melted at 151° (cor.) after recrystallization from xylene. No other crystalline product could be isolated.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.50; H, 5.56. Found: C, 62.29; H, 5.32.

Summary

1. The reactions of 2-pyridone were studied with the objective of finding the best route to α-amino-β-(N-2-pyridone)-propionic acid, an analog of leucenol. The addition of 2-pyridone to α-acetamidoacrylic acid, followed by hydrolysis of the adduct, resulted in the product desired and provided the procedure for the successful synthesis of leucenol.

2. Other reactions of 2-pyridone which were explored during this investigation were numerous. β-(N-2-Pyridone)-propionic acid upon treatment with bromine and phosphorus gave β-(3,5-dibromo-N-2-pyridone)-propionic acid. 2-Pyridone gave the expected N-substituted products upon condensation with chloroacetaldehyde and bromopyruvic acid. It added to butadiene sulfone.

3. An extensive study was made of the condensation product of sodium 2-pyridone with α,β-dibromopropionic acid. The product was water soluble and contained ionizable bromine. It could be made more advantageously from 2-pyridone and α-bromoacrylic acid.

4. The 2-pyridone α-bromoacrylic acid adduct reacted with ammonia to give α-(N-2-pyridone)-β-aminopropionic acid or with aqueous alkali to give the corresponding β-hydroxy compound. Upon reduction with hydrogen and palladium–charcoal catalyst two moles of hydrogen were absorbed and the piperidone analog resulted as shown by treatment with ammonia to give α-(N-2-piperidone)-β-aminopropionic acid which was also made by the reduction of the α-(N-2-pyridone)-β-aminopropionic acid. When the adduct was reduced with hydrogen and platinum oxide as a catalyst, four moles of hydrogen were absorbed and α-hydroxy-β-piperidinopropionic acid was the product as shown by synthesis from piperidine and α-hydroxy-β-chloropropionic acid or from piperidinoacetaldehyde through the cyanohydrin. The mechanism of these transformations is discussed.

5. The 2-pyridone α-bromoacrylic acid adduct was titrated as a monobasic acid. With one molecule of silver oxide it yielded a betaine and with one-half mole of silver oxide a betaine hemihydrobromide. The infrared spectra of betaine hydrobromide and betaine compared closely with those of the 2-pyridone α-bromoacrylic acid adduct and the hydrobromide-free analog, thus showing similar groupings. The structure of the adduct is postulated as an ethylene-immonium bromide which permits a satisfactory explanation of all the experimental facts.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

An Improved Apparatus for the Study of Reactions in Liquid Ammonia[1,2]

BY GEORGE W. WATT AND C. W. KEENAN[3]

Apparatus of the type described by Johnson and Fernelius[4] and modified extensively by Watt and Moore[5] for the conduct of reactions in liquid ammonia at its boiling point involves two serious shortcomings. Neither the original nor the modified apparatus provides for (a) the possibility of conducting titrations in a closed system (a procedure frequently advantageous in establishing the stoichiometry of reactions of liquid ammonia solutions of alkali and alkaline earth metals), or (b) the substantially quantitative removal of solid reaction products following *in situ* filtration and washing, without exposure of these products to the atmosphere. Both of these objectives are realized through use of the apparatus described in the present paper.

Two relatively simple reactions were chosen to demonstrate the operability of the equipment, *i. e.*, the reduction of ammonium bromide and silver(I) bromide with liquid ammonia solutions of potassium.[6] These cases show that the equipment described below permits one to exercise close analytical control over all reactants and products, including gaseous products; the importance of so-doing has been emphasized elsewhere.[7]

Experimental

Apparatus.—The apparatus designed to meet the needs indicated above is shown in Fig. 1. In general, this equipment is similar to that described by Watt and Moore[5]; consequently only the improvements will be pointed out here.

(1) The major part of this work was done under the sponsorship of the Office of Naval Research, Contract N6onr-26610.

(2) The liquid ammonia employed in these studies was generously supplied by E. I. du Pont de Nemours and Company.

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(4) Johnson and Fernelius, *J. Chem. Education*, **7**, 981 (1930).

(5) Watt and Moore, THIS JOURNAL, **70**, 1197 (1948).

(6) Several investigators have shown that silver(I) salts other than the bromide are reduced to elemental silver by the action of liquid ammonia solutions of alkali and alkaline earth metals [*cf.*, Kraus and Kurtz, THIS JOURNAL, **47**, 43 (1925); Burgess and Smoker, *ibid.*, **52**, 3573 (1930); *Chem. Revs.*, **8**, 265 (1931); Zintl, Goubeau and Dullenkopf, *Z. physik. Chem.*, **A154**, 1 (1931); Burgess and Smoker, THIS JOURNAL, **59**, 459, 462 (1937)].

(7) Fernelius and Watt, *Chem. Revs.*, **20**, 202, 216 (1937).

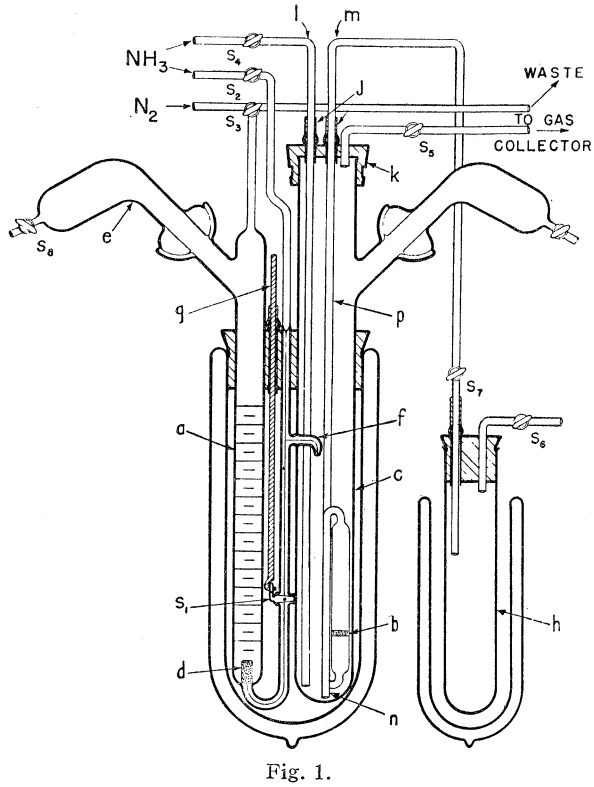

Fig. 1.

The novel features are the buret a and the internal in-line filter[8] b. Both the buret and the main reaction cell c are provided with addition bulbs connected by ball-socket joints held by spring clamps (not shown). In actual operation, ammonia is condensed in the buret until it is approximately one-half full, a known weight of alkali metal[9] is added from tube e, the solution is stirred by a stream of ammonia through the fritted glass filter[10] d, and sufficient additional ammonia is then condensed in a to give a metal solution of the desired concentration. Stopcock s_1 is closed and ammonia is condensed in c, which contains the substance which it is intended to bring into reaction with the metal solution.

Titrations with metal solutions are conducted as follows. With stopcock s_5 open, a positive pressure of dry oxygen-free nitrogen is exerted (through stopcock s_3) upon the surface of the metal solution in a. While the solution (or suspension) in c is stirred by a slow stream of ammonia gas, stopcock s_1 is opened and metal solution is delivered dropwise into c *via* the capillary delivery tip f, and at the same time the metal solution is filtered through d. Addition of metal solution may be interrupted upon the appearance in c of a color change, a precipitate, the beginning or cessation of gas evolution, or the first appearance of the characteristic blue color denoting the presence of excess metal solution.

[Stopcock s_1 is submerged in the coolant ammonia contained in the outer Dewar flask and is lubricated with Dow–Corning high vacuum grease. This stopcock is held in place by a spring clamp (not shown) and is manipulated by means of the metal rod g which is connected through a glass ring sealed onto the handle of the stopcock s_1. This rod extends through a glass sleeve in the rubber stopper and the closure between rod and sleeve is made with rubber tubing.]

Upon completion of a reaction that yields a solid product, filtration, washing, and collection of the solid are accomplished as follows. With controlled reduction of the pressure in tube h (evacuated *via* stopcock s_6), stopcock s_7 is opened and the contents of c filtered through b. The solid on the filter b is washed with fresh portions of ammonia successively condensed in c and drawn over through b as described above.[11] At the same time, the filtrate and washings are collected quantitatively in h. *While the solid on the filter is still wet with ammonia*, cap k (together with tubes l, m, and the gas exit tube) is removed from reaction cell c and, with stopcock, s_7 open, a small rubber cap (small bore pressure tubing closed at one end with a screw clamp) is quickly placed over the intake end of the filter tube, *i. e.*, at n. Tube m is then broken off at point p, attached to the vacuum line at point p, evacuated for a few minutes, and sealed off just above n. Following thorough evacuation to remove excess ammonia, tube m is sealed off between p and the top of the filter tube, and transferred to a dry box for all subsequent manipulations. Thus the solid sample is isolated without exposure to the atmosphere.[12]

The cap k is a rubber stopper bored out to fit over the tube c and held firmly in place by a metal collar (not shown) which is tightened with a screw. This type of cap obviates use of a thick stopper which would restrict the side-to-side movement of tubes l and m which are connected through k by means of rubber-to-glass seals which are kept gas-tight by means of spring clamps (not shown).

Titration of Ammonium Bromide Solution with Potassium Solution.—Weighed samples of am-

(8) Ace Glass, Inc., Cat. No. 8570, filter tube, porosity C or D.

(9) The metal is cut under dry xylene, so that only freshly cut surfaces are exposed. While still wet with xylene, the metal is transferred to tube e while a current of dry ammonia gas is admitted *via* stopcock s_8. The xylene is volatilized in the ammonia gas stream, tube e is tightly stoppered, stopcock s_8 is closed, and the tube and its contents are weighed. Thereafter, tube e is attached to the side-arm on buret a which is previously flushed out with dry ammonia gas.

(10) Ace Glass, Inc., Cat. No. 8575, filter tube, porosity C.

(11) An alternative procedure is used with very finely divided solids which tend to clog the filter medium. The initial reaction is conducted with filter b raised upward in c so that the intake tip of the filter is above the level of the solution in c. The solid is allowed to settle, filter b is lowered carefully and the supernatant solution is drawn off with minimum disturbance of the settled solid. Thereafter, the solid is washed several times by condensation of fresh ammonia, settling, and decantation, before the bulk of the solid is finally drawn over onto the filter.

(12) While this procedure may appear to involve risk of exposure of the sample to the atmosphere, samples of highly pyrophoric metals which react violently upon the slightest exposure have been handled in this manner without any evidence of atmospheric oxidation.

monium bromide dissolved in approximately 50 ml. of liquid ammonia in c were titrated with potassium solutions of known concentration delivered from the calibrated buret a. The first appearance of a permanent blue color (characteristic of solutions of metals in ammonia) was taken as the end-point. Data for two such titrations are given in Table I (Expts. 1 and 2).

TABLE I

REDUCTION OF AMMONIUM BROMIDE AND SILVER(I) BROMIDE

Expt.	Substance	Reactants, g. Measured	Reactants, g. Calcd.[a]	Products Measured	Products Calcd.[a]	Acctd. for, %
1	NH_4Br	1.0061				
	K	0.397[b]	0.402			99
	H_2			109 cc.	115 cc.	95
2	NH_4Br	1.0518				
	K	0.418[b]	.420			100
	H_2			119 cc.	120 cc.	99
3	AgBr	.3173				
	K	.0667[b]	.0660			101
	Ag			0.1818 g.	0.1822 g.	99.8
4	AgBr	.2877				
	K	.0598[b]	.0599			100
	Ag			0.1646 g.	0.1653 g.	99.6

[a] Calcd. on the basis of the weight of ammonium bromide or silver(I) bromide used. [b] Measured as a portion (15–20 ml.) of a known volume (25–30 ml.) of potassium solution containing a weighed quantity of potassium.

Reduction of Silver(I) Bromide with Potassium.—Solutions containing known weights of silver(I) bromide were similarly titrated with potassium solutions. In these cases, however, the end-point could not be detected as indicated above, owing to the presence of the black finely divided precipitate of elemental silver. Consequently, a calculated volume of potassium solution was added, the precipitate allowed to settle, and drops of potassium solution were added to the clear supernatant solution until there was no further evidence of reaction. The combined supernatant solution and washings gave a negative test for silver ion. The resulting data are shown as Expts. 3 and 4, Table I.

Summary

An improved apparatus for the conduct of reactions in liquid ammonia at its boiling point has been described, and its utility demonstrated. This apparatus provides for titrations employing liquid ammonia solutions of metals and permits one to carry out filtration and purification operations at the boiling point of the solvent.

It has been demonstrated that silver(I) bromide is reduced to elemental silver by reaction with solutions of potassium in liquid ammonia.

AUSTIN, TEXAS RECEIVED MARCH 25, 1949

NOTES

Preparation of Radioactive Cyanide from Carbon Dioxide

BY RICHARD ABRAMS

For synthesis of labeled compounds it is often necessary to convert $BaC^{14}O_3$ to $HC^{14}N$. Available methods treat carbon dioxide with ammonia and potassium metal[1] (yield is a sensitive function of experimental conditions[2]), or treat barium carbonate with sodium azide[3] (yields are low in our experience). A method which has been found to be very satisfactory is based upon the reduction of carbon dioxide to carbon with magnesium powder,[4] and the conversion of amorphous carbon to hydrocyanic acid with ammonia gas at 1000°.[2,5,6] Yields are usually between 60 and 70% and not particularly dependent upon carbon dioxide pressure or magnesium excess.

(1) Cramer and Kistiakowsky, *J. Biol. Chem.*, **137**, 549 (1941).
(2) Loftfield, *Nucleonics*, **1**, 54 (1947).
(3) Adamson, THIS JOURNAL, **69**, 2564 (1947).
(4) Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Co., London, England, 1925, Vol. 6, p. 71.
(5) Mellor, *ibid.*, 1924, vol. 5, p. 827.
(6) Cramer, Thesis, Harvard, 1941.

In a typical experiment, carbon dioxide was liberated into a vacuum system from 1.1 mmoles. of barium carbonate by mixing with 1.6 g. of lead chloride and heating with a micro-burner.[7] Traces of water were removed by sublimation at −80°. The carbon dioxide was then admitted to a quartz tube containing 2.5 mmoles. of magnesium powder in a thin-walled iron thimble. The tube was heated rapidly with an oxygen flame until the thimble glowed red, and reaction began as noted by the sharp pressure drop. Intermittent heating was continued until the pressure remained constant. The contents of the thimble were washed with 1 *M* hydrochloric acid and with water, transferred as a slurry to a quartz boat, and dried under an infrared lamp. The yield was 0.76 mmole. of carbon which was 89% pure. Based upon the residual pressures of condensable and non-condensable gases and the acetylene liberated upon wetting the reaction mixture, the 30% loss consisted of approximately 5% unreacted carbon dioxide, 10% carbon monoxide, and 15% magnesium carbide.

The boat containing the carbon was placed in a quartz tube surrounded by an electric furnace. Ammonia gas was allowed to flow directly from the tank through the quartz tube and out through a wash bottle containing a 10% excess of 0.1 *M* sodium hydroxide. When all the air had been displaced by ammonia, the furnace was turned on so that the temperature rose to 1000° in thirty minutes, and stayed between 1000° and 1100° for two and one-half hours. All the hydrocyanic acid formed was carried out by the ammonia which flowed through the tube continuously at a

(7) Zwiebel, Turkevich and Miller, THIS JOURNAL, **71**, 376 (1949).

rate of 2 to 3 bubbles/second. The cyanide accumulated in the alkaline solution in the wash bottle which was removed at the termination of the heating period. Yields in this step were quantitative.

In a series of four runs, using approximately 1 mmole. of barium carbonate, in which the magnesium excess ranged from 14 to 48% over the stoichiometric amount, and the carbon dioxide pressure from 278 to 385 mm., the yields of cyanide obtained were 67, 69, 72 and 59%. The value of 59% was obtained by radioactivity assay, the others by silver nitrate titration.

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RECEIVED JULY 27, 1949

2,4-Dinitrophenylhydrazones of Methoxy- and Methylcyclohexanones

BY HOMER ADKINS AND A. G. ROSSOW

Since the literature record of the melting points of these derivatives is confused and contradictory, we have re-examined the behavior of their ketones in the procedure described by Shriner and Fuson.[1]

2-Methoxycyclohexanone gave in our hands not the 2,4-dinitrophenylhydrazone, m. p. 135°, reported by others[2] but slowly and in low yield a red product, m. p. 218–219° uncor., whose analysis corresponded to cyclohexandione-1,2-bis-(2,4-dinitrophenyl)-osazone. *Anal.* Calcd. for $C_{18}H_{16}N_8O_8$: N, 23.72. Found: N, 23.62. This reaction is analogous to the prior[3] record for 3-methoxy-2-butanone. 3-Methoxycyclohexanone by similar treatment did not yield a 2,4-dinitrophenylhydrazone, m. p. 133.5°,[2] but instead gave rapidly in quantitative yield a product, m. p. 170–170.5° uncor., whose analysis indicated loss of methanol as well as water during the condensation. *Anal.* Calcd. for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.30; H, 4.42; N, 20.54. Our product may therefore be either a ring-closed derivative or cyclohexen-2-one 2,4-dinitrophenylhydrazone; the latter has previously been reported as m. p. 163[4] and 117°.[5] From the 4-methoxy ketone we obtained 4-methoxycyclohexanone 2,4-dinitrophenylhydrazone, orange crystals from ethanol, m. p. 142.5–143.5° uncor. *Anal.* Calcd. for $C_{13}H_{16}N_4O_5$: N, 18.18. Found: N, 18.20. This accords with the m. p. of 141.5–142.5°[6] but disagrees with the values of 150°[2,7] from the prior literature.

The behavior of 2-methylcyclohexanone was not examined, but its position isomers gave conventional results. 3-Methylcyclohexanone gave an orange-yellow 3-methylcyclohexanone 2,4-dinitrophenylhydrazone, m. p. 153.5–155.0° uncor., which appeared to be a mixture of stereoisomers. *Anal.* Calcd. for $C_{13}H_{16}N_4O_4$: N, 19.17. Found: N, 19.22. The same procedure on 4-methylcyclohexanone gave 4-methylcyclohexanone 2,4-dinitrophenylhydrazone, golden yellow crystals from ethanol, m. p. 134.7–135.1° uncor. *Anal.* Found: N, 19.47.

DEPARTMENT OF CHEMISTRY
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MADISON, WIS.

RECEIVED NOVEMBER 12, 1948

(1) Shriner and Fuson, "The Systematic Identification of Organic Compounds," p. 148, John Wiley and Sons, Inc., New York, N. Y., 1935; the preparation and properties of the ketones are given in another paper. Adkins, Elofson, Rossow and Robinson, THIS JOURNAL, **71**, 3622 (1949).

(2) Ferrante and Bloom, *Am. J. Pharm.*, **105**, 381 (1933).

(3) Aston, Clarke, Burgess and Greenburg, THIS JOURNAL, **64**, 300 (1942).

(4) Bartlett and Woods, *ibid.*, **62**, 2933 (1940).

(5) Whitmore and Pedlow, *ibid.*, **63**, 758 (1941).

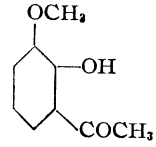
(6) Adamson and Kenner, *J. Chem. Soc.*, 188 (1939).

(7) Marvel and Walton, *J. Org. Chem.*, **7**, 92 (1942).

The Reaction of *o*-Veratronitrile with Methylmagnesium Iodide

BY E. D. AMSTUTZ

In the course of other work to be reported later relatively large quantities of *o*-acetovanillone (I) were required.



I

The usual method of synthesis involves the successive conversion of *o*-veratric aldehyde to the methylcarbinol,[1] acetophenone,[2] and demethylation.[3] It has now been found that several of these steps may be obviated with improvement in yield and facility. Although ether splitting is by no means new, the reaction of *o*-veratronitrile with methylmagnesium iodide has previously been reported[4] to yield the dimethoxyketone. Apparently the phenol formed escaped attention.

The present work has shown that the 2,3-dimethoxyacetophenone may be the main product of the reaction but also that conditions may be so arranged that it appears only as a minor product with 2-demethylated ketone assuming major importance. For example, using double the calculated quantity of Grignard reagent over a total reaction time of sixty hours the yield of *o*-acetovanillone rises to about 75% and the yield of non-phenolic ketone drops to about 18%.

Since the methoxyl group ortho to the acetyl is vinylogous with methyl acetate it is not inconceivable that it could have suffered hydrolysis during the acid treatment to destroy the magnesium complex. A sample of the solid magnesium-containing complex was therefore removed from the reaction mixture and rapidly decomposed with cold ammonium chloride solution. Ether extraction removed a yellow material which exhibited (in alc. soln.) a definitely positive test for the phenolic group with ferric chloride. Since it is hardly likely that the hydrolysis could have occurred under these mild conditions and in such a short interval of time, it appears necessary to suppose that the splitting occurred during the reaction of the Grignard reagent. The same conclusion is indicated by the fact that 2,3-dimethoxyacetophenone (in ether soln.) did not yield phenolic bodies on gentle warming and stirring for three hours with dilute hydrochloric acid, although it was obvious other changes were taking place. Also Fuson and Chadwick[5] have

(1) Pauly, *et al.*, *Ann.*, **383**, 317 (1911).

(2) Krannichfeldt, *Ber.*, **46**, 4016 (1913).

(3) Reichstein, *Helv. Chim. Acta*, **10**, 392 (1927).

(4) Richtzenhain and Nippus, *Ber.*, **77B**, 566 (1914); Baker and Smith, *J. Chem. Soc.*, 346 (1936).

(5) Fuson and Chadwick, *J. Org. Chem.*, **13**, 484 (1948).

shown that such hydrolysis is quite liable to remove the acyl group. The production of *o*-acetovanillone therefore appears to be analogous to the formation of isobutyl 3,5-dimethoxy-4-hydroxyphenyl ketone from 3,4,5-trimethoxybenzonitrile and isobutylmagnesium bromide.[6] It differs, however, in the fact that methylmagnesium iodide does not require high temperatures and apparently does not alkylate at the position of attachment of the *o*- or *p*-methoxyl group.

Similar observations have been made on 2-benzyloxy-3-methoxybenzonitrile in which the benzyl ether is split. Since there is no preparative advantage accruing to the use of the benzyl ether rather than the methyl ether, details of these experiments are omitted.

Experimental

An ether solution of 16.3 g. (0.1 mole) of *o*-veratronitrile was added rapidly to an ether solution of Grignard reagent prepared from 28.4 g. (0.2 mole) of methyl iodide and 4.8 g. (0.2 g.-atom) of magnesium. No refluxing was observed and no precipitate formed for about one hour. The solution was therefore refluxed and stirred for eight hours during a total time of about sixty hours. Although a small amount of Grignard reagent was still present the mixture was then worked up in the usual way with water, ammonium chloride solution and finally dilute hydrochloric acid. Phenolic material, removed from the ethereal solution with dilute alkali, proved to be almost pure *o*-acetovanillone and amounted to 12.36 g. (74.5%), m. p. 50–53.1°, mixed with authentic *o*-acetovanillone, m. p. 51.8–53°. The crude neutral material amounted to 3.25 g. (18%), $n^{30.5}D$ 1.5282, observed for authentic *o*-acetoveratrone $n^{26.5}D$ 1.5368. Starting material unaccounted for above was obtained as a water-, ether- and alkali-insoluble resinous gum.

A second run of the same size using a nitrile to Grignard ratio of 1:1.5, refluxing for one hour and standing overnight yielded some tar and 25.6% of *o*-acetovanillone (m. p. 51.8–53°; mixed with authentic, m. p. 51.8–53°) and 32.2% of *o*-acetoveratrone, $n^{26.5}D$ 1.5368. The neutral fraction yielded iodoform (m. p. 121–123°) and an acid, m. p. 118–120.4° (reported for *o*-veratric acid, m. p. 122°).[7] It also formed a 2,4-dinitrophenylhydrazone, m. p. 150–151.8° which did not depress the melting point of an authentic specimen.

(6) Hurd and Winberg, THIS JOURNAL, **64**, 2085 (1942).

(7) Perkin and Robinson, *J. Chem. Soc.*, **105**, 2383 (1914).

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RECEIVED JULY 1, 1949

Purification of Xanthopterin[1]

BY A. G. ANDERSON, JR., AND JERRY A. NELSON

In connection with the studies on the physiological properties of xanthopterin in this Laboratory,[2] xanthopterin free of other pterin impurities was desired. A purification procedure satisfactory as a routine method for this purpose was not found in the literature. In this investigation xanthopterin has been purified *via* a new crystalline derivative, xanthopterin hydrochloride. Crystalline xanthopterin sulfate has also been prepared. The hydrochloride salt affords a simple, effective means for the purification of synthetic xanthopterin as prepared in this Laboratory. Purification was also effected by sublimation *in vacuo*. This procedure gave poor yields and thus was not practical.

(1) This investigation was supported in part by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

(2) Norris and Majnarich, *Amer. J. Physiol.*, **152**, 175, 179, 652 (1948); **153**, 133, 483, 488, 492, 496 (1949); *Science*, **109**, 32, 33 (1949).

Experimental

Xanthopterin.—Leucopterin and, from it, xanthopterin were prepared by the procedures of Purrmann[3] and Totter,[4] respectively, as modified by Dauben and Goheen,[5] the modified procedure being similar to that recently reported by Hitchings and co-workers.[6] The xanthopterin so obtained was used in the experiments described below.

Xanthopterin Hydrochloride.—To 100 mg. of finely powdered xanthopterin was added 20 ml. of concentrated hydrochloric acid and the mixture heated on a steam-bath for ten minutes and filtered by suction while hot. The insoluble material (approximately 20 mg.) was largely xanthopterin hydrochloride and to this was added 5 ml. of hydrochloric acid and the mixture heated and filtered as before. The small quantity (5 mg.) of insoluble material was discarded. The two filtrates were placed in a refrigerator at −5° overnight. The hydrochloride precipitated as tiny, tan hexagonal plates which were separated by filtration, washed with a few ml. of cold alcohol, then with ether and dried. The yield from the first filtrate was 86 mg. (71.5%) and from the second filtrate 10 mg. (8.4%); total yield 96 mg. (79.9%). The salt was recrystallized from hydrochloric acid in corresponding yield. It was soluble in hot water or hot dilute hydrochloric acid but the hydrochloride could not be recovered from these solutions by cooling or concentration. On heating the crystals darkened at 200° and above but no melting point was observed up to 320°.

Anal. Calcd. for $C_6H_6O_2N_5Cl$: N, 32.48. Found: N, 32.41.

Amorphous xanthopterin was recovered quantitatively as a yellow solid on treatment of the hydrochloride with just sufficient 0.1 *N* ammonium hydroxide to effect solution (the xanthopterin began to precipitate a few seconds after the salt had dissolved) and then adjustment of the acidity to *p*H 5–6 by addition of dilute hydrochloric acid. The mixture was cooled, filtered and the collected precipitate washed with a few ml. of cold water, then acetone and dried.

Xanthopterin Sulfate.—Eighty-six mg. of finely powdered xanthopterin was dissolved in 2.3 ml. of sulfuric acid–water (1:1) solution by heating on a steam-bath. As the xanthopterin dissolved the solution became orange in color. On cooling the solution in tap water and scratching the sides of the flask, crystallization occurred and, after standing overnight in a refrigerator, the tiny, tan boat-shaped crystals were separated by filtration, washed with a few ml. of cold alcohol, then with ether and dried; yield 45 mg. (36%). The crystals gradually darkened and decomposed above 200° leaving a black residue at 280°. The sulfate could be recrystallized from the same sulfuric acid solution in corresponding yield. Attempts to obtain a second crop from the filtrate were unsuccessful. Xanthopterin sulfate is quite soluble in dilute or concentrated sulfuric acid and undergoes hydrolysis with water to precipitate amorphous xanthopterin. Recovery of xanthopterin from the sulfate was best effected in the manner described for the hydrochloride.

Anal. Calcd. for $C_6H_7O_6N_5S$: N, 25.27. Found: N, 25.80.

(3) Purrmann, *Ann.*, **544**, 182 (1940).

(4) Totter, *J. Biol. Chem.*, **154**, 105 (1944).

(5) Dauben and Goheen, private communication.

(6) Elion, Light and Hitchings, THIS JOURNAL, **71**, 741 (1949).

Chromatographic Analysis of Purified Xanthopterin.—Paper chromatographs of the xanthopterin purified *via* the hydrochloride and by sublimation *in vacuo* were obtained by the method of Good and Johnson[7] who employed the *n*-butanol–acetic acid–water mixture of Partridge.[8] Under ultraviolet light the chromatographs showed only one fluorescent spot (Rf = 0.35–0.38) which was in agreement with the value (Rf = 0.38) reported by Good and Johnson.[7] The material was thus free of leucopterin (Rf = 0.12), dihydroxanthopterin (Rf = 0.26) and other fluorescent pterin impurities. It should be noted that some samples of synthetic xanthopterin prepared as indicated did not contain these impurities and thus required no further purification.

Absorption Spectra of Purified Xanthopterin.—Ultraviolet absorption spectra of an aqueous solution (*p*H of 11.25) of the xanthopterin purified by sublimation and *via* the hydrochloride showed absorption maxima at 255 mμ. ($E_m \times 10^{-3} = 18.2$) and 392 mμ; ($E_m \times 10^{-3} = 7.0$) in agreement with other reported spectra.[4,9]

(7) Good and Johnson, *Nature*, **163**, 31 (1949).
(8) Partridge, *Biochem. J.*, **42**, 238 (1948).
(9) Rickes, Chaiet and Keresztesy, THIS JOURNAL, **69**, 2749 (1947).

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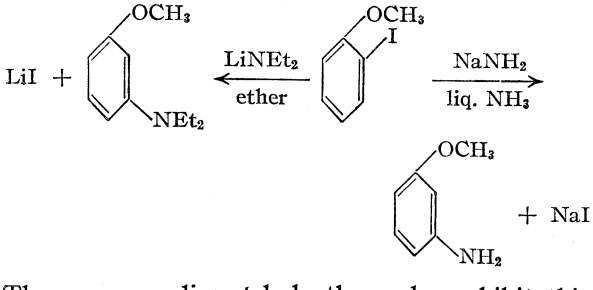
RECEIVED JUNE 4, 1949

The Reaction of Sodium Amide with *o*- and *m*-Chlorotrifluoromethylbenzene

BY ROBERT A. BENKESER AND ROLAND G. SEVERSON[1]

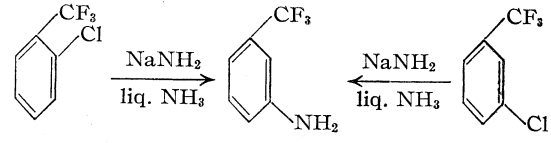
Recently it was reported that certain aryl halides react with a liquid ammonia solution of sodium[2] or potassium amide.[3] It has also been found that ether solutions of aryl halides are attacked by lithium dialkylamides.[4] When the aryl halide has an ether, sulfide or dialkylamino group ortho to the halogen, it was observed that the amino or dialkylamino group does not take up the position which the halogen originally occupied, but rather a meta-substituted product[5,6,7] is formed



The corresponding *p*-haloethers also exhibit this tendency to undergo rearrangement when treated with lithium dialkylamides in ether, but to a somewhat lesser extent.[8]

(1) Research Corporation Fellow.
(2) Gilman and Avakian, THIS JOURNAL, **67**, 349 (1945).
(3) Urner and Bergstrom, *ibid.*, **67**, 2108 (1945).
(4) Horning and Bergstrom, *ibid.*, **67**, 2110 (1945).
(5) Gilman and Nobis, *ibid.*, **67**, 1479 (1945).
(6) Gilman, *et al.*, *ibid.*, **67**, 2106 (1945).
(7) Gilman, Kyle and Benkeser, *ibid.*, **68**, 143 (1946).
(8) Gilman and Kyle, *ibid.*, **70**, 3945 (1948).

It has now been observed that the same rearrangement occurs even when the halogen is ortho to a strong meta-directing group. Thus, *o*-chlorotrifluoromethylbenzene upon treatment with sodium amide in liquid ammonia for five hours at −33° gives a 52% yield of pure *m*-aminotrifluoromethylbenzene. Efforts to isolate any of the ortho isomer have been unsuccessful. In contrast, *m*-chlorotrifluoromethylbenzene gives the expected *m*-aminotrifluoromethylbenzene. It is noteworthy that the yield here is only 35%.



Experimental

***m*-Aminotrifluoromethylbenzene. (a) From *o*-Chlorotrifluoromethylbenzene.**—Sodium amide[9] was prepared from 16.1 g. (0.7 g. atom) of sodium and 750 ml. of liquid ammonia containing 0.4 g. of hydrated ferric nitrate. To this mixture was added 90.3 g. (0.5 mole) of *o*-chlorotrifluoromethylbenzene[10,11] (b. p. 149–150°) during a period of one hour. After stirring for an additional four hours, ammonium chloride was added and the solvent was allowed to evaporate. The residue was dissolved in ether, filtered and treated with anhydrous hydrogen chloride which precipitated 62 g. of a brown hydrochloride. From the ether filtrate 14.4 g. of *o*-chlorotrifluoromethylbenzene (b. p. 149–150°) was recovered. Crystallization of the crude hydrochloride from an ethanol–ether mixture gave 53 g. of white crystals from which the free base was obtained by adding concentrated ammonium hydroxide. After extracting the basic solution with ether, drying the ether extract over Drierite, removing the solvent, and fractionating the product through a small helices-packed column, there was obtained 35.1 g. (52% yield) of *m*-aminotrifluoromethylbenzene boiling at 86° (20 mm.), $n^{20}D$ 1.4801, $n^{25}D$ 1.4775.

The acetyl derivative[12] melted at 103–104° and the benzoyl derivative[13] at 110–111°. A mixed melting point between this acetyl derivative and that obtained from an authentic sample of *m*-aminotrifluoromethylbenzene[10] showed no depression.[14]

(b) **From *m*-Chlorotrifluoromethylbenzene.**—This procedure was identical with that described above. From 90.3 g. (0.5 mole) of *m*-chlorotrifluoromethylbenzene,[10] 47.8 g. of crude hydrochloride was obtained. This gave 36 g. of pure salt when crystallized from an ethanol–ether mixture and 23.9 g. (35% yield) of the free base boiling at 86° (20 mm.), $n^{20}D$ 1.4800. The acetyl and benzoyl derivatives melted at 103–104° and 110–111°, respectively.

(9) Vaughn, Vogt and Nieuwland, *ibid.*, **47**, 2002 (1925).
(10) Kindly supplied by the Hooker Electrochemical Company, Niagara Falls, N. Y.
(11) For a description of numerous ortho and para derivatives of benzotrifluoride see Jones, THIS JOURNAL, **69**, 2346 (1947).
(12) Swarts, *Bull. acad. roy. Belg.*, 389 (1920); *C. A.*, **16**, 2316 (1922).
(13) *Anal.* Calcd. for $C_{14}H_{10}OF_3N$: N, 5.28. Found: N, 5.35.
(14) The literature[11,12] values for the physical constants of *o*-, *m*- and *p*-aminotrifluoromethylbenzene are

	B. p. °C.	Mm.	n_D	Acetyl deriv.	Benzoyl deriv.
ortho-	72–74	21	1.4785 (25°)	94.5–95°	140–141°
meta-	74–75	10	1.481 (20°)[10]	103°	.....
para-	91	19	1.4815 (25°)	152°	.....

There was recovered 14.3 g. of unreacted *m*-chlorotrifluoromethylbenzene.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

RECEIVED JULY 1, 1949

Preparation of Wüstite

BY R. W. BLUE AND H. H. CLAASSEN

For X-ray diffraction studies of iron oxides it is frequently helpful to have diffraction patterns of the pure oxides for purposes of comparison. Samples of magnetite, ferric oxide and iron are readily obtained but a sample having the ferrous oxide structure is less easily prepared. Fusion of higher oxides with iron often results in samples which do not give clean diffraction patterns.

Previous work[1] indicates that the lower limit for oxygen content of this sodium chloride-type structure is 23.1% oxygen as compared with 22.27% for ferrous oxide. The name wüstite has been given to the material in the composition range, 23.1 to 25.6% oxygen, in which the sodium chloride-type of structure occurs.

A convenient way to prepare a sample of wüstite is to take advantage of the simultaneous reactions

$$\text{Iron} + H_2O \longrightarrow \text{wüstite} + H_2$$
$$\text{Magnetite} + H_2 \longrightarrow \text{wüstite} + H_2O$$
$$\text{Iron} + \text{magnetite} \longrightarrow \text{wüstite}$$

When equimolal amounts of iron and magnetite are placed in an atmosphere of water vapor in the temperature region 750 to 900°, some hydrogen is immediately formed and the water hydrogen ratio is automatically regulated for conversion of both iron and magnetite to wüstite. By keeping the iron and magnetite in separate boats one can use an excess of either reactant; the reactant not in excess is converted to material giving a clean diffraction pattern of the sodium chloride-type of structure but there is a slight difference between the diffraction patterns of the two samples which may be described as follows:

In practice magnetite obtained by burning pure iron at fusion temperatures contains 10 to 50% ferrous oxide.[2] The ferrous oxide diffraction lines obtained with these ferrous oxide–magnetite samples are doublets which become single lines when reduction occurs. When the samples are reduced in a stream of hydrogen the line in each doublet which corresponds to the smaller lattice disappears first. When reduction is carried out by the double-boat method described above, the line corresponding to the larger lattice disappears first; and when wüstite is formed from iron by the double-boat method the diffraction lines are in the mean position between the doublet positions. The latter differences correspond to only a few thousandths of an ångström but they can be clearly seen by comparing XRD patterns of samples prepared simultaneously by the double-boat method.

Oxides in the composition range 23.2 to 24.3% oxygen have been prepared under various conditions. All samples in this composition range give the same XRD pattern with the exceptions noted above depending on the source material.

In a typical experiment magnetite containing about 40% wüstite was prepared by burning Armco iron in an atmosphere of oxygen. Some of this material, after crushing and screening to 60 to 120 mesh, was reduced with hydrogen at 450° to iron. Thirty-three and one-quarter grams of the magnetite and 3.0 g. of the iron were weighed into separate alundum boats and placed in a quartz tube closed at one end and joined at the other end by a wax seal to a Pyrex tube equipped with a side tube and vacuum connection. A few cc. of water was placed in the side tube and, after the apparatus was assembled, the side tube was cooled in liquid air. The apparatus was then evacuated and the side tube was warmed to room temperature. That part of the tube containing magnetite and iron was then heated to 900°. After seventy-two hours the tube was cooled in a stream of air and the iron oxide samples were removed. (Cooling to room temperature required about five minutes.) Examination by X-ray diffraction revealed that both the wüstite from the iron and that from magnetite contained no other crystalline materials. Reduction in a stream of hydrogen at 450° showed that the wüstite from the oxide contained 23.2% oxygen.

PHILLIPS PETROLEUM COMPANY
RESEARCH DEPARTMENT
BARTLESVILLE, OKLAHOMA

RECEIVED JUNE 23, 1949

N-(Dialkylaminoalkyl)-amides

BY R. O. CLINTON, U. J. SALVADOR AND S. C. LASKOWSKI

Since only a few simple aromatic amide derivatives have been tested as local anesthetics,[1] it seemed desirable to extend these types to include 4-aminobenzamides and related compounds. However, the initially prepared compounds proved relatively inactive in comparison with their ester analogs, and the investigation was terminated after the preparation of only a few compounds.

Attempts were also made to prepare 4-aminobenzamides derived from imino-interrupted side chains, analogous to those derived from sulfur- and oxygen-interrupted side chains.[2] Because of the complex mixtures formed, we were unable to prepare pure 4-aminobenzamides of this type.

Experimental[3]

Nitriles.—The reaction of a primary or secondary amine with acrylonitrile was carried out by the method of Whitmore, *et al.*[4]

(1) R. W. G. Wyckoff and E. D. Crittenden, THIS JOURNAL, **47**, 2876 (1925); E. R. Jette and F. Foote, *J. Chem. Phys.*, **1**, 29 (1933); *Trans. Am. Inst. Min. and Met. Engrs., Iron and Steel Div.*, **105**, 276 (1933); L. S. Darken and R. W. Gurry, THIS JOURNAL, **67**, 1398 (1945).

(2) J. A. Almquist and E. D. Crittenden, *Ind. Eng. Chem.*, **18**, 1307 (1926).

(1) *Cf.* Wenker, THIS JOURNAL, **60**, 1081 (1938); Blicke, Parke and Jenner, *ibid.*, **62**, 3316 (1940).

(2) Clinton, Salvador, Laskowski and Suter, *ibid.*, **70**, 950 (1948).

(3) All melting and boiling points are corrected. The authors desire to thank Mr. Morris E. Auerbach and staff for the analyses.

(4) Whitmore, *et al.*, *ibid.*, **66**, 725 (1944).

TABLE I

4-SUBSTITUTED BENZAMIDES

X	R_2	Derivative	M. p., °C.	Formula	Nitrogen analyses, % Calcd.	Found
4-Nitrobenzamides, NO_2–C$_6$H$_4$–CONH—X—NR_2						
$-(CH_2)_3-$	$(C_2H_5)_2$	Picrate	147.5–148.5	$C_{20}H_{24}N_6O_{10}$	16.53	16.30
$-(CH_2)_3-$	C_5H_{10}[a]	Base	50.5–51.0	$C_{15}H_{21}N_3O_3$	14.42	14.34
$-(CH_2)_3-$	C_5H_{10}[a]	Picrate	206.0–206.5	$C_{21}H_{24}N_6O_{10}$	16.15	16.27
$-(CH_2)_3-$	C_6H_{12}[b]	Base	71.5–72.5	$C_{16}H_{23}N_3O_3$	13.81	14.15
$-(CH_2)_3-$	C_6H_{12}[b]	Picrate	174.0–175.0	$C_{22}H_{26}N_6O_{10}$	15.76	16.14
$-(CH_2)_3-$	C_7H_{14}[c]	Picrate	190.0–191.0	$C_{23}H_{28}N_6O_{10}$	10.22[d]	10.43[d]
$-(CH_2)_3NH(CH_2)_3-$	$(C_2H_5)_2$	Dipicrate	161.0–162.0	$C_{29}H_{34}N_{10}O_{17}$	17.63	17.42
$-(CH_2)_3NH(CH_2)_3-$	C_5H_{10}[a]	Dipicrate	170.0–171.0	$C_{30}H_{34}N_{10}O_{17}$	17.37	17.00
$-(CH_2)_3NH(CH_2)_3-$	C_6H_{12}[b]	Picrate	165.0–166.0	$C_{25}H_{33}N_7O_{10}$	9.46[d]	9.50[d]
4-Aminobenzamides, NH_2–C$_6$H$_4$–CONH—X—NR_2						
$-(CH_2)_3-$	$(C_2H_5)_2$	Dipicrate	149.0–150.5	$C_{26}H_{29}N_9O_{15}$	11.88[d]	11.62[d]
$-(CH_2)_3-$	$(C_2H_5)_2$	Dihydriodide[e]	202.0–203.5	$C_{14}H_{25}I_2N_3O$	8.31	8.05
$-(CH_2)_3-$	C_5H_{10}[a]	Base[f]	168.3–169.5	$C_{15}H_{23}N_3O$	16.14	15.96
$-(CH_2)_3-$	C_5H_{10}[a]	Dipicrate	120.5–122.0	$C_{27}H_{29}N_9O_{15}$	11.68[d]	11.90[d]
$-(CH_2)_3-$	C_6H_{12}[b]	Base[g]	121.0–122.8	$C_{16}H_{25}N_3O$	15.26	15.24

[a] 1-Piperidyl. [b] 2-Methyl-1-piperidyl. [c] 2,6-Dimethyl-1-piperidyl. [d] Nitro nitrogen by titration with titanous chloride. [e] Calcd.: HI, 50.65. Found: HI, 50.13. [f] Calcd.: C, 69.19; H, 8.90. Found: C, 69.15; H, 8.73. [g] Calcd. C, 69.78; H, 9.15. Found: C, 70.01; H, 9.17.

3-(2-Methyl-1-piperidyl)-propionitrile, 87% yield, b. p. 126.4° at 18.0 mm., $n^{25}D$ 1.4689.

Anal. Calcd. for $C_9H_{16}N_2$: N, 18.41. Found: N, 18.31.

The picrate had m. p. 132.5–133.5°.

Anal. Calcd. for $C_{15}H_{19}N_5O_7$: N, 18.37. Found: N, 18.56.

A compound believed to be 3-(2,6-dimethyl-1-piperidyl)-propionitrile (*vide infra*) was obtained in 30% crude yield, b. p. 137–149° at 14 mm. The condensation required prolonged heating; the low yield was probably due to steric effects.[4] The crude compound could not be obtained sufficiently pure for analysis, nor did it yield a crystalline derivative.

3-(3-[1-Piperidyl]-propylamino)-propionitrile, 67% yield, b. p. 116.0° at 0.45 mm., $n^{25}D$ 1.4790.

Anal. Calcd. for $C_{11}H_{21}N_3$: N, 21.52. Found: N, 21.28.

The dipicrate had m. p. 177.0–178.3°.

Anal. Calcd. for $C_{23}H_{27}N_9O_{14}$: N, 19.28. Found: N, 19.22.

3-(3-[2-Methyl-1-piperidyl]-propylamino)-propionitrile, 86% yield, b. p. 110.0° at 0.15 mm., $n^{25}D$ 1.4794.

Anal. Calcd. for $C_{12}H_{23}N_3$: N, 20.08. Found: N, 20.01.

The dipicrate had m. p. 163.5–165.0°.

Anal. Calcd. for $C_{24}H_{29}N_9O_{14}$: N, 18.89. Found: N, 19.18.

Amines.—The propionitriles were reduced in methanolic ammonia at 100° and 1200 lb. pressure, using Raney nickel catalyst.[4]

3-(2-Methyl-1-piperidyl)-propylamine, 62% yield, b. p. 77.0° at 0.42 mm., $n^{25}D$ 1.4742.

Anal. Calcd. for $C_9H_{20}N_2$: N, 17.93. Found: N, 18.20.

The dipicrate had m. p. 216.5–218.0°.

Anal. Calcd. for $C_{21}H_{26}N_8O_{14}$: N,[5] 4.56. Found: N,[5] 4.54.

The cinnamamide hydrochloride had m. p. 181.0–183.2°.

Anal. Calcd. for $C_{18}H_{27}ClN_2O$: N, 8.67; Cl, 10.98. Found: N, 8.50; Cl, 10.89.

3-(2,6-Dimethyl-1-piperidyl)-propylamine, 58% yield, b. p. 66.3° at 0.20 mm., $n^{25}D$ 1.4714.

Anal. Calcd. for $C_{10}H_{22}N_2$: N, 16.46. Found: N, 16.84. A crystalline derivative could not be obtained.

3-(3-[1-Piperidyl]-propylamino)-propylamine, 83% yield, b. p. 111.0° at 0.44 mm., $n^{25}D$ 1.4844.

Anal. Calcd. for $C_{11}H_{25}N_3$: N, 21.08. Found: N, 21.15.

The tripicrate had m. p. 208.0–209.0°.

Anal. Calcd. for $C_{29}H_{34}N_{12}O_{21}$: N, 18.96. Found: N, 18.84.

3-(3-[2-Methyl-1-piperidyl]-propylamino)-propylamine, 91% yield, b. p. 104.5° at 0.25 mm., $n^{25}D$ 1.4843.

Anal. Calcd. for $C_{12}H_{27}N_3$: N, 19.69. Found: N, 19.57.

The tripicrate melted at 184.5–186.0°.

Anal. Calcd. for $C_{30}H_{36}N_{12}O_{21}$: N,[6] 13.99. Found: N,[6] 13.82.

4-Nitrobenzamides and 4-Aminobenzamides.—The 4-nitrobenzamides were prepared from 4-nitrobenzoyl chloride and the amine by the sodium bicarbonate–chloroform–water procedure.[2] The yields were good, but the compounds derived from the tribasic amines proved extremely difficult to purify. The 4-aminobenzamides were obtained by reduction with ferrous sulfate and ammonia. Purification proved difficult in most cases, and with the more complex imino-interrupted side-chain compounds a pure base or characteristic derivative could not be obtained. The 4-nitro- and 4-aminobenzamides are listed in Table I.

STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, NEW YORK

RECEIVED JULY 2, 1949

(5) Basic amino nitrogen by titration with perchloric acid in glacial acetic acid solution.

(6) Nitro nitrogen by titration with titanous chloride.

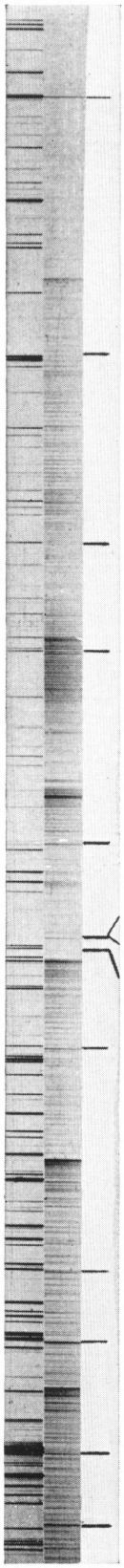


Fig. 1.—Arc emission spectrum of the 3260–3500 Å. region (sample 3). Spectra from the top down: Element 61, Fe. Wave lengths followed by A are those in Table A; wave lengths followed by B are those in Table B. Emission lines are black.

Note on the Arc Spectrum of Element 61[1]

BY CYRUS FELDMAN

An examination has been made of the arc emission spectra of three samples of the chloride of element 61 prepared by Paul Lantz. This material was separated from a mixture of uranium fission products by fractionation and concentration on a series of Amberlite IR-I and Dowex resin columns.[1a] Detailed accounts of the isolation of milligram amounts of element 61 are to be reported elsewhere by G. W. Parker and P. Lantz of this Laboratory. The amount of element 61 present in these samples was estimated on the basis of published values[1a] of the half-life and energy of the β-radiation of this element. The characterization of material which is radiochemically and spectrographically identical with these samples as element 61 has been confirmed by X-ray emission work.[2]

Once isolated, the material was prepared in the form of approximately 0.05 ml. of a hydrochloric acid solution. A thin layer of Zapon lacquer was deposited on a flat-topped 1/4" diam. high purity graphite electrode; the sample solution was deposited atop this and dried under an infrared lamp. This electrode was made the anode of a 220-volt, 9-ampere d.c. arc. A 1/8" diameter high purity graphite rod served as cathode. The arc gap was 4 mm. The burning took place inside a chamber which permitted light to enter the spectrograph without allowing the vapor containing element 61, which is highly radioactive, to escape into the laboratory.

The light was focused on the slit of a 21-foot (6.5-meter) Jarrel-Ash spectrograph. Further details of dispersion, etc., are given in Table A.

When sample 1 was exposed, spectra of iron, neodymium, element 61, and samarium were obtained in juxtaposition in the order mentioned; in the other two cases, only the spectra of iron, and element 61 were photographed. The placement of the spectra on the plate was effected by means of a Hartmann diaphragm at the slit; the camera was not moved at any time during the exposure. The exposure conditions were essentially the same as those used by Harris, Yntema and Hopkins.[3]

A search was made for the five lines specifically mentioned by them as being common to the spectra of the neodymium and samarium fractions and being somewhat more intense in the fractions intermediate between them.[3,4] Wave lengths were located by interpolation between iron lines of known wave length; observations were made on an ARL–Dietert projection comparator, which gives an enlargement of twenty-one-fold.

In all, three samples were tested; the results are summarized in Table A.

TABLE A

Sample no.		1	2	3
Purity		Impure (see text)	Very pure	Very pure
61 content, in μg		50	50	100
Dispersion of spectrum in Å./mm.		5.0	2.5	2.5
Observations in connection with given lines	3305.8	Doubtful	Absent	Absent
	3329.1	Absent	Absent	Absent
	3342.5	Doubtful	Absent	Absent
	3378.0	Absent	Absent	(see text)
	3379.2	Absent	Absent	Absent

Sample 1 was received on February 20, 1948; its spectrum showed the presence of comparatively large amounts of calcium and magnesium, moderate amounts of iron, nickel, sodium and chromium, and small amounts of neodymium. Calcium was easily the major metallic constituent of this sample.

Although no definite line was seen in its spectrum at 3305.8, the proximity of iron 3305.98, which was present, might have masked a weak line at 3305.8. A line was observed at 3342.5, but this line may have been chromium 3342.586.

Two highly purified samples were received from the same source on March 7, 1949. The two samples contained 50 and 100 micrograms, respectively, of element 61. Arc spectra of these samples were taken under the same conditions as used for sample 1, except that higher dispersion was used. The spectrum of sample 3 is shown in Fig. 1.

The results are summarized in Table A. A weak line, not assignable to any known element, was found at 3377.64±0.03 Å. in the high dispersion spectra, but in view of the fact that Yntema's observations were also made in the second order of a 6.5-meter spectrograph,[4] this line cannot be assumed to be identical with 3378.0. It was the weakest of several lines believed due to element 61 which were observed in the 3000–3450 Å. region of spectra 2 and 3. Seven such lines are listed in Table B; although these lines are fairly close to minor lines of various elements listed in the M. I. T. Wavelength Tables, qualitative examination of the spectrum showed that the only impurities present in samples 2 and 3 were faint traces of copper and calcium, and these did not interfere with the lines listed. A detailed study of the arc spectrum of element 61 is being made by W. F. Meggers and B. F. Scribner, Jr., of the National Bureau of Standards.

(1) This document is based on work performed under Contract No.7405 eng. 26 for the Atomic Energy Project, and the information covered therein will appear in the National Nuclear Energy Series (Manhattan Project Technical Section) as part of the contribution of the Oak Ridge National Laboratory.

(1a) *Chem. Eng. News*, **26**, 205 (1948); J. A. Marinsky, L. E. Glendenin and C. D. Coryell, THIS JOURNAL, **69**, 2781 (1947); W. E. Cohn, E. R. Tompkins and J. X. Khym, *ibid.*, **69**, 2769 (1947); B. H. Ketelle and G. E. Boyd, *ibid.*, **69**, 2800 (1947).

(2) L. E. Burkhart, W. Peed and E. Spitzer, *Phys. Rev.*, **75**, 86 (1949).

(3) J. A. Harris, L. F. Yntema and B. S. Hopkins, THIS JOURNAL, **48**, 1585 (1926).

(4) L. F. Yntema, *ibid.*, **46**, 37 (1924).

TABLE B

STRONGEST ARC LINES OF ELEMENT 61 IN THE 3000–3450 Å. REGION

Wave length, Å.	Relative intensity
3366.05 ± 0.03	Weak
3377.64 ± .03	Weak
3391.25 ± .03	Medium
3418.67 ± .03	Weak
3427.42 ± .03	Strong
3441.09 ± .03	Weak
3449.81 ± .03	Medium

Unfortunately, it was impossible to compare these (arc) spectra with the (spark) spectrum observed by Timma.[5] His observations covered the 3630–4400 Å. region; aside from the fact that the methods of excitation used were different, his principal lines could not be looked for in the present arc spectrum with any hope of success because of interference by C_2 and CN bands. However, the spark lines he mentioned as due to element 61 were observed in the spectrum of aliquots of samples 1, 2 and 3 when excited by the copper spark technique.

(5) D. Timma, MonC-166 (U. S. Atomic Energy Commission).

OAK RIDGE NATIONAL LABORATORY
OAK RIDGE, TENN. RECEIVED JANUARY 26, 1949

A Convenient Synthesis of Phenaceturic Acid[1]

BY JARED H. FORD

Phenaceturic acid was required as a starting material in numerous experiments directed toward the synthesis of benzylpenicillin.[2] The following method which employs methyl phenylacetate as the starting material was found to be more convenient than the literature method[3] in which phenylacetyl chloride was used.

Experimental

Glycine (75.1 g.) was added to a solution of 23 g. of sodium in 850 ml. of anhydrous methanol, and the mixture was boiled under reflux a few minutes to obtain a clear solution. One hundred fifty grams of methyl phenylacetate was then added and the solution was boiled under reflux for three days. The methanol was distilled off and the residue was dissolved in 400 ml. of cold water which contained 20 g. of sodium bicarbonate. The resulting solution was twice extracted with ether to remove unchanged methyl phenylacetate, and then acidified to *p*H 2 with concentrated hydrochloric acid. After standing overnight in a refrigerator, the product was filtered, washed with cold water and dried in a vacuum oven. The resulting white crystals melted at 139–141° (lit.,[3] 143°); yield, 122.6 g. (63.5%). One recrystallization from hot water (400 ml.) gave 114.2 g. of product which melted at 143–144°. From the ether extracts were obtained 42.1 g. (28%) of methyl phenylacetate; b. p. 96–98° (14 mm.).

A longer period of heating did not increase the yield and it appears likely that an equilibrium is involved

$$C_6H_5CH_2COOCH_3 + NH_2CH_2COONa \rightleftharpoons C_6H_5CH_2CONHCH_2COONa + CH_3OH$$

(1) This work was done under contract between the Office of Scientific Research and Development and The Upjohn Company (Contract OSRD-cmr-399).

(2) Clarke, Johnson and Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949.

(3) Hotter, *J. prakt. Chem.*, [2] **38**, 98 (1888).

ANTIBIOTICS RESEARCH DEPARTMENT
THE UPJOHN COMPANY
KALAMAZOO 99, MICHIGAN RECEIVED MAY 5, 1949

Alkyl Derivatives of Ethylenediamine

BY ALBERT E. FROST, JR., STANLEY CHABEREK, JR., AND ARTHUR E. MARTELL

In the course of other work a number of symmetrical dialkyl ethylenediamines have recently been prepared and characterized. A number of other amines, containing a smaller or larger number of alkyl groups, and a few dialkyl piperazines were obtained as by-products. The by-products not previously reported for this method and their properties are listed in Table I. The method of preparation, which involved the reaction of ethylene dichloride with an excess of primary amine, has been described by others.[1,2,3,4,5] The main products were characterized as the dipicrates and as the phenylureas, which are listed in Table II. Attempts to prepare the phenylurea from tribenzylethylenediamine were unsuccessful, and it was found that picrates could not be formed readily from dioctylpiperazine, tetraoctylethylenediamine, didodecylpiperazine and tribenzylethylenediamine. The picrate obtained with dibenzylethylenediamine was shown by analysis to be the monopicrate. Repeated recrystallization from various solvents did not change the melting point or the analysis.

TABLE I

BY-PRODUCTS

Amine	B. p., °C.	Mm.	M. p., °C.	N, % Calcd.	N, % Found
N,N′-Dioctylpiperazine	187–190	1	53–55	9.02	9.09
N,N,N′,N′-Tetraoctylethylenediamine	.....		130–133	5.51	5.29
N,N′-Didodecylpiperazine	265–275	8	54–56	6.63	6.34
N-Monobenzylethylenediamine	155–160	5	.....	18.65	18.72
N,N,N′-Tribenzylethylenediamine	225–235	4	99–100	8.48	8.64
Trioctyldiethylenetriamine[a]	213–215	2	.....	9.55	9.28

[a] *Anal.* Calcd. for $C_{28}H_{61}N_3$: C, 76.5; H, 14.0. Found: C, 76.4; H, 14.0.

For this method of preparation, it was found that the separation of the insoluble crystalline monohydrate obtained by treating the reaction product with a dilute aqueous solution of strong base provided the most convenient method of

(1) Sebrell and Clifford, U. S. Patent 1,948,317 (Feb. 20, 1934).

(2) Kyrides, U. S. Patent 2,126,560 (Aug. 9, 1938); U. S. Patent 2,267,685 (Dec. 23, 1941).

(3) Zienty and Thielke, THIS JOURNAL, **67**, 1040 (1945).

(4) Zienty, *ibid.*, **68**, 1388 (1946).

(5) Clifford, U. S. Patent 2,216,620 (Aug. 9, 1938).

TABLE II

Amine	Derivatives: Dipicrate M. p., °C.	Dipicrate N, % Calcd.	Dipicrate N, % Found	Phenylurea M. p., °C.	Phenylurea N, % Calcd.	Phenylurea N, % Found
N,N′-Dibutylethylenediamine	148–149.5[a,6]	17.78	17.43	174–174.5	13.65	13.31
N,N′-Dioctylethylenediamine	158–159.5[b,7]	15.09	14.73	129.5–130	10.72	10.30
N,N′-Didodecylethylenediamine	152–154.5[c,7]	13.11	13.11	235 (subl.)	8.83	8.64
N,N′-Dicyclohexylethylenediamine	210 (dec.)	16.42	16.04	206	12.11	12.45
N,N′-Dibenzylethylenediamine	208–210[d] (dec.)	14.93	14.71	182[8]	11.71	11.73
N,N′-Dibutylpiperazine	155–156	17.07	16.89	.....	...	...

[a] King and McMillan reported 188°. [b] Linsker and Evans reported 108°. [c] Linsker and Evans reported 112°. [d] Monopicrate.

isolation. This was not possible in the case of dibenzylethylenediamine, which did not form a solid monohydrate under the conditions employed. The by-products listed in Table I were obtained by fractional distillation of the dialkyl ethylenediamines.

Acknowledgment.—The authors are indebted to F. C. Bersworth, of the Bersworth Laboratories, Framingham, Massachusetts, for financial support for this research.

(6) King and McMillan, THIS JOURNAL, **68**, 1776 (1946).
(7) Linsker and Evans, *ibid.*, **68**, 1432 (1946).
(8) Van Alphen, *Rec. trav. chim.*, **54**, 93 (1935).

DEPARTMENT OF CHEMISTRY
CLARK UNIVERSITY
WORCESTER, MASSACHUSETTS RECEIVED JUNE 17, 1949

Acetyldesoxycellulose Quaternary Salts

BY F. N. HAYES AND CHAO-HAN LIN

A cellulose acetate tosylate was prepared by the method of Malm, Tanghe and Laird.[1] Separate portions of it were heated with pyridine, 3-picoline and isoquinoline to give quaternary salts, resulting from displacement of tosylate ions. Similar reactions of *p*-toluenesulfonate esters with tertiary amines are well known.[2,3] Table I gives analytical data and the calculated values for free hydroxyls, unreacted tosylate ester groups, and quaternary salt groups per glucose unit for each of the three products.

The average over-all percentage conversion of the original hydroxyl groups to quaternary salt groups may be used as an estimate of the per cent. primary free hydroxyl in the original cellulose acetate. Our value of 28% compares favorably with a reported value of 25% on a similar sample,[1] determined by the method of tosylation and iodination.

TABLE I

Sample	Percentage N[a]	Percentage S[a]	Amount per g. u. Free[b] OH	Amount per g. u. Tos.[b] ester	Amount per g. u. Quat.[b] salts	Percentage Conv. of OH to quat. Tos. replaced	Percentage Conv. of OH to quat. salt
I	..	6.85	0.96	0.69	..	..	..
II	1.93	5.81	1.02	.14	0.49	71	30
III	1.77	5.96	0.97	.26	.42	61	26
IV	1.72	5.74	0.96	.22	.47	68	29

[a] Analyses by Micro-Tech Laboratories, Skokie, Ill. [b] Calculated from the analyses, assuming that the acetyl content remains unchanged.

(1) Malm, Tanghe and Laird, THIS JOURNAL, **70**, 2740 (1948).
(2) Cary, Vitcha and Shriner, *J. Org. Chem.*, **1**, 280 (1936).
(3) King, Dodson and Subluskey, THIS JOURNAL, **70**, 1176 (1948).

A sample of cellulose acetate, EK-102893,[4] was tosylated[1] and the product (I) was reprecipitated from acetone by alcohol. Pyridine, 3-picoline and isoquinoline were dried and redistilled.

A solution of 6.0 g. of cellulose acetate tosylate in 60 ml. of pyridine was heated on a steam-bath for twenty-four hours, at the end of which time, it was diluted with 40 ml. of acetone and treated with just enough water to obtain a homogeneous solution. This was slowly poured into excess acetone with good stirring. The precipitated product was filtered, washed with acetone and twice reprecipitated from hot alcohol by ether. The yield of the purified product (II) was 5.5 g.

In a similar manner, 3.0 g. of the tosyl ester gave 2.8 g. of a 3-picolinium salt (III) and 8.0 g. yielded 7.8 g. of an isoquinolinium salt (IV).

(4) Kindly supplied for this project by Eastman Kodak Company, with analysis: 1.35 acetyls per glucose unit.

DEPARTMENT OF CHEMISTRY
ILLINOIS INSTITUTE OF TECHNOLOGY
CHICAGO, ILLINOIS RECEIVED JUNE 30, 1949

Separation of Hafnium and Zirconium by a Fractional Distillational Procedure

BY D. M. GRUEN AND J. J. KATZ

In view of current interest in hafnium–zirconium separations,[1] we have investigated a separation method first reported by van Arkel and De Boer.[2] This method involves fractional distillation at atmospheric pressure of the volatile complex compounds formed by reaction of zirconium and hafnium tetrachlorides with either phosphorus pentachloride or phosphorus oxychloride. Although van Arkel and De Boer showed that distillation resulted in considerable separation of hafnium and zirconium they gave no quantitative data on the relative volatilities of the zirconium and hafnium compounds.

The present work is concerned chiefly with the phosphorus oxychloride complexes, since these have lower boiling points and greater thermal stability than the corresponding phosphorus

(1) K. Street and G. T. Seaborg, THIS JOURNAL, **70**, 4268 (1948).
(2) A. E. van Arkel and J. H. De Boer, *Z. anorg. Chem.*, **141**, 289–296 (1924).

pentachloride compounds. van Arkel and De Boer assigned the formula 2 $ZrCl_4 \cdot POCl_3$ on the basis of zirconium and chlorine analyses. However, analyses for phosphorus, a more sensitive criterion of composition, indicate a more probable formula $3ZrCl_4 \cdot 2POCl_3$ (phosphorus: Calcd. 6.17%; found, 6 27, 6.12, 6.10%).

The vapor pressures of pure $3ZrCl_4 \cdot 2POCl_3$ and $3HfCl_4 \cdot 2POCl_3$ have been determined in the range 0.1–1.0 atmosphere and are represented graphically in Fig. 1. The boiling points are 360 and 355° for the zirconium and hafnium compounds, respectively; the 5° difference in boiling points (which we feel is accurate to ±1°) leads to a calculated value of $\alpha_0 = 1.14$ for the ratio of the vapor pressures at the boiling points. The heat of vaporization for both complexes is 20.5 ± 0.5 kcal.

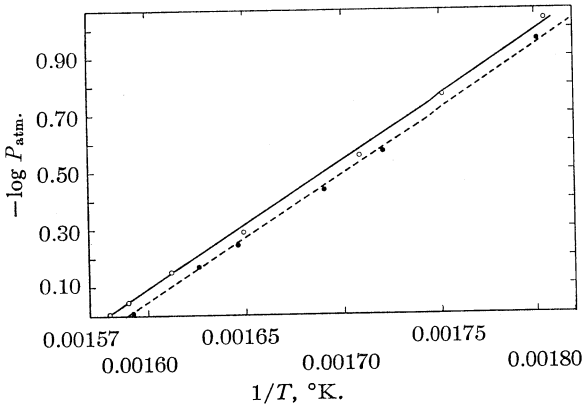


Fig. 1.—Vapor pressure of $HfCl_4$–$POCl_3$ and $ZrCl_4$–$POCl_3$ complexes: —, Zr complex; - - -, Hf complex.

A glass perforated plate column[3] with 50 physical plates was used in the distillation. In a typical experiment $3ZrCl_4 \cdot 2POCl_3$ containing 2.5% hafnium (on the weight of zirconium) yielded a first fraction (5%) containing 16% hafnium. The residue, after distilling 40% away, contained <0.2% hafnium.

Calculation shows the column can also be operated to yield essentially pure hafnium. This aspect, as well as further studies of the chemical and physical properties of these interesting compounds, is presently being investigated.

(3) C. F. Oldershaw, *Ind. Eng. Chem., Anal. Ed.*, **13**, 265 (1941).

CHEMISTRY DIVISION
ARGONNE NATIONAL LABORATORY
CHICAGO, ILLINOIS

RECEIVED MAY 19, 1949

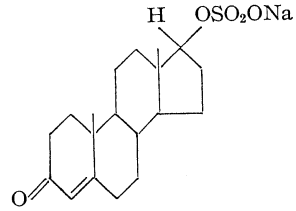
Sodium Testosterone Sulfate

BY G. W. HOLDEN, I. LEVI AND R. BROMLEY

Sodium testosterone sulfate has been prepared with the object of comparing its androgenic activity with that of testosterone and other of its derivatives. The results of the biological tests will be reported later.

With the exception of the use of charcoal in the purification procedure, the method followed was that described by Butenandt and Hofstetter[1] for the preparation of sodium estrone sulfate.

In alcohol, sodium testosterone sulfate exhibits an absorption maximum at 241 mμ, characteristic of testosterone. In water the maximum is shifted to 248–249 mμ.



A solution of chlorosulfonic acid, prepared by dissolving chlorosulfonic acid (1 ml.) in dry chloroform (30 ml.), cooling to 0° and adding pyridine (15 ml.), was added to a solution of testosterone (1.5 g.) in dry pyridine (20 ml.) and dry chloroform (50 ml.). After forty-eight hours at room temperature the solvent was removed *in vacuo* with a water-bath temperature of 40–50°. The solid residue was dissolved in methanol and the acidic solution almost neutralized (litmus) by the addition of methanolic sodium hydroxide. Aqueous sodium bicarbonate was then added to make the solution alkaline and the methanol removed *in vacuo* in the presence of water. The final volume of about 50 ml. was quite clear. This solution was shaken occasionally with Nuchar C (3 g.) at room temperature during one day. The Nuchar was filtered, washed several times with water (negative test for chloride) and eluted by suspending in methanol while still moist. Sodium testosterone sulfate (714.8 mg., 35%) was obtained by concentrating the methanol to small volume, clarifying by filtration using a little Nuchar to remove some yellow color, and precipitating with several volumes of ether. The product, thus obtained, is almost colorless. The m. p. (Fisher–Johns) is quite sharp at 215° with a green color changing to a clear brown at practically the same temperature; $[\alpha]^{25}D$ +74.5° (1% in water), +68° (1% in ethanol); $\epsilon_{(248-249)}$ 20,300 (in water): $\epsilon_{(240.5-241)}$ 17,700 (in ethanol). *Anal.* Calcd. for $C_{19}H_{27}O_5SNa$: C, 58.43; H, 6.97; Na, 5.88. Found: C, 58.54; H, 6.38; Na, 6.03. The semicarbazone precipitated at once on addition of semicarbazide hydrochloride to an aqueous solution of sodium testosterone sulfate. It does not melt up to 300° but starts to darken at 240° becoming slate-gray and finally chocolate-brown. For the determination of testosterone, 53.4 mg. of sodium testosterone sulfate was added to the barium chloride sodium acetate solution described by Talbot[2] for the hydrolysis of sodium dehydroisoandrosterone sulfate. After four hours heating on the steam-bath the solution was extracted with ether. Only 6.5% of the theoretical weight of residue was obtained. Fifty milligrams of sodium testosterone sulfate was then hydrolyzed by refluxing one hour with a mixture of 100 ml. of water and 15 ml. of concd. hydrochloric acid in the presence of 75 ml. of toluene. The toluene was separated, the aqueous solution further extracted with ether and the combined extracts distilled after washing with sodium bicarbonate and water. The yellowish gummy residue weighed 26.8 mg. (68%). It was crystallized by means of aqueous acetone to yield 9.3 mg. (25.3%) of testosterone m. p. 153.5° and mixed m. p. with pure testosterone undepressed.

RESEARCH LABORATORIES
CHARLES E. FROSST & CO.
MONTREAL, CANADA

RECEIVED JULY 11, 1949

(1) Butenandt and Hofstetter, *Z. physiol. Chem.*, **259**, 222 (1939).
(2) Talbot, Ryan and Wolfe, *J. Biol. Chem.*, **148**, 593 (1943).

Mechanism of the Polymerization of Propylene with Aluminum Bromide-Hydrogen Bromide Catalyst[1]

BY FRANK R. MAYO AND CHEVES WALLING

The recent excellent experimental work of Fontana and Kidder[2] on the kinetics of the polymerization of propylene by aluminum bromide-hydrogen bromide at about $-80°$ showed that, after the steady rate is obtained, the rate of polymerization is consistent with the equation

$$\frac{-\mathrm{d}[\mathrm{m}]}{\mathrm{d}t} = \frac{kKc[\mathrm{m}]}{1 + K[\mathrm{m}]}$$

where [m] is the monomer concentration, c is the total concentration of catalyst in all forms, K is the equilibrium constant for the reversible formation of a postulated complex formed from a catalyst–monomer complex plus additional monomer, and k is the rate constant for chain lengthening, considered to be rearrangement of the catalyst–polymer–monomer complex into a stable form.

The object of this communication is to present an alternative interpretation of their data. Our scheme assumes (1) that essentially all of the catalyst (or promoter) is bound to the polymer as an un-ionized complex such as $\mathrm{H(-CH_2-\overset{H}{\underset{CH_3}{C}}-)_n-Br\cdot AlBr_3}$, (2) that the first rate determining step in the propagation reaction is the dissociation of this complex into $\mathrm{H(-CH_2-\overset{H}{\underset{CH_3}{C}}-)_n^+}$ and $\mathrm{AlBr_4^-}$, (3) that actual chain propagation involves addition of the carbonium ion and anion to the propylene before recombination of the original ions occurs. Since, in a solvent of low dielectric constant, the dissociated complex will exist as an *ion pair* surrounded by a cage of solvent and propylene molecules, recombination will be kinetically first order, and the situation parallels that suggested by Matheson[3] for peroxide-initiated polymerizations. Thus, the fraction of the dissociations in which the carbonium ion will add a propylene unit before recombining with the negative ion will be $K'[\mathrm{m}]/(1 + K'[\mathrm{m}])$ where K' is the ratio of the rate constant for the reaction of the ion pair with propylene divided by the rate constant for recombination of the ion pair. The over-all rate of polymerization is then

$$\frac{-\mathrm{d}[\mathrm{m}]}{\mathrm{d}t} = \frac{k'K'c\ [\mathrm{m}]}{1 + k'\ [\mathrm{m}]}$$

where k' is the rate of dissociation of the catalyst-polymer complex, c.

The form of the equation shows that an appreciable fraction of the dissociations are accompanied by growth, and also that only one growth step occurs at a time. These requirements are easily met if both ions simultaneously add to the propylene. Experiments with scale models indicate the probability of this course; they also show that the two mechanisms here considered differ only in details. When this interpretation is applied to isobutylene[4], styrene[5] and vinyl ethers[6] the integral orders of these polymerizations with respect to monomer suggest that the fraction of ionizations resulting in chain growth is lower, a result to be expected if the respective complexes ionize more readily but give less reactive carbonium ions.

Our proposed interpretation provides a mechanism for carbonium ion polymerizations in solvents of low dielectric constant similar to that proposed for the polymerization of alkenes by sulfuric acid, the solvolyses of alkyl halides, and the Friedel–Crafts reaction. Further, it accounts more readily than the mechanism of Fontana and Kidder for observations[5,6] that the rates of carbonium ion polymerizations increase very rapidly with the dielectric constant of the solvent. However, our interpretation is inconsistent with one conclusion of Fontana and Kidder, that ΔH for reversible addition of monomer to complex is 8.9 kcal./mole and that K decreases with increasing temperature. In our scheme, this corresponds to the anomaly that the activation energy for simple recombination of two ions is 8.9 kcal./mole *larger* than for addition of propylene to a carbonium ion. Since, in the experiments cited, an appreciable but unknown proportion of catalyst precipitated in an inactive form from each reaction mixture, we suggest that experiments at different temperatures have not yielded correct temperature coefficients, a point which is a critical test of our proposal.

(1) Contribution No. 95 from the General Laboratories of the United States Rubber Company.
(2) Fontana and Kidder, THIS JOURNAL, **70**, 3745 (1948).
(3) Matheson, *J. Chem. Phys.*, **13**, 584 (1945).
(4) Evans and Meadows, *J. Polymer Sci.*, **4**, 359 (1949).
(5) Pepper, *Trans. Faraday Soc.* **45**, 397, 404 (1949).
(6) Eley and Richards, *ibid.*, 425.

UNITED STATES RUBBER CO.
PASSAIC, N. J.

RECEIVED AUGUST 25, 1949

Investigation of Possible Interactions between Thallium(I) and Thallium(III) in Solution and in the Crystalline Thallium Sesqui-halides

BY HARDEN MCCONNELL AND NORMAN DAVIDSON

The discovery[1] that the rate of radioactive exchange between Tl(I) and Tl(III) in aqueous solutions is slow has prompted us to: (1) examine, by a radiochemical method, whether or not the substances $\mathrm{Tl_2Cl_3}$ and $\mathrm{Tl_2Br_3}$ contain non-equivalent Tl(I) and Tl(III) ions; (2) look for non-additive light absorption[2] in some aqueous solutions containing Tl(I) and Tl(III). Problems (1) and (2) are related because the $\mathrm{Tl_2X_3}$ compounds are more colored than the corresponding TlX or $\mathrm{TlX_3}$ compounds.[3]

(1) Harbottle and Dodson, THIS JOURNAL, **70**, 880 (1948); Prestwood and Wahl, *ibid.*, **71**, 3137 (1949); see also pp. 226, 205 of "Isotopic Exchange Reactions and Chemical Kinetics," Brookhaven National Laboratory, Patchogue, New York, Dec., 1948.
(2) Whitney and Davidson, THIS JOURNAL, **69**, 2076 (1947).
(3) Benrath, *Z. anorg. Chem.*, **93**, 161 (1915); **136**, 358 (1924).

(1) For the exchange experiment with Tl_2Cl_3, 4 ml. of dilute HCl solution containing 5.2 mg. of dissolved Tl_2Cl_3 and 1.46 mg. of active $TlCl_3$ (containing Tl^{204}) were evaporated nearly but not quite to dryness by evacuation at room temperature for forty-five minutes. It follows from the data of Benrath that under these conditions essentially all of the Tl(I) was initially precipitated as Tl_2Cl_3, and there might be small amounts of $TlCl_2$ or hydrated $TlCl_3$ formed subsequently, depending on the completeness of evaporation.[3] (Furthermore by visual inspection of the precipitate one saw only the characteristic hexagonal yellow flakes of Tl_2Cl_3.)[4] This entire residue, the yellow solid Tl_2Cl_3 and the adhering excess of $TlCl_2$ or $TlCl_3$ (solid or solution), was redissolved in water and divided into two 2-ml. samples. Thallous chromate was precipitated from one portion, using the conditions developed by Harbottle and Dodson,[1] washed, and slurried onto a counting plate. The second sample was reduced with sulfur dioxide so that all the thallium could be precipitated as the chromate and the total activity counted. There was no appreciable self absorption in the samples.

A blank experiment was performed which was identical to the above except that the evaporation to give solid Tl_2Cl_3 was omitted, and the sample was allowed to stand for twenty minutes.

For the Tl_2Br_3 experiment, 30 ml. of a solution containing 1.2 g. of $TlBr_3$ was saturated with inactive TlBr at room temperature to insure the absence of bromine. The solution was then saturated with active TlBr at 50°. Two 10-ml. aliquots of this solution were allowed to cool to room temperature, and the red Tl_2Br_3 precipitated out.[5] The thallous activity was determined with one sample and the total activity with the other. For control measurements, the thallous and total activities of 1-ml. aliquots of the solution at 50° were determined.

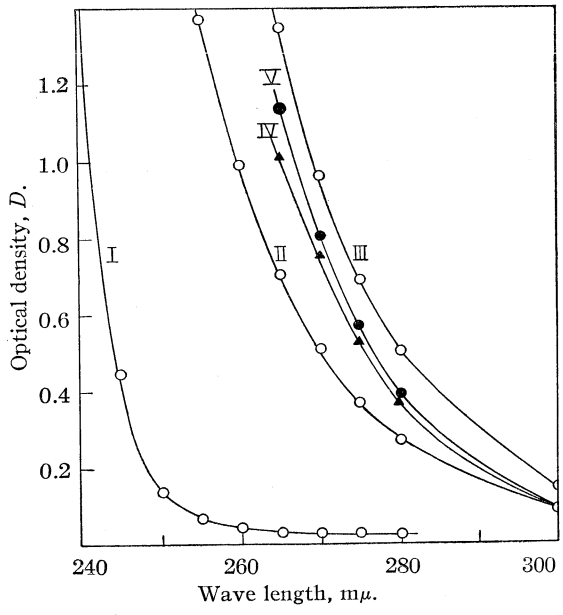


Fig. 1.—The absorption spectra of some thallium(I) and (III) solutions in perchloric acid: I, Tl(I) 0.068 *F*; II, Tl(I) 0.034 *F*, Tl(III) 0.079 *F*; III, Tl(III) 0.157 *F*, I, II, III in 3.2 *F* $HClO_4$; IV, Tl(III) 0.079 *F*; V, Tl(I) 0.113 *F*, Tl(III) 0.079 *F*; IV, V in 1.6 *F* $HClO_4$.

(4) Another sample of Tl_2Cl_3 was further identified by a thallium analysis; for a description of the crystalline form, *cf.* Meyer, *Z. anorg. Chem.*, **24**, 354 (1900).

(5) The identification of this substance as Tl_2Br_3 is based on its color and crystalline form corresponding to the descriptions given by Benrath[3] and Meyer[4] and on the solubility data determined by Benrath.

TABLE I

EXCHANGE EXPERIMENTS WITH THALLIUM SESQUI-HALIDES

Experiment	Composition of exchange mixture, mg. Tl(I)	Tl(III)	Specific activities,[a] c./min. mg. Tl(I)	Tl(III)	Ratio of specific activities of Tl(III) and Tl(I)
Solid Tl_2Cl_3	3.12	2.00[b]	31.5	321	10 (±1)
Tl_2Cl_3 control	3.12	2.00[b]	18.6	241	13 (±1)
Solid Tl_2Br_3	32.4[c]	10.8[c]	102	27.8	0.27 ± (0.05)
Tl_2Br_3 control	6.1	18.4	87.7	20.2	0.23 ± (.05)

[a] For the Tl_2Cl_3 experiment, the specific activities were calculated on the basis of the amounts of Tl(I) and Tl(III) added; for the Tl_2Br_3 experiment, see footnote (c). [b] Including 0.96 mg. of active Tl(III). [c] These numbers, estimated from the solubility data of Benrath, are included to indicate the probable size of the Tl_2Br_3 precipitate; only the ratio of activities is important for the interpretation of the experiment.

The experimental results (Table I) are that within the uncertainties of the experiments there is no exchange in the solid state. These uncertainties are due to experimental errors and due to the possibilities of differences between the control experiments and the experiments in which solid Tl_2X_3 compounds were separated as to: (a) degree of homogeneous exchange in solution, (b) degree of induced exchange on precipitation of thallous chromate. For the Tl_2Cl_3 experiment, the calculated ratio of specific activities of Tl(III) and Tl(I) for complete equivalence in the solid is 2.1 accepting the validity of the control experiment (and assuming no exchange between the solid Tl_2Cl_3 and the excess adhering Tl(III)). For the Tl_2Br_3 experiment this ratio is 1.0. Because of the evidence that Tl_2Cl_3 has 64 thallium atoms per unit cell,[6] it is worthwhile to emphasize that our data are not sufficiently accurate to exclude the possibility that a small fraction of the Tl(I) and Tl(III) atoms occupy equivalent positions in the Tl_2X_3 lattice.

(2) Figure 1 exhibits the absorption spectra of some thallium (I) perchlorate, thallium (III) perchlorate, and mixed solutions in 3.2 and 1.6 *F* perchloric acid. Thallium (III) is more colored than Tl(I) and there is no appreciable non-additive absorption in the mixed solutions. The extinction coefficients of Tl(III) calculated from these data (Table II) show that Tl(III) is more colored at lower acidities, suggesting an increased hydrolysis of Tl^{+++} to $Tl(OH)^{++}$ or $Tl(OH)_2^{+}$. Harbottle and Dodson[1] and Prestwood and Wahl[1] have previously suggested such a hydrolysis to explain the variation of the rate of exchange between Tl(I) and Tl(III) with acidity.

TABLE II

EXTINCTION COEFFICIENTS OF Tl(III) AS A FUNCTION OF ACIDITY

λ (mμ)	290	280	270	265
ε (Tl(III))(1.6 *F* $HClO_4$)	2.25	4.6	9.5	13.3
ε (Tl(III))(3.2 *F* $HClO_4$)	1.8	3.25	6.1	8.5

Most of the known cases of interaction absorption in solution are in media containing excess

(6) Jerslev and Hägg, *Experientia*, **2**, 495 (1946).

chloride ions. The insolubility of thallous chloride in water and dilute solutions of thallic chloride, and the presence of free chlorine in concentrated thallic chloride solutions (3.5 *F*) in which thallous chloride has an appreciable solubility[3] prevented an exact spectrophotometric study of solutions having significant concentrations of thallous and thallic chlorides. We can report however that as successive portions of solid thallous chloride were added to a 3.4 *F* thallic chloride solution containing some (*ca.* 0.03 *F*) free chlorine, the optical density of the resulting solutions decreased (as the chlorine was removed) and became constant at the values: $\lambda = 380$ mμ, $D = 0.065$; $\mu = 360$ mμ, $D = 0.66$, for a solution that contained 0.04 *F* excess Tl(I). Since the optical densities of the solutions never increased as the TlCl was added, there was probably no significant interaction absorption in the solution.

This work has been supported by the Office of Naval Research. We are grateful to Dr. German Harbottle for communicating to us his excellent method of separating thallous and thallic ions.

CONTRIBUTION NO. 1307 FROM THE
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA 4, CALIFORNIA RECEIVED JUNE 8, 1949

The Lactal Ring Structures of Some Synthetic Pyrimidine Nucleosides[1]

BY MARJORIE ZEIGER NEWMARK, IRVING GOODMAN AND KARL DITTMER[2]

The ribosyl, arabinosyl, glucosyl and galactosyl nucleosides of uracil and thymine and the corresponding 5-bromo-uracil derivatives were prepared in our laboratories[3,4] and tested for biological activity[5] on two strains of *Escherichia coli*, two strains of *Neurospora crassa*, a strain of *Lactobacillus casei*, and one of *Streptococcus faecalis* R.

A uracil-requiring mutant of *E. coli* was unaffected by any of the synthetic nucleosides although uracil or natural uridine produced good growth. A uracil-less mutant of *N. crassa* which was shown by Loring to grow well on uracil, uridine or uridylic acid was also unaffected by the synthetic products. Results of studies of *L. casei* and *S. faecalis* R showed a similar lack of biological activity. These studies emphasized the need for complete elucidation of the detailed structure of these synthetic nucleosides.

In order to establish the nature of a possible relationship between structure and activity, a number of naturally occurring and synthetic nucleosides were analyzed by the periodate method as adapted by Davoll, Lythgoe and Todd[6] to determine the ring structures of the sugar component of the nucleosides. In this method glycofuranosyl nucleosides of the pentoses require one mole of periodate per mole of nucleoside for oxidation, whereas glycopyranosides of this type require two moles of periodate. Aldohexoses in the pyranoside form require two moles of periodate for oxidation and liberate one mole of formic acid during the course of the reaction; aldohexoses in the furanoside form also require two moles of periodate for oxidation but liberate no formic acid.

Table I summarizes the results of the periodate oxidation of a number of synthetic pyrimidine nucleosides as well as the naturally occurring pyrimidine nucleosides, uridine and cytidine. All of the synthetic nucleosides here reported possess the pyranoside structure. These results would indicate in part that the known biological activity of uridine and cytidine are dependent upon the furanoside structure.

TABLE I

PERIODATE OXIDATION OF SOME PYRIMIDINE NUCLEOSIDES

N-Glycoside	Moles IO_4^- / Mole glycoside	Moles HCOOH / Mole glycoside
Uridine[a]	1.14	..
Cytidine[a]	1.20	..
1-D-Ribosyl uracil	2.02	..[b]
1-D-Arabinosyl uracil	2.07	..[b]
1-D-Xylosyl uracil	1.89	0.86
1-D-Glucosyl uracil	2.01	0.95
1-D-Galactosyl uracil	2.03	..[b]
1-D-Arabinosylthymine	2.03	..[b]
1-L-Arabinosylthymine	1.92	..[b]
1-D-Galactosylthymine	2.04	0.99
1-D-Glucosylcytosine	1.98	0.88

[a] We are indebted to Dr. H. S. Loring of Stanford University for the samples of uridine and cytidine. [b] The theoretical amount of formic acid expected is 1 mole, but due to limited amounts of material the determinations were not made.

(1) This work was supported in part by a research grant-in-aid from the National Institutes of Health.

(2) Present address: Dept. of Chemistry, Florida State University, Tallahassee, Florida.

(3) D. Visser, K. Dittmer and I. Goodman, *J. Biol. Chem.*, **171**, 377 (1947).

(4) D. Visser, I. Goodman and K. Dittmer, THIS JOURNAL, **70**, 1926 (1948).

(5) K. Dittmer, I. Goodman, D. Visser and H. P. McNulty, *Proc. Soc. Exp. Biol. Med.*, **69**, 40 (1948).

(6) J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 833 (1946).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF COLORADO
BOULDER, COLO. RECEIVED JUNE 16, 1949

A Complex Praseodymium Fluoride Readily Soluble in Dilute Acids[1]

BY THEODORE P. PERROS AND CHARLES R. NAESER

The insolubility of praseodymium trifluoride in dilute mineral acids is well known. In the course of investigations concerning this compound a complex potassium–praseodymium–fluoride compound, possibly new, which was easily soluble in dilute acids was prepared.

(1) From the thesis for the M.S. degree of T. Perros, The George Washington University.

Experimental

About 10 g. of technical grade potassium hydrogen fluoride was placed in a platinum crucible and heated over a burner until molten. Approximately 0.5 g. of praseodymium trifluoride was placed in the melt and stirred with a platinum rod. Within five minutes the praseodymium fluoride had dissolved completely, giving a pale yellow-green color to the melt. After the melt had cooled and solidified to a hard, brittle mass, it was placed in a beaker and water (containing a few drops of ammonium hydroxide solution) was added to dissolve the excess potassium fluoride and potassium hydrogen fluoride. After several leachings with water, a pale green residue mixed with dark particles of impurities from the potassium hydrogen fluoride remained. The washings, even after concentration, gave no evidence for the presence of praseodymium ions. However, light reflected from the green residue gave the characteristic absorption spectrum of praseodymium ions.

This green residue, but not the black particles, was readily soluble in 3 *N* hydrochloric acid when slightly warmed. This behavior is quite different from that of praseodymium trifluoride.

Purification of potassium hydrogen fluoride by crystallization eliminated the dark impurities. The purified material with praseodymium trifluoride gave a residue completely soluble in the 3 *N* hydrochloric acid. This marked difference in solubility of the two praseodymium–fluoride compounds indicates the formation of a complex ion containing both praseodymium and fluorine.

When Pr_6O_{11} was added to fused potassium hydrogen fluoride a vigorous reaction took place, and the final green residue showed the same characteristics as that obtained by treatment of the praseodymium trifluoride with potassium hydrogen fluoride.

Investigations to determine whether the composition of this substance is similar to the $KLaF_4$ described by W. H. Zachariasen[2] and also to determine the properties of this substance are being continued.

(2) Zachariasen, THIS JOURNAL, **70**, 2147 (1948).

DEPARTMENT OF CHEMISTRY
THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, D. C. RECEIVED JULY 11, 1949

Acid Catalyzed Reaction of Diarylformamidines with Ethyl Orthoformate

BY ROYSTON M. ROBERTS

Ethyl N-phenylformimidate (I) was first prepared by Comstock and Clapp[1] from ethyl iodide and the silver salt of formanilide; the yield was low, and although it has been improved by Smith and Nichols[2] the procedure is expensive and tedious. Claisen[3] prepared this compound from aniline and ethyl orthoformate. He reported that the preparation was accomplished only after numerous unsuccessful attempts and that his directions must be followed exactly; even so, the yield he obtained was only 44% from a reaction mixture heated nine hours. Our attempt to repeat this work resulted in a yield of 11%. Claisen postulated a two-step mechanism for the reaction: first, the formation of N,N′-diphenylformamidine (rapid), and second, reaction of this compound with a second mole of ethyl orthoformate (much slower).

$$2C_6H_5NH_2 + (C_2H_5O)_3CH \longrightarrow C_6H_5N{=}CH{-}NH{-}C_6H_5 + 3C_2H_5OH \quad (A)$$

$$C_6H_5{-}N{=}CH{-}NH{-}C_6H_5 + (C_2H_5O)_3CH \rightleftharpoons 2C_6H_5N{=}CHOC_2H_5 + C_2H_5OH \quad (B)$$

I

There is no doubt regarding the ease with which the first step (A) takes place, but we have found that the second step (B), is practically completely dependent on acid catalysis. This undoubtedly explains the many unsuccessful experiments mentioned by Claisen and also our first attempt in which we took some care to avoid traces of acid. When we heated pure N,N′-diphenylformamidine with ethyl orthoformate containing a little anhydrous potassium carbonate for twenty-four hours, we found practically no alcohol was produced and the N,N′-diphenylformamidine was recovered unchanged. Prompted by the observation of acid catalysis in the reaction of ethyl N-phenylformimidate with amines (to be published separately) we added a small amount of aniline hydrochloride to the ethyl orthoformate and N,N′-diphenylformamidine and found that the calculated amount of ethanol was evolved rapidly and a 96% yield of ethyl N-phenylformimidate was produced. Other acids are also effective in catalyzing the reaction; sulfuric and *p*-toluenesulfonic acids gave comparable results and even acetic acid was fairly effective. Ethyl N-*p*-tolylformimidate[4] was produced from *p*-toluidine or N,N′-di-*p*-tolylformamidine under similar conditions. The formamidines need not be isolated when the aromatic amine is the starting material. In fact, the acid catalyzed reaction of orthoformate with aromatic amine may not proceed by intermediate formamidine formation but may be more direct. The mechanism of this reaction will be discussed more completely in a subsequent paper. It is interesting to note that reaction (B) is apparently reversible and has previously been described as it occurs in the opposite direction from that reported here! Knott[5] treated ethyl N-phenylformimidate in alcoholic solution with carboxylic and sulfonic acids; he obtained N,N′-diphenylformamidine salts and was able to identify ethyl orthoformate as the other product in one case.

Recently Hamer, Rathbone and Winton have reported modifying Claisen's procedure obtaining yields of 81–85% by "including aniline hydrochloride to inhibit the formation of carbylamine."[6] Their reason for choosing aniline hydrochloride for this function is not given and there is no mention of acid catalysis.

It is perhaps pertinent to recall attention to the fact that in 1941 Smith and Nichols[2] showed that the reaction of Grignard reagents with ethyl N-phenylformimidate was the most satisfactory general method for the synthesis of aromatic

(1) Comstock and Clapp, *Am. Chem. J.*, **13**, 527 (1891).
(2) Smith and Nichols, *J. Org. Chem.*, **6**, 489 (1941)
(3) Claisen, *Ann.*, **287**, 363 (1895).
(4) Wheeler and Johnson, *Ber.*, **32**, 35 (1899).
(5) Knott, *J. Chem. Soc.*, 686 (1945).
(6) Hamer, Rathbone and Winton, *J. Chem. Soc.*, 954 (1947).

aldehydes from the corresponding halides except for the difficulty of obtaining the ethyl N-phenylformimidate, a reagent which is now easily available.

Experimental

Materials.—Ethyl orthoformate, Eastman Kodak Co., redistilled, b. p. 142–144°; N,N′-diphenylformamidine (m. p. 138.5–139.5°, cor.), N,N′-di-*p*-tolylformamidine (m. p. 141.4–142.8°, cor.), prepared from the amines and ethyl orthoformate[7]; aniline hydrochloride, *p*-toluidine hydrochloride, prepared from the amines and concentrated hydrochloric acid, dried in a vacuum desiccator.

N,N′-Diphenylformamidine and Ethyl Orthoformate. A. Aniline Hydrochloride as Catalyst.—In a 200-ml. flask was placed 19.6 g. (0.10 mole) of N,N′-diphenylformamidine, 29.6 g. (0.20 mole) of ethyl orthoformate and 1.0 g. (0.008 mole) of dry aniline hydrochloride. An efficient 40-cm. distilling column having a total reflux partial take-off type head was attached and the reaction mixture was heated. Ethanol began to reflux immediately. After one hour of reflux the ethanol was distilled; 6.7 ml. was collected in about fifteen minutes. Anhydrous potassium carbonate (2.0 g.) was added and the mixture was shaken and allowed to stand two hours. The reaction mixture was then distilled through the same column under reduced pressure. Excess ethyl orthoformate was first recovered, 12.3 g., b. p. 83–85° (93 mm.). The pressure was then lowered to 40 mm. and colorless ethyl N-phenylformimidate distilled constantly at 117° (40 mm.); 28.7 g. or 96% of the theoretical amount was obtained.

The difference in the conditions under which the two steps of the reaction take place is illustrated by the following experiment. A mixture of 0.40 mole of aniline and 0.60 mole of ethyl orthoformate was heated in a flask to which was attached a 40-cm. distilling column. During one and one-quarter hours 36 ml. of ethanol distilled and then the distillation practically stopped. Aniline hydrochloride (1.30 g., 0.01 mole) was added to the reaction mixture and heating was resumed; distillation of ethanol now took place again at a rapid rate and 11.5 ml. was collected in thirty minutes, then the evolution practically stopped again. Anhydrous potassium carbonate (2.60 g.) was added and the mixture was distilled under reduced pressure. The excess ethyl orthoformate (27.2 g.) was removed first, b. p. 83° (90 mm.), then the product was distilled at 10-mm. pressure; 53.2 g. (89% of the amount calculated from aniline was obtained, b. p. 87–88° (10 mm.), $n^{25}D$ 1.5275 (lit., 1.527878).

B. Sulfuric Acid as Catalyst.—Aniline (1 mole), ethyl orthoformate (1.5 moles) and sulfuric acid (10 drops, *ca.* 0.04 mole) were heated under reflux thirty minutes and then 117 ml. of ethanol was distilled through a short column. The catalyst was neutralized with 3.5 g. of dry sodium *t*-butoxide and the mixture was distilled under reduced pressure. After the excess ethyl orthoformate was recovered, 121.6 g. (82% of the theoretical amount) of ethyl N-phenylformimidate was obtained, b. p. 117–119° (40 mm.).

C. Acetic Acid as Catalyst.—N,N′-Diphenylformamidine (0.10 mole), ethyl orthoformate (0.20 mole) and glacial acetic acid (0.6 ml., 0.01 mole) were heated under reflux for one hour, then 4.5 g. of distillate, b. p. 76–80°, was collected during forty minutes; the distillation temperature then began to rise sharply. Ethyl orthoformate (*ca.* 17 g.) was recovered at 82–83° (90 mm.), and 14.6 g. (55% of the theoretical amount calculated from 0.09 mole of N,N′-diphenylformamidine) of ethyl N-phenylformimidate was obtained, b. p. 117–118° (40 mm.).

N,N′-Di-*p*-tolylformamidine and Ethyl Orthoformate; *p*-Toluenesulfonic Acid as Catalyst.—N,N′-Di-*p*-tolylformamidine (0.10 mole), ethyl orthoformate (0.20 mole) and *p*-toluenesulfonic acid (0.001 mole) were heated in a 100-ml. flask to which was attached a 15-cm. Vigreux column with a total reflux partial take-off head. After one hour of reflux 5.8 ml. of ethanol, b. p. 75–79°, was removed. Calcium carbonate was added and the mixture was stirred overnight. Distillation of the filtered reaction mixture gave *ca.* 12 ml. of ethyl orthoformate, b. p. 83° (93 mm.), and 24.0 g. of ethyl N-*p*-tolylformimidate,[4] b. p. 133.5–134° (40 mm.). This was 74% of the calculated amount of product.

Treatment of *p*-toluidine or N,N′-di-*p*-tolylformamidine with ethyl orthoformate in the presence of *p*-toluidine hydrochloride or sulfuric acid as described above gave similar results—yields of 74–76% of ethyl N-*p*-tolylformimidate.

Acknowledgment.—The author gratefully acknowledges the assistance of Mr. Robert H. DeWolfe, who carried out some of the experiments, and a grant from the University of Texas Research Institute which made this assistance possible.

DEPARTMENT OF CHEMISTRY
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RECEIVED JUNE 18, 1949

(7) Roberts, *J. Org. Chem.*, **14**, 277 (1949).
(8) Schmidt, *Z. physik. Chem.*, **58**, 523 (1907).

Chemistry of Epoxy Compounds. X.[1] Polymerization of the Isomeric 9,10-Epoxyoctadecanols

BY DANIEL SWERN AND GERALDINE N. BILLEN

The thermal polymerization of the isomeric 9,10-epoxystearic acids was recently reported.[2] The present note reports the results of the thermal polymerization of the isomeric 9,10-epoxyoctadecanols (I), m. p. 54 and 48°, respectively, in

$$CH_3—(CH_2)_7—\underset{\diagdown\,O\,\diagup}{CH—CH}—(CH_2)_7—CH_2OH \quad (I)$$

the presence of naphthalene-2-sulfonic acid as catalyst.

Starting Materials.—The isomeric 9,10-epoxyoctadecanols, m. p. 54 and 48°, were prepared from oleyl[3] and elaidyl[4] alcohols, respectively, by epoxidation with peracetic[5] or perbenzoic acid.[6] Calcd. for $C_{18}H_{36}O_2$, oxirane oxygen,[7] 5.62%; found, 5.62%.

Polymerization Procedures.—9,10-Epoxyoctadecanol (either isomer) and the required quantity of naphthalene-2-sulfonic acid were mixed and then ground until the catalyst was uniformly distributed. Approximately 5-g. portions of the mixture were then weighed into a series of test-tubes which had been flushed with nitrogen or carbon dioxide. After being filled, the tubes were again flushed with inert gas, stoppered tightly, and then immersed in a constant-temperature oil-bath which maintained the desired temperature to ±0.2°. Fifteen minutes was allowed for the establishment of temperature equilibrium before the polymerization time was counted. During the equilibration period, the tubes were shaken occasionally to ensure homogeneity. At selected time intervals, a tube was removed from the oil-bath, cooled rapidly to room temperature, and then analyzed within twenty-four hours.

(1) For the previous paper in this series, see THIS JOURNAL, **71**, 2219 (1949).
(2) Swern, Billen and Eddy, THIS JOURNAL, **70**, 1228 (1948).
(3) Swern, Knight and Findley, *Oil and Soap*, **21**, 133 (1944).
(4) Swern, Jordan and Knight, THIS JOURNAL, **68**, 1673 (1946).
(5) Swern, Findley and Scanlan, *ibid.*, **66**, 1925 (1944).
(6) Findley, Swern and Scanlan, *ibid.*, **67**, 412 (1945).
(7) Swern, Findley, Billen and Scanlan, *Anal. Chem.*, **19**, 414 (1947); Nicolet and Poulter, THIS JOURNAL, **52**, 1186 (1930).

Analytical Procedures.—Analyses were carried out as previously reported.[2] Carbonyl oxygen was determined by the procedure reported by Knight and Swern.[8]

Discussion

Figure 1 shows the course of the catalyzed polymerization of 9,10-epoxyoctadecanol (ol), m. p. 54°, at 60, 80, 90 and 100°. Figure 2

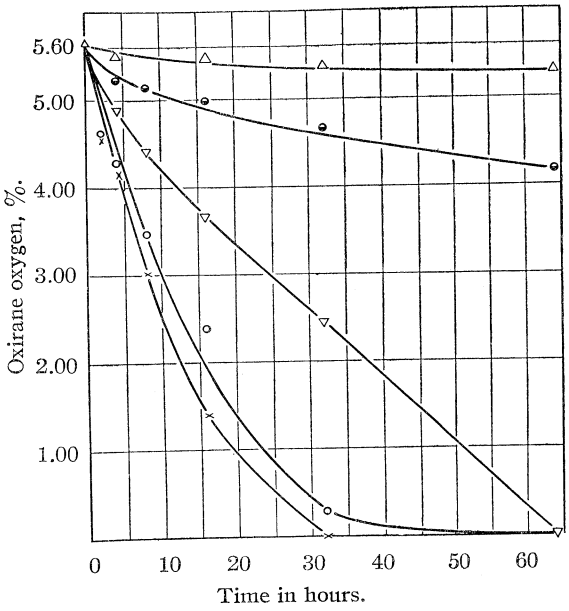


Fig. 1.—Thermal polymerization of 9,10-epoxyoctadecanol(ol), m. p. 54°, with naphthalene-2-sulfonic acid as catalyst: O, 90°, 2% catalyst; △, 60°, 0.75% catalyst; ×, 100°, 2% catalyst; ◒, 80°, 0.75% catalyst; ▽, 100°, 0.75% catalyst.

shows the course of the catalyzed polymerization of 9,10-epoxyoctadecanol (el), m. p. 48°, at 80, 90, 100, 120 and 140°. These data may be briefly summarized as follows: (a) under identical conditions, the high-melting epoxyoctadecanol (ol) polymerizes at a more rapid rate than does the low-melting isomer (el); (b) both isomers can be converted to viscous liquids if the polymerization is permitted to proceed far enough; (c) when the oxirane oxygen value is substantially zero, the molecular weight is about 900, or approximately that of a trimer; (d) in all the polymerizations except the one at 60°, about 20 to 30% of the reduction in oxirane oxygen can be accounted for by isomerization to the carbonyl group; (e) in two cases in which the comparison has been made, molecular weights determined ebulliosopically in benzene differ from those calculated from the oxirane oxygen analyses by only 7 to 15%; (f) the isomerization of the oxirane group to the carbonyl group is a function of both the temperature and the percentage of catalyst, although there appears to be no simple relationship involved; and (g) the refractive index of the polymers levels off at 1.462 to 1.464 (60°).

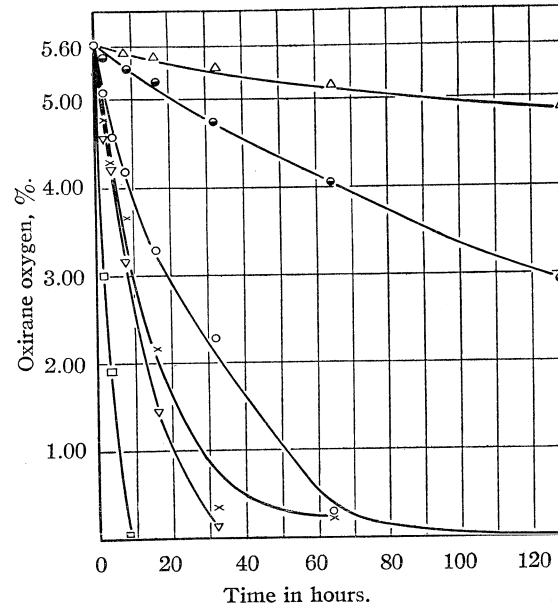
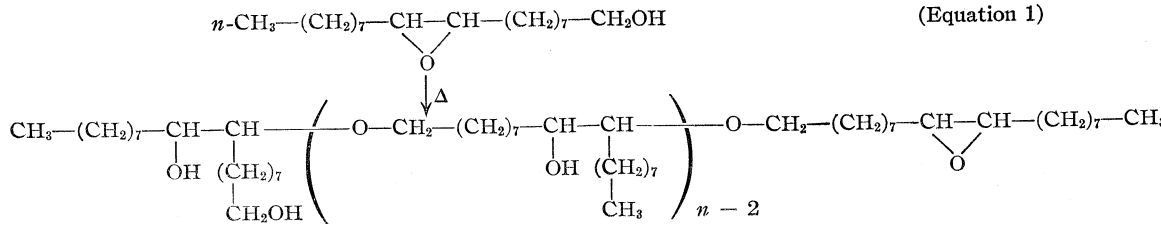


Fig. 2.—Thermal polymerization of 9,10-epoxyoctadecanol(el), m. p. 48°, with naphthalene-2-sulfonic acid as catalyst: O, 90°, 2% catalyst; △, 80°, 0.75% catalyst; ▽, 120°, 0.75% catalyst; ×, 100°, 2% catalyst; ◒, 100°, 0.75% catalyst; □, 140°, 0.75% catalyst.

On the basis of the data reported here and the known reactions of oxirane groups, it can be concluded that the main reactions which occur during the thermal polymerization of the 9,10-epoxyoctadecanols are (a) a condensation reaction between the oxirane and primary hydroxyl groups, yielding a polyether, as shown in Equation I, and (b) isomerization of the oxirane group to the carbonyl group. All the polymers are readily soluble in the common organic solvents, with the exception of petroleum naphtha, thus indicating that cross-linking reactions occur only to a limited extent, if at all.



(Equation 1)

(8) Knight and Swern, *J. Am. Oil Chem. Soc.*, **26**, 366 (1949).

No information is available on the occurrence

of other possible acid-catalyzed condensation and addition reactions, such as dioxane or polyethylene oxide formation.[2]

EASTERN REGIONAL RESEARCH LABORATORY[9]
PHILADELPHIA 18, PENNSYLVANIA RECEIVED JUNE 8, 1949

(9) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Note not copyrighted.

NEW COMPOUNDS

2-Methyl-4,6-Dichlorophenoxyacetic Acid

2-Methyl-4,6-dichlorophenoxyacetic Acid.—4,6-Dichloro-*o*-cresol[1] (3.82 g.) dissolved in 10 ml. of aq. 20% sodium hydroxide was added hot in 1-ml. portions to a hot solution of 4.75 g. of chloroacetic acid in 10 ml. of 20% sodium hydroxide, and the mixture refluxed for four hours. The solution was then made acid and the precipitate removed by filtration. It was dissolved in dilute sodium carbonate and the excess phenol extracted with ether. The product was precipitated from the carbonate solution with acid and crystallized from alcohol–water; yield 3.3 g., m. p. 187–187.5°.

Anal. Calcd. for $C_9H_8O_3Cl_2$: C, 45.95; H, 3.40. Found: C, 45.87; H, 3.54.

This compound was checked for plant growth activity using the Avena test. The work was done by Dr. Robert Muir, Dept. of Botany, University of Iowa. The compound was found to be inactive. Complete results of these tests will be published elsewhere.

(1) Claus and Riemann, *Ber.*, **16**, 1598 (1883).

DEPARTMENT OF CHEMISTRY
POMONA COLLEGE
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RECEIVED JUNE 25, 1949

Some Derivatives of Benzylvanillin and Benzylvanillic Acid

The benzyl ethers of the monochloro and monobromo derivatives of vanillin and benzyl-2-nitrovanillin were prepared by the alkylation of the appropriate vanillin derivative and benzyl chloride in the presence of sodium hydroxide.[1]

Benzyl Ethers of Derivatives of Vanillic Acid.—Five grams of the benzyl ether of the requisite vanillin derivative was dissolved in 50 cc. of pyridine and the solution heated to 60–70°. A hot (90–100°), concentrated aqueous solution of 5 g. of potassium permanganate was added in small portions. A vigorous reaction ensued with the immediate precipitation of manganese dioxide. The mixture was cooled and filtered. The residue was washed with a little pyridine and the filtrate and washing were combined. The manganese dioxide in the residue was dissolved in sodium bisulfite solution and dilute hydrochloric acid. A white precipitate remained which was extracted with ethyl ether. The pyridine was removed from the filtrate by steam distillation and the residue was extracted with the ether previously used. The ether layer was repeatedly extracted with sodium hydroxide solution until acidification gave no precipitate. The aqueous extracts were combined, acidified and the resultant precipitate filtered, washed with water and dried. It was then recrystallized from the appropriate solvent (either aqueous ethanol or aqueous acetic acid). The properties of some benzyl ethers of derivatives of vanillin and vanillic acid are listed in the accompanying table. The ethers crystallized as colorless needles except where otherwise noted.

BENZYL ETHERS OF DERIVATIVES OF VANILLIN AND OF VANILLIC ACID

Substituent	Yield, %	M. p., °C.	Halogen, % Calcd.	Halogen, % Found
Vanillin Derivatives				
2-Bromo-	48	99–99.5	24.88	24.61
5-Bromo-	52	49–50	24.88	24.80
6-Bromo-	71	96–97	24.88	24.83
2-Chloro-	73	94	12.81	12.79
5-Chloro-	54	43–44	12.81	12.80
6-Chloro-	58	101–102[a]	12.81	12.92
2-Nitro-	41	106–107[b]		
Vanillic Acid Derivatives				
2-Bromo-	74	162–163[c]	23.70	23.73
5-Bromo-	83	157–157.2	23.70	23.77
6-Bromo-	76	173–174	23.70	23.64
2-Chloro-	74	149–150	12.11	11.94
5-Chloro-	81	154	12.11	12.01
6-Chloro-	60	164–165	12.11	12.09
2-Nitro-	78	183–184[d]	4.62[e]	5.08[e]

[a] Pale orange prisms. [b] Brown needles. [c] Light yellow needles. [d] White plates. [e] % Nitrogen.

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W. S. PORT[3]
R. P. PERRY[4]

RECEIVED APRIL 4, 1949

(1) Späth, Orechoff and Kuffner, *Ber.*, **67B**, 1214–1217 (1934).

(2) Deceased January 8, 1944.

(3) Present address: Eastern Regional Research Laboratory, U. S. Department of Agriculture, Philadelphia 18, Pa.

(4) Present address: Langston University, Langston, Oklahoma.

COMMUNICATIONS TO THE EDITOR

RELATIONSHIP OF THE FOLINIC ACID GROUP AND THE LEUCONOSTOC CITROVORUM FACTORS

Sir:

The reported nutritional requirement of *Leuconostoc citrovorum* 8081 for thymidine[1] or a factor(s) in refined liver extracts[2] suggested the possibility that the organism required an antipernicious anemia principle. In the isolation of thymidine,[3] this factor and erythrotin,[4] a member of the vitamin B_{12} group and probably identical with vitamin B_{12}, were separated quantitatively. While neither of these fractions possess the activity of the original liver extract for *Leuconostoc citrovorum* in a previously described medium[5] supplemented with pyridoxine, the two fractions on recombination possessed the full activity. The thymidine containing fraction could be replaced by 0.03–0.1 γ per cc. of crystalline thymidine while the erythrotin-containing fraction could not be replaced by crystalline erythrotin. However, concentrates of the folinic acid[6] were found to be highly effective in replacing the erythrotin fraction, and the relative potencies of these fractions determined by *Lactobacillus casei* test and this modified test parallelled closely.

A concentrate of folinic acid 200,000 times as active as an enzymatic digest of liver in the *Lactobacillus casei* test, elicited a half-maximal response in the *Leuconostoc citrovorum* test at 0.0001–0.0002 γ per cc. In the absence of thymidine, 0.001 γ per cc. of this factor was required for the same response. Thymidine at a concentration of 10–20 γ per cc. can also replace the folinic acid group; consequently, the synergistic action of the folinic acid group and thymidine in stimulating the growth of the organism resulted in the high activity of purified liver extracts which we have previously found to contain large amounts of thymidine.[3]

Other factors associated with the folinic acid appear to be effective for this organism, but folic acid is essentially inactive under our testing conditions. Very mild acid hydrolysis destroys folinic acid but forms a compound with biological activities corresponding to folic acid.

This synergistic action and interchangeability of thymidine and the folinic acid group indicate the functioning of this group in the biosynthesis of thymidine as well as further involvement of thymidine concerning the biosynthesis of the active coenzyme form of folinic acid for this organism.

THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS, AND THE CLAYTON FOUNDATION FOR RESEARCH AUSTIN, TEXAS

THOMAS J. BARDOS
THOMAS J. BOND
JEAN HUMPHREYS
WILLIAM SHIVE

RECEIVED SEPTEMBER 23, 1949

(1) Snell, *et al.*, *J. Biol. Chem.*, **175**, 473 (1948).
(2) Sauberlich and Baumann, *ibid.*, **176**, 165 (1948).
(3) Shive, *et al.*, THIS JOURNAL, **70**, 2299 (1948).
(4) Shive, *Ann. New York Acad. Science*, in press, presented before the New York Acad. Science, Feb., 1949.
(5) Snell, *et al.*, *J. Biol. Chem.*, **143**, 519 (1942).
(6) Bond, *et al.*, THIS JOURNAL, **71**, 3852 (1949).

THE FOLINIC ACID GROUP, A SERIES OF NEW VITAMINS RELATED TO FOLIC ACID

Sir:

By application of *inhibition analysis* to a study of factors functionally related to *p*-aminobenzoic and folic acids, testing procedures for a wide variety of new factors occurring in refined liver extracts have been developed.[1,2] One of these methods developed about two years ago, involved the prevention of the toxicity of methylfolic acid for *Lactobacillus casei* in a previously described medium[3] supplemented with thymine, purines, folic acid (0.001 γ per cc.) and methylfolic acid (1 γ per cc.). Under these conditions, only the folic acid group was known to prevent competitively the toxicity of methylfolic acid. However, liver extracts, both crude and refined, which prevent the toxicity in a competitive manner, are approximately 15 times as active as can be accounted for on the basis of their folic acid content determined by assay with *Lactobacillus casei* in the absence of the inhibitor. A similar technique has been employed with *Streptococcus faecalis* R in demonstrating an unusual activity for formylfolic acid.[4]

With the aid of this assay based on this differential in activity, one of the active principles has been concentrated more than 200,000 fold from enzymatic digests of hog liver. A half-maximal response of *Lactobacillus casei* is obtained in the presence of 0.002 γ per cc. of the concentrate which is somewhat more active than folic acid under these testing conditions. Depending upon the time of incubation and response at which the comparison is made, the concentrate is from 10 to 100 times as active as folic acid in preventing the toxicity of methylfolic acid (1 γ per cc.) for *Streptococcus faecalis* R. On the basis of structure and functional relationship to folic acid, this active principle has been termed folinic acid. On the basis of estimated purity of the concentrate, folinic acid does not appear to be less active than folic acid in promoting the growth of either organism in the absence of the inhibitor.

(1) Shive, *et al.*, THIS JOURNAL, **70**, 2299 (1948).
(2) Shive, *Ann. New York Acad. Science*, in press, presented before the New York Acad. of Science, Feb., 1949.
(3) Rogers and Shive, *J. Biol. Chem.*, **172**, 100, 751 (1947).
(4) Gordon, *et al.*, THIS JOURNAL, **70**, 878 (1948).

While folinic acid accounts for the major portion of the activity of extracts of hog liver, another factor with similar physical and biological properties occurs in these extracts. At least two other substances possessing activity in the assay have been detected by means of paper chromatography. Consequently, it appears that a group of compounds, the folinic acid group, possess activity similar to that of folinic acid.

Since the folinic acid group is utilized more effectively than folic acid for several organisms, the possibility exists that it may be more active than folic acid in the treatment of sprue, nutritional and pernicious anemia, and other nutritional deficiencies related to the folic acid and vitamin B_{12} groups.

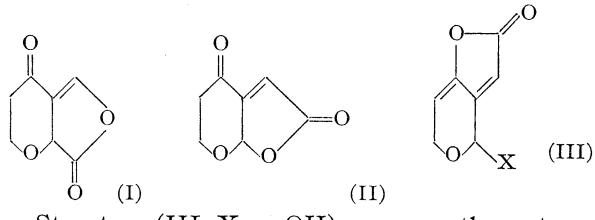
THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS, AND THE CLAYTON FOUNDATION FOR RESEARCH, AUSTIN, TEXAS
THOMAS J. BOND
THOMAS J. BARDOS
MARGARET SIBLEY
WILLIAM SHIVE

RECEIVED SEPTEMBER 23, 1949

THE STRUCTURE OF PATULIN

Sir:

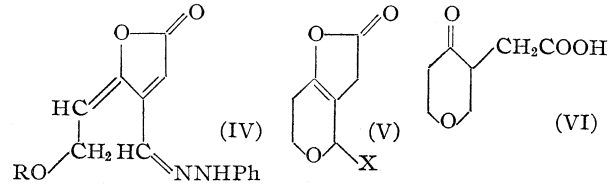
Recent evidence has required revision of the accepted structure (I)[1] of the antibiotic mold metabolite, patulin, and two new formulations, (II)[2] and (III, X = OH),[3] have been advanced. The following data now afford additional strong support for (III, X = OH) as the structure of patulin.



(I) (II) (III)

Structure (III, X = OH) possesses three structural characteristics: free hydroxyl group, lactal ring and doubly-unsaturated lactone system. Presence of a free O–H band (2.73μ), in the infrared spectrum of patulin and its absence in patulyl acetate (III, X = OAc) and in patulyl chloride (III, X = Cl), retention of the characteristic double bond ultraviolet and infrared spectra of patulin in these derivatives (Patulin: u.v., 275 mμ, log ϵ 4.22; ir., 5.58μ, 5.94μ, 6.11μ. Acetate: u.v., 277 mμ, log ϵ 4.24; ir., 5.58μ, 5.93μ, 6.11μ. Chloride: u.v., 277 mμ, log ϵ 4.18; ir., 5.61μ, 5.94μ, 6.13μ), and conversion of each in high yield to patulin phenylhydrazone by aqueous phenylhydrazine indicate the presence of a non-enolic hydroxyl group and exclude occurrence of enolization or isomerization during their preparation.

Patulin shows reactions (negative Schiff, positive Tollens, positive Fehling)[1] characteristic of a lactal ring. Lactal ring opening by phenylhydrazone formation usually unmasks a hydroxyl group and the conversion of patulin phenylhydrazone (IV, R = H) by treatment with sodium



(IV) (V) (VI)

acetate–acetic anhydride to patulin phenylhydrazone acetate (IV, R = Ac), m. p. 143° (calcd. for $C_{15}H_{14}O_4N_2$: C, 63.00; H, 4.93. Found: C, 63.40; H, 5.27) fits this interpretation. Infrared spectra of patulin phenylhydrazone (5.86μ, 6.04μ, 6.23μ) and its acetate (5.84μ, 6.00μ, 6.22μ) indicate retention of the doubly-unsaturated lactone system in these derivatives. Demonstration of a lactone ring in the phenylhydrazone and its acetate is shown by consumption of 1.05 and 1.92 equivalents, respectively, of sodium hydroxide. Dihydropatulin (V, X = OH) phenylhydrazone[4] contains only a singly-unsaturated lactone system (u.v., 380 mμ, log ϵ 4.55; 1.07 equivalents sodium hydroxide).

Treatment of patulin with warm excess thionyl chloride followed by sublimation furnishes unstable patulyl chloride (III, X = Cl) in 78% yield, m. p. 92–94° (calcd. for $C_7H_5O_3Cl$: C, 48.70; H, 2.92; Cl, 20.55. Found: C, 48.94; H, 2.63; Cl, 20.43); structural evidence given above. Patulyl chloride in anhydrous dioxane with palladium–barium sulfate catalyst absorbs 2.0 of moles hydrogen in two hours to give a neutral fraction which furnishes on distillation oily dihydrodesoxypatulin (V, X = H) in 34% yield, b. p. 90–95° (0.5 mm.). (Calcd. for $C_7H_8O_3$: sapon. equiv. 140.1. Found: 141.2); immediate Legal test; u.v., at 212 mμ, log ϵ 3.93; ir., 5.57μ, 6.01μ. Accordingly, dihydrodesoxypatulin contains a β,γ-unsaturated-γ-lactone system and its exact structure is established by hydrolysis in aqueous alcoholic sodium hydroxide to dihydrodesoxypatulinic acid (VI), identified by its well-known derivatives[2,3,4,5]: 2,4-dinitrophenylhydrazone, m. p. 193–195°; methyl ester 2,4-dinitrophenylhydrazone, m. p. and m. m. p. 149–150° (calcd. for $C_{14}H_{16}O_7N_4$: C, 47.70; H, 4.58. Found: C, 47.50; H, 5.02); *p*-phenylphenacyl ester, m. p. 124–127°.

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HYP J. DAUBEN, JR.
FRANK L. WEISENBORN

RECEIVED SEPTEMBER 9, 1949

(1) Birkinshaw, Bracken, Michael and Raistrick, *Lancet*, **245**, 625 (1943); *cf. Quart. Revs. Chem. Soc.*, **2**, 53 (1948).

(2) Engel, Brzecki and Plattner, *Helv. Chim. Acta*, **32**, 1166, 1752 (1949).

(3) Woodward and Singh, THIS JOURNAL, **71**, 758 (1949).

(4) Bergel, Morrison, Moss and Rinderknecht, *J. Chem. Soc.*, 415 (1944).

(5) Acknowledgments are made gratefully to Professor Raistrick and the Therapeutic Research Corporation of Great Britain for the supply of patulin, to Professor Woodward and Dr. Singh for helpful discussions, spectral determinations on the phenylhydrazone derivatives and an authentic sample of the methyl ester dinitrophenylhydrazone, and to E. I. du Pont de Nemours and Co. for the Fellowship granted to one of us (F. L. W.).

POLARIZED INFRARED SPECTRA FOR SILKWORM-GUT AND OTHER FIBROUS PROTEINS

Sir:

Infrared spectra observed with anisotropic specimens in polarized light depend upon their orientations relative to both direction of incidence and plane of polarization of the light. Spectra for different orientations of the same specimen can be correlated with structure and arrangement of its molecules. We have been employing this technique to study fibrous proteins. A recent account[1] of results obtained in this way by others encourages us to report some of our own findings at this time.

Polarized spectra for silkworm-gut, a material giving[2] the X-ray diffraction pattern characteristic of fibroin, are shown in Fig. 1. Each spectrum was traced from original instrumental records of *per cent.* transmission through two different samples, one about twenty, another about five microns thick, at left and right, respectively.

These spectra indicate an arrangement that is highly ordered in some respects. The degree of polarization exhibited by several bands approaches the best observed here for single crystals of favorably arranged, simple molecules, exceeding that for the other fibrous proteins we have examined.

The *rachis* of seagull feather exhibited many features appearing in Fig. 1 while quill from pigeon feather was polarized perceptibly at the lower frequencies only. Several natural collagens gave spectra similar to ones described above, with polarizations varying vicariously like ones for feather keratins. Films of rabbit myosin, oriented[3] so as to produce the α-keratin structure, and porcupine quill, showed only small effects of different sort.

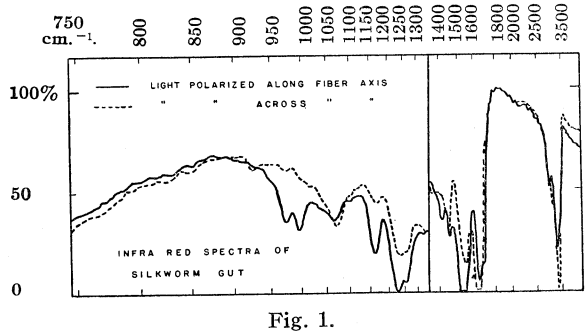

Fig. 1.

Our findings are confirmed in part by those of Ambrose, Elliott and Temple,[1] who worked just in the limited spectral range between 2800 and 3500 cm.$^{-1}$. There they found only slight differences for myosin (91% *vs.* 87% absorption, recalculated from their optical densities) and even smaller ones for porcupine quill and tropomyosin. They report larger effects, however, with feather keratin, as do we.

A full report will be submitted when our work has been completed.

DEPARTMENT OF CHEMISTRY
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MARTIN GOLDSTEIN
RALPH S. HALFORD

RECEIVED JULY 25, 1949

(1) E. J. Ambrose, A. Elliott, and R. B. Temple, *Nature*, **163**, 859 (1949).

(2) R. S. Bear, THIS JOURNAL, **66**, 2043 (1944).

(3) W. T. Astbury and S. Dickinson, *Proc. Roy. Soc. (London)*, **B129**, 307 (1940).

USE OF *p*H INDICATORS WITH ION EXCHANGE RESINS

Sir:

I wish to report the use of *p*H indicators as a means of detecting acids adsorbed on a strong base type resin, Amberlite I.R.A 400.[1]

When the basic form of this resin is treated with phenolphthalein the indicator is quantitatively removed from solution and the resin becomes the characteristic deep pink. Washing has no effect and even strong acid or base will not elute the indicator. Acid decolorizes the resin but base restores the color. If the resin is left for a few days in neutral solution, however, the color is destroyed and base will not restore it. When methyl orange is adsorbed the characteristic color is given with hydrogen ion. Washing removes the color. Again neither strong acid or base will elute the indicator.

The following experiment on the determination of I.R.A 400 capacity for aspartic acid will serve to illustrate the use of a column indicator: Aspartic acid solution was exchanged on the basic form of the resin. The column was washed and 50–100 drops of 1% phenolphthalein passed through. The top of the column remained colorless and a pink zone formed at the junction of the aspartic acid and unreacted resins. The columns were micro burets containing 5–6 g. of 20–30 mesh resin. The acid was 4 mg./ml. and a flow rate of 0.2 ml./min. was used. The value obtained was: 1.5 cc. wet R:NOH resin = 100 mg. aspartic acid.

The method gave a visual illustration of resin efficiency. Not one colored particle was located in the aspartic resin. The pink zone was perfectly even. There was no measurable displacement of aspartic by phenolphthalein.

(1) Rohm & Haas Co.

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RECEIVED SEPTEMBER 19, 1949

THE HYDROLYSIS OF NICOTINYL-L-TYROSYL-HYDRAZIDE BY CHYMOTRYPSIN

Sir:

The recent report that benzoyl-L-tyrosylhydrazide is ineffective as an inhibitor in the chymotrypsin catalyzed hydrolysis of benzoyl-L-tyrosylamide or ethyl ester[1] would lead one to infer

(1) S. Kaufman, H. Neurath and G. W. Schwert, *J. Biol. Chem.*, **177**, 793 (1949).

that the hydrazide analogs of the specific chymotrypsin amide or ester type substrates[2–5] are not hydrolyzed by this enzyme. We therefore wish to point out that at least one of the acylated α-amino acid hydrazides possessing the structural characteristics required of ester or amide type specific chymotrypsin substrates,[2–5] *i. e.*, nicotinyl-L-tyrosylhydrazide is hydrolyzed by this enzyme (Table I).

TABLE I

HYDROLYSIS OF NICOTINYL-L-TYROSYLHYDRAZIDE BY CHYMOTRYPSIN

t, min.	Hydrolysis, %	$\frac{1}{t}\log\frac{s_0}{s}$
1.2	1.2	0.064
6.6	7.0	.064
10.6	10.0	.061
20.3	21.8	.067
61.0	49.4	.064
91.0	63.0	.063

Nicotinyl-L-tyrosylhydrazide, m.p. 242–243° (cor.)(*Anal.* Calcd. for $C_{15}H_{16}O_3N_4$; C, 60.0; H, 5.4; N, 18.7. Found; C, 59.9; H, 5.3; N, 18.6) was prepared from nicotinyl-L-tyrosine ethyl ester, m.p. 147–149° (cor.) obtained by the acylation of L-tyrosine ethyl ester with nicotinyl azide.[6] The enzymatic hydrolysis was conducted at 25° and *p*H 7.9 (0.02 *F* ethylenediamine–hydrochloric acid buffer) with an initial substrate concentration, s_0 of 5.0 micromoles per ml. reaction mixture and an initial enzyme concentration, E_0, of 0.075 mg. protein nitrogen per ml. reaction mixture. A formol titration was used to determine the extent of hydrolysis.

(2) M. Bergmann and J. S. Fruton, *J. Biol. Chem.*, **118**, 405 (1937).
(3) J. S. Fruton and M. Bergmann, *ibid.*, **145**, 253 (1942).
(4) J. E. Snoke and H. Neurath, *Arch. Biochem.*, **21**, 351 (1949).
(5) S. Kaufman and H. Neurath, *ibid.*, **21**, 437 (1949).
(6) T. Curtius and E. Mohr, *Ber.*, **31**, 2493 (1898).

CONTRIBUTION NO. 1335 R. V. MACALLISTER
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CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA CARL NIEMANN

RECEIVED SEPTEMBER 29, 1949

SEPARATION OF COLUMBIUM AND TANTALUM WITH ANION EXCHANGE RESINS[1]

Sir:

In a previous communication[2] an experiment was described indicating a partial separation of zirconium and hafnium on an anion exchange column in HCl–HF mixtures. While this separation was unusually difficult, the separation of the adjacent elements columbium and tantalum by the same method, under similar conditions, was very efficient.

The experiments were carried out with a 12.5-cm. column (0.0226 sq. cm. cross-section) of the anion exchange resin Dowex-1 using columbium[95] (β-emitter $T_{1/2}$ = 35 days[3]) and tantalum[182] (β-emitter $T_{1/2}$ = 117 days[3]). The columbium was carrier-free fission product and the tantalum was prepared by a neutron bombardment of tantalum metal. In a typical experiment, the tracers were added to the column in a mixture of 9 *M* HCl and 0.05 *M* HF and elution carried out in the same medium at an average flow rate of *ca.* 0.3 ml./sq.cm./min.

The results are shown in Fig. 1 which represents a transcribed continuous record of the activity of the eluent. The bands were identified by standard radiochemical procedures.

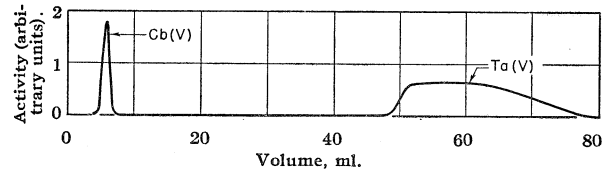


Fig. 1.—Separation of columbium (V) and tantalum (V) by anion exchange: dowex-1 column 12.5 cm. length 0.0226 sq. cm. cross-section, average flow rate; 0.3 ml./sq. cm./min.

Columbium eluted relatively rapidly in a sharp, well-shaped band and the tantalum very much more slowly in a somewhat diffuse band with a sharp front edge. The separation appears to be complete and could probably be achieved with better than 99% purity of the fractions using columns of considerably shorter length.

The experiments prove that both columbium and tantalum can form negatively charged complexes in this medium with probable negative charge minus two or greater. From the slower elution rate of the tantalum one can conclude that the average negative charge on this element is greater than that on columbium.

The very large difference in elution behavior of these two elements is somewhat surprising since both elements, in some complexes at least, show practically the same size. Thus Hoard[4] found no significant difference in the lattice constants of the complex fluorides K_2CbF_7 and K_2TaF_7. The rather large difference in the behavior of these elements on anion-exchangers may thus be due to comparatively large differences in their polarizability, causing considerable differences in the chloride complex constants, or to small differences in the value of each stability constant with a resulting large difference in the negatively charged series due to the fact that for these the product of a considerable number of such constants is involved.

OAK RIDGE NATIONAL LABORATORY KURT A. KRAUS
OAK RIDGE, TENNESSEE GEORGE E. MOORE

RECEIVED AUGUST 20, 1949

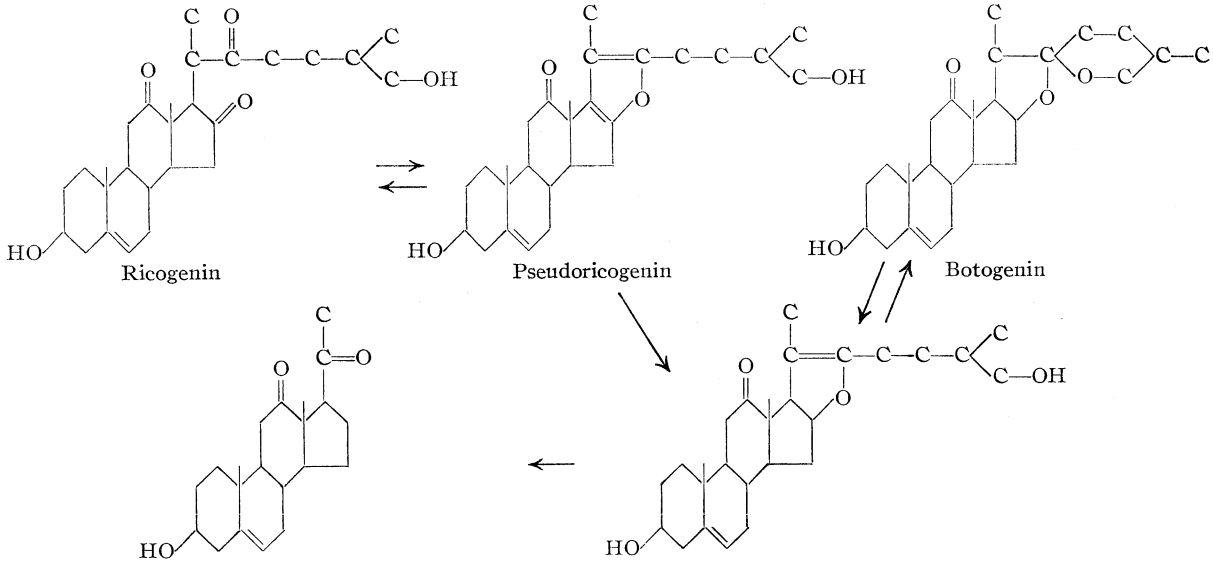
(1) This document is based on work performed under Contract Number W-7405 eng 26 for the Atomic Energy Project at Oak Ridge National Laboratory.

(2) K. A. Kraus and G. E. Moore, THIS JOURNAL, **71**, 3263 (1949).
(3) Information from G. T. Seaborg and I. Perlman, "Table of Isotopes," *Rev. Mod. Phys.*, **20**, 585 (1946).
(4) J. L. Hoard, THIS JOURNAL, **61**, 1252 (1939).

STEROIDAL SAPOGENINS, 173. 16-DEHYDROPREGNEN-5-OL-3-DIONE-12,20 FROM RICOGENIN, A NEW STEROIDAL SAPOGENIN

Sir:

In an extensive search for naturally occurring steroidal sapogenins having substituents in ring C which may be utilized for the synthesis of cortisone, the anti-arthritic hormone, a new saponide, riconin, m.p. 285–289° dec., was isolated from the mixture of glycosides occurring in *Dioscorea Macrostachya*.



Hydrolysis of riconin with alcoholic hydrochloric acid gave ricogenin, m.p. 225–227°. *Anal.* Calcd. for $C_{27}H_{40}O_5$: C, 72,9; H, 9.1. Found: C, 72.9; H, 9.1.

Ricogenin formed a diacetate, m.p. 195–197°, and contains three ketonic groups having the same side-chain structure as kryptogenin. *Anal.* Calcd. for $C_{31}H_{44}O_7$: C, 70.4; H, 8.4. Found: C, 70.2; H, 8.2.

Treatment of ricogenin with acetic anhydride at 195° for eight hours followed by hydrolysis gave pseudoricogenin, m.p. 220–222°. *Anal.* Calcd. for $C_{27}H_{38}O_4$: C, 76.0; H, 9.0. Found: C, 76.2; H, 9.0.

When heated with alcoholic hydrochloric acid for fifteen minutes, pseudoricogenin was converted into ricogenin, m.p. and mixed m.p. 225–227°. Catalytic reduction of the diacetate of pseudoricogenin, using palladium-on-barium sulfate as catalyst, saturated only the conjugated double bond in ring D, giving the diacetate of pseudobotogenin. This product upon alkaline hydrolysis followed by isomerization with alcoholic hydrochloric acid gave botogenin, m.p. and mixed m.p. 260–262°. *Anal.* Calcd. for $C_{27}H_{40}O_4$: C, 75.7; H, 9.4. Found: C, 75.5; H, 9.4.

Acetylation of this product gave botogenin acetate, m.p. and mixed m.p. 246–248°. *Anal.* Calcd. for $C_{29}H_{42}O_5$: C, 74.0; H, 9.0. Found: C, 74.1; H, 9.3.

The pseudobotogenin diacetate produced by the catalytic reduction of the diacetate of pseudoricogenin was oxidized with chromic anhydride in acetic acid, followed by hydrolysis,[1] giving 16-dehydropregnen-5-ol-3-dione-12,20 acetate, m.p. and mixed m.p. with the product prepared from naturally occurring botogenin, 225–227°. *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.8; H, 8.2. Found: C, 74.6; H, 81.

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RECEIVED OCTOBER 4, 1949

(1) Marker, THIS JOURNAL, 71, 2656 (1949).

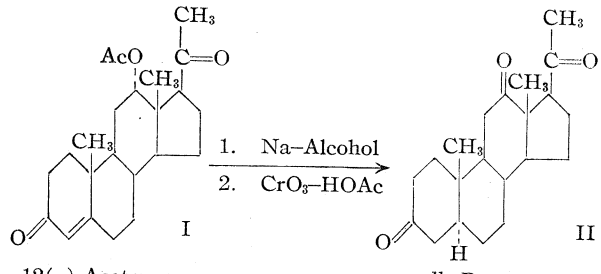
ALLO-PREGNAN-3,12,20-TRIONE

Sir:

The current interest in Kendall's substance E for rheumatoid arthritis has stimulated great interest in the search for starting materials for its synthesis. Recently, Marker reported the possibility of utilizing a steroidal sapogenin, botogenin, isolated from *Dioscorea Mexicana*.[1] Its degradation product was 5-pregnen-3(β)-ol-12,20-dione, characterized by conversion to *allo*-pregnan-3,12,-20-trione, m.p. 264°. The latter was identical with *allo*-pregnan-3,12,20-trione[2] from the degradation of hecogenin.

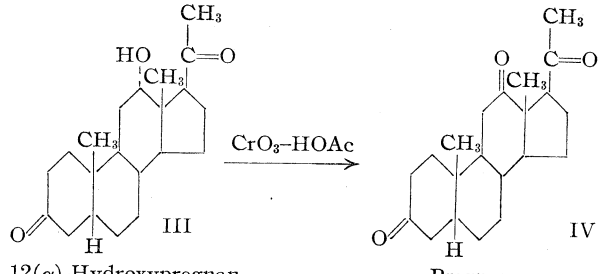
We have prepared an authentic sample of *allo*-pregnan-3,12,20-trione by an entirely different route and have found it completely different from the trione from hecogenin. Desoxycholic acid has been degraded to 12(α)-acetoxyprogesterone (I), m.p. 181°, $[\alpha]^{26}D$ +215°, $[\alpha]^{26}_{5461}$ +259° (chloroform), absorption maximum at 240mμ(log ε 4.14 in ethanol).[3] This compound (I) upon sodium–alcohol reduction followed by chromic acid oxidation furnished *allo*-pregnan-3,12,20-trione (II), m.p. 206–208°, $[\alpha]^{23}D$ +184°, $[\alpha]^{23}_{5461}$ +224° (chloroform), no maximum at 240mμ. *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.2. Found: C, 76.0; H, 8.9. The reduction was also accomplished with hydrogen and Adams catalyst in acetic acid; subsequent hydrolysis and oxidation gave the same product (II). The course of these methods of reduction has been shown previously[4]

(1) Marker, THIS JOURNAL, 71, 2656 (1949).
(2) Marker, Wagner and co-workers, *ibid.*, 69, 2167 (1947).
(3) Shoppee and Reichstein, *Helv. Chim. Acta*, 24, 351 (1941).
(4) Marker and Wittle, THIS JOURNAL, 59, 2704 (1937); Butenandt and Fleischer, *Ber.*, 68, 2094 (1935).



12(α)-Acetoxyprogesterone

allo-Pregnan-3,12,20-trione



12(α)-Hydroxypregnan-3,20-dione

Pregnan-3,12,20-trione

to lead to the *allo*-configuration at C-5. Nevertheless, we have prepared the corresponding isomer, pregnan-3,12,20-trione (IV), by the mild oxidation of an authentic sample of 12(α)-hydroxypregnan-3,20-dione (III). It had the following properties: m.p. 204–206°, $[\alpha]^{26}D$ +181°, $[\alpha]^{26}_{5461}$ +225° (chloroform). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.2. Found: C, 76.0; H, 9.1. Reichstein and von Arx[5] report for pregnan-3,12,20-trione: m.p. 201–202°; $[\alpha]^{17}D$ +182 ± 7, $[\alpha]^{17}_{5461}$ +219 ± 8 (ethanol). A mixture of IV with II showed a melting point depression of 36°. The melting point of each of these compounds was depressed 10–20° by the trione from hecogenin.

Since the properties of *allo*-pregnan-3,12,20-trione (II) are different from those of the samples derived from hecogenin and botogenin, some doubt must be entertained as to the structures of the degradation products from both of these sapogenins.

We thank Parke, Davis and Company for their help.

(5) Reichstein and von Arx, *Helv. Chim. Acta*, **23**, 747 (1940).

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SCHOOL OF CHEMISTRY AND PHYSICS — R. B. WAGNER
THE PENNSYLVANIA STATE COLLEGE — JAMES A. MOORE
STATE COLLEGE, PENNSYLVANIA — ROBERT F. FORKER

RECEIVED OCTOBER 10, 1949

SYNTHESES IN THE DIRECTION OF MORPHINE. I. 7-METHOXY- AND 7,8-DIMETHOXY-2-TETRALONE.

Sir:

We wish to report the synthesis of 7,8-dimethoxy-2-tetralone, which may serve as a useful intermediate for elaboration in the direction of morphine and certain of its degradation products,[1] and may open a way for the preparation of physiologically active substances oxygenated at points corresponding to the 3 and 4 positions in morphine. 7-Methoxy-2-tetralone may serve in the syntheses of substances similarly substituted in the 3 position; and is of particular interest in view of the recent report that 3-hydroxymorphinane is a powerful analgesic surpassing morphine in clinical tests[2].

1,2,7-Trimethoxynaphthalene,[3] m.p. 38.5–39.5°, b.p. 133° at 1 mm. (picrate[3], m.p. 113°), gave by reduction[4] with sodium and alcohol, the crystalline ketone, m.p. 76° (*anal.* calcd. for $C_{10}H_8O(OCH_3)_2$: OCH_3, 30.1. Found: OCH_3, 29.5, 29.3), characterized as the semicarbazone, m.p. 191–191.5°, and the 2,4-dinitrophenylhydrazone, m.p. 167° dec. (*anal.* calcd. for $C_{18}H_{18}O_8N_4$: C, 56.0; H, 4.7; N, 14.5. Found: C, 55.7; H, 4.6; N, 15.0, 14.8). The structure of the ketone was shown by oxidation, with alkaline permanganate, to hemipinic acid, identified by its m.p.[5] (177–179°) and by the m.p.[6] (166–167°) and characteristic fluorescence[6] of the pure anhydride.

2,7-Dimethoxynaphthalene similarly[4] gave on reduction 7-methoxy-2-tetralone, m.p. 27–28°, b.p. 124–126° (1.5 mm.); semicarbazone, m.p. 174–176° (*anal.* calcd. for $C_{12}H_{15}O_2N_3$: C, 61.8; H, 6.5. Found: C, 62.1, 62.1; H, 6.4, 6.4); 2,4-dinitrophenylhydrazone m.p. 177–181° (*anal.* calcd. for $C_{17}H_{16}N_4O_5$: C, 57.3; H, 4.5. Found: C, 57.2, 57.5; H, 4.4, 4.6).

(1) Fieser and Holmes, THIS JOURNAL, **60**, 2548 (1938); **58**, 2319 (1936); Cahn, *J. Chem. Soc.*, 2565 (1926).

(2) Schnider and Grussner, *Helv. Chim. Acta*, **32**, 821 (1939).

(3) Chakravarti and Pasupati, *J. Chem. Soc.*, 1859 (1937).

(4) Cornforth, Cornforth and Robinson, *ibid.*, 689 (1942).

(5) Perkin, *ibid.*, **109**, 922 (1916).

(6) Dobbie and Lauder, *ibid.*, **67**, 19 (1895).

DEPARTMENT OF CHEMISTRY — MILTON D. SOFFER
SMITH COLLEGE — J. CHARLES CAVAGNOL
NORTHAMPTON, MASS. — HILDA E. GELLERSON

RECEIVED OCTOBER 19, 1949

DEGRADATION OF GLYCOGEN TO ISOMALTOSE

Sir:

Methylation studies[1] have indicated that the glycogen molecule has a highly ramified structure composed of α-D-glucopyranosyl units joined 1,4 with branching at C6 on one out of twelve units. As additional evidence in support of this structure we report the isolation of crystalline 6-α-D-glucopyranosyl-β-D-glucopyranose octaacetate (β-D-isomaltose octaacetate)[2] from an acetylated acid hydrolysate of glycogen.

Animal (rabbit liver) glycogen (5.00 g., $[\alpha]^{25}D$ +200°, *c* 0.92, water) in 2% concentration was hydrolyzed at 100° in 0.05 *N* sulfuric acid for nine hours (degree of hydrolysis *ca.* 75%). After acid neutralization with barium carbonate and ion removal with exchange resins (Amberlite IR-100 and IR-4), the amorphous solid obtained on solvent removal was acetylated with hot acetic anhydride and sodium acetate. The resultant sugar acetate mixture (6.08 g.) was chromatographed[2] on Magnesol–Celite under such developmental conditions that monosaccharides were removed from the column. β-D-Glucose pentaacetate was identified,

(1) W. N. Haworth and E. G. W. Percival, *J. Chem. Soc.*, 2277 (1931); W. N. Haworth, E. L. Hirst and F. Smith, *ibid.*, 1914 (1939).

(2) M. L. Wolfrom, L. W. Georges and I. L. Miller, THIS JOURNAL, **69**, 473 (1947); **71**, 125 (1949).

by melting point and rotation, in the effluent. The material from the lowest zone consisted of β-D-maltose octaacetate (m. p. 158–160°, unchanged on admixture with an authentic specimen; $[\alpha]^{25}D$ +62.5°, *c* 1.1, chloroform). The material from the next higher zone was rechromatographed in the same manner, and the eluent from the lower zone which crystallized from ethanol was identified as β-D-isomaltose octaacetate (m. p. 144–145°, unchanged on admixture with an authentic specimen; $[\alpha]^{26}D$ +98°, *c* 1.0, chloroform); yield 92 mg.

DEPARTMENT OF CHEMISTRY
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M. L. WOLFROM
A. N. O'NEILL[3]

RECEIVED OCTOBER 8, 1949

(3) Corn Industries Research Foundation Fellow in the Department of Chemistry.

ERYTHEIN AND APOERYTHEIN AND THEIR RELATION TO THE ANTIPERNICIOUS ANEMIA PRINCIPLE

Sir:

Normal gastric juice has been found to contain a non-dialyzable, heat labile substance which combines, apparently stoichiometrically, with erythrotin,[1] (vitamin B_{12})[2] to form a complex (erythein) which is non-dialyzable and not dissociated by dialysis. Erythrotin in this combination is not available to microörganisms (*Escherichia coli, Lactobacillus lactis Dorner, Lactobacillus leichmannii*), but is released by heat, much as biotin is released from avidin, whereupon it is again microbiologically active. Heated gastric juice contains no principle capable of combining with erythrotin.

Quantitative determination of heat labile principle (apoerythein) is readily performed by measuring in an erythrotin assay (*Escherichia coli*)[1] the inhibition of growth resulting when aliquots of the juice are added (unheated) to cultures containing just sufficient erythrotin to elicit a maximum response. The erythrotin combining capacities (millimicrograms of erythrotin per ml. of secretion) of samples of gastric juice from normal and anemic subjects were found to be respectively, 20, 60[3], 60, 15; and 5, <5,[3] <1, <1 >15.

Commercial preparations of hog gastric mucosa made for therapeutic use have been found to be rich in a principle which appears on the basis of chemical and biological properties to be analogous to the apoerythein in gastric juice. Other biological materials tested, including commercial pepsins, contain very little or none of the active substance. Less than 2000 parts by weight of a concentrate prepared from hog gastric mucosa completely counteracted consistently the microbiological growth stimulation of one part of erythrotin.

For preparative purposes hog gastric mucosa has been used, and the principle can be precipitated from an aqueous extract by alcohol, acetone or ammonium sulfate (80% saturation). The principle is highly selective in its action and inactivates erythrotin but does not diminish the biological action of the end-products of erythrotin-catalyzed processes which can substitute for this vitamin in microbiological assays—methionine (*Escherichia coli* test)[1] and desoxyribosides (*Lactobacilli* tests).[4]

The complex formed when erythrotin combines with apoerythein decomposes upon heating (120° fifteen minutes) into erythrotin (or a compound which cannot be distinguished from it biologically or chromatographically), and a residue no longer possessing the ability to bind erythrotin. In combined form erythrotin is not as susceptible to destruction by alkaline or oxidative treatments which inactivate the unbound vitamin, since heat liberation following such treatment of the complex yields the original erythrotin activity.

These experiments point to the probability that apoerythein is the intrinsic factor of Castle or an important component thereof. Clinical trials are now in progress to test this conclusion.

We are deeply indebted to Dr. William Shive for generous supplies of erythrotin before vitamin B_{12} was available and for prepublication disclosures concerning erythrotin tests, and to Dr. Edward Campbell, Eli Lilly and Company, who furnished biological preparations and gastric samples.

THE BIOLOGICAL INSTITUTE AND
THE DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS, AND
THE CLAYTON FOUNDATION FOR
RESEARCH, AUSTIN, TEXAS
JESSIE L. TERNBERG
ROBERT E. EAKIN

RECEIVED SEPTEMBER 20, 1949

(1) W. Shive, *Ann. N. Y. Acad. Sci.*, in press.
(2) E. L. Rickes, *et al.*, *Science*, **107**, 396 (1948).
(3) Pooled samples from at least three subjects.
(4) W. Shive, J. M. Macow and R. E. Eakin, THIS JOURNAL, **70**, 2614 (1948).

NEW BOOKS

The Optical Principles of the Diffraction of X-Rays. By R. W. JAMES, M.A., B.Sc., F.Inst.P., Professor of Physics in the University of Cape Town. (The Crystalline State. Vol. II. Editor: Sir Lawrence Bragg.) The Macmillan Company, 60 Fifth Ave., New York, N. Y., 1948. xv + 623 pp. 15 × 23.5 cm. Price, $17.50.

To serious students of X-ray diffraction, the publication of this book is an important event, for it is unquestionably one of the great books in this field. It has been awaited ever since it was announced in 1933 in the first volume of the three volume series on "The Crystalline State," edited by Sir Lawrence Bragg. The fifteen year period that elapsed between the appearance of the two volumes is accounted for in part by the war, of course, and in part by the author's moving and taking up new duties in a new country; but no small part must be ascribed simply to the magnitude of the task of writing the book. It is twice the size of Vol. I, and is filled with detailed mathematical treatments, careful comparisons of different theories with each other and with experimental results, and a great many carefully worded discussions, all of which must have required a great amount of effort on the part of the author.

Seldom are advanced scientific books written with such clear presentation of material. Because of this and because of its completeness and authoritativeness, it is sure to become a great favorite with students, as well as with teachers; and for the same reasons it is very unfortunate that the book is so expensive—many students will feel they cannot afford it. The high quality and the pleasing nature of the book is to be expected, of course, from an author who has made fundamental contributions to the subject for over twenty-five years, and at the same time has possessed the faculty of presenting crystallographic matters clearly and concisely, as demonstrated by his little monograph "X-Ray Crystallography" (Dutton & Co., 1930) that has helped many a student pass his examinations.

The book logically begins in the appendices in which are presented principles of vector algebra that are used throughout the book, and the various reciprocal lattice relations of such importance in X-ray crystallography. There is probably no more convenient derivation of these relations published anywhere than this one. In the early chapters the author derives the geometrical theory of diffraction, with intensity formulas for the case of no appreciable rescattering or absorption of radiation in the crystal. The treatment of the case with re-scattering of the waves in the crystal is based on Darwin's treatment; this is followed by Ewald's dynamical theory, which is presented with emphasis on the physics and with a minimum of the mathematical detail, so as to keep the main lines of the argument clear. Later in the book the dynamical theory is extended from the case of dipoles at lattice points to scattering matter distributed uniformly through the crystal (Laue's theory) and to the theory and observation of Kossel lines, Kikuchi lines in electron diffraction, and divergent beam X-ray photography.

The atomic scattering factor, dispersion and the influence of temperature on the diffraction of X-rays takes up a quarter of the book. In the treatment of diffuse scattering arising from thermal vibration of the atoms in crystals, a subject that has seen more than its share of controversy in the past, each party is given his "day in court." The author points out the true conclusions along with the mistakes and shortcomings of the contributors to the field, and continually compares theory with experiment. Few would have objected if less space had been devoted to certain early theories that are now superseded, but the author includes them because "they have had an important place in the development of the subject." This summary and the other brief historical summaries in the book, which are well documented with references, are very effective and interesting guides to a complex literature.

Although the book is not devoted to methods of crystal analysis, an excellent treatise is included on the use of Fourier series in crystal analysis, including Patterson and Patterson–Harker series, as well as the older series, and discussions of the determination of phases and the optical synthesis of series.

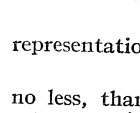
Electron diffraction receives little attention, and molecular and neutron scattering none. The last chapters cover the theory of scattering of X-rays by gases, liquids, amorphous solids, small crystallites with different shapes, lattices with faulty stacking and with periodic disturbances, and fibrous materials.

C. S. BARRETT

The Electronic Theory of Organic Chemistry. By M. J. S. DEWAR. Oxford University Press, 114 Fifth Avenue, New York 11, N. Y. (Oxford at the Clarendon Press). 1949. x + 324 pp. Illustrated. 15.5 × 24.5 cm. Price, $7.50.

On the advanced level in a field such as theoretical organic chemistry, books should be written by only two classes of authors—mature scholars bent on accuracy and young enthusiasts with fresh viewpoints. The claims of Dr. Dewar to a hearing are under the second classification. In a clearly and vigorously written book, he sweeps across theoretical organic chemistry with a point of view which, while by no means revolutionary, is fresh enough to be stimulating.

"The Electronic Theory of Organic Chemistry" is the first general discussion of the problems of organic structure and mechanisms in the language of molecular orbitals. The resonance approach, Dewar says, "is most unsuitable from the organic chemist's point of view since it involves a new symbolism and a novel and uncongenial outlook." The hope of better things which this statement raises is, in the reviewer's opinion, not fulfilled in the book; for no general operational superiority is demonstrated for the rather nebulous notation of molecular orbitals as an instrument of correlation and prediction, in comparison to the well-developed qualitative resonance scheme. It is healthy, nevertheless, to have this substantial reminder that resonance is not a phenomenon of nature.

As those familiar with Dewar's research papers would anticipate, the so-called π-complexes occupy a prominent place in his discussions of structure and reaction mechanisms. The π-complexes are not as new as the reader might conclude from their presentation here; the economical representation  implies no more, and perhaps no less, than the equivalent representation in terms of resonance given by Winstein and Lucas in 1938. The fact that the π-complex notation is a matter of language is often lost sight of in the discussion, as where it is said that the bromonium ion "was originally formulated with a three-membered ring but it is more probably a π-complex." At several points the fertility of the notation is demonstrated, notably by anticipation, in the discussion of the Wagner–Meerwein rearrangement, of current developments indicating the mesomeric nature of the intermediate carbonium ions.

One who expresses forthright and unreserved opinions on many things is sure to share, from time to time, the position of Mr. Gallup on the day after election. While page 86 was being printed, devoted to an explanation of why a bimolecular allylic rearrangement (S_N2') will probably never

be found, a paper appeared by Kepner, Winstein and Young proving the existence of this mechanism. Even without such experimental work, it would be hard to credit Dewar's transition state involving five collinear atoms in view of the ease of the ortho Claisen rearrangement and consideration of models.

The book shows broad interest in fundamentals and an unusual feeling for reaction mechanisms. However, the problems are often not simple and the facts are not treated in as careful a manner as is usually necessary for reliable conclusions to be reached. For example, few of the mechanisms given for prototropy and carbonyl reactions would retain their simple beauty if the facts of general acid-base catalysis were considered. References are provided unevenly; of the ideas discussed, the disapproved ones are credited to their authors with more regularity than those which are believed to be correct. The contents of some cited papers are ignored to the point of presenting a superficial conclusion already recognized as untenable. Internal evidence suggests that the author has not had time to become familiar with the details of all the problems he discusses. These facts impose a serious limitation on the use of the book; for it is not an authoritative review of the status of the numerous problems considered. It is, as Sir Robert Robinson says in the foreword, a "connected series of original essays." As such, it promises to start many discussions and to stimulate a number of researches.

PAUL D. BARTLETT

Recent Advances in Analytical Chemistry. Editors: R. E. BURK, Plastics Dept., E. I. du Pont de Nemours and Co., Wilmington, Delaware, and OLIVER GRUMMITT, Morley Chemical Laboratory, Western Reserve University, Cleveland, Ohio. (Frontiers in Chemistry, Vol. VII.) Interscience Publishers, Inc., 215 Fourth Ave., New York 15, N.Y., 1949. v + 209 pp. Illustrated. 15.5 × 23.5 cm. Price, $4.50.

Like previous volumes of the "Frontiers" series, the current volume includes reports by the authorities who presented the specific lectures. The reports are in the form of summaries of the seven lectures presented which, for this series, included the following phases of analytical chemistry: Voltammetry (polarography) and amperometric titrations (I. M. Kolthoff); inorganic analysis with organic reagents, and some recent colorimetric and gravimetric organic reagents (John H. Yoe); application of infrared spectroscopy in analysis (Otto Buck); electron microscopy and microanalysis—new methods in chemistry (James Hillier); fractionation, analysis and purification of hydrocarbons (Frederick D. Rossini); and applications of the mass spectrometer (J. A. Hipple).

Each chapter includes a brief historical and theoretical introduction, a discussion of the principles involved and equipment (where pertinent) used and available, typical applications and usefulness of the technique. The lectures are not designed to add to the knowledge of the specialist in a specific field, but rather to present a comprehensive picture of current knowledge which will enable the nonspecialist to understand and evaluate the possibilities of each technique. Copious illustrations, together with data, diagrams and typical graphs help to give a clear cut picture of the capabilities of the specialty covered. The two chapters by Yoe deal with the general qualifications required of suitable organic reagents and with the use of specific recent reagents for silver, palladium, iron, titanium and tungsten.

The chapter on infrared includes the history, origin of infrared spectra, design and development of some instruments, applicability to quantitative analysis with particular emphasis on the hydrocarbons and usefulness in structure studies. The other instrumental chapters are similar in purpose, all being supplied with a small, though sufficient, number of literature references.

Each chapter comprises a readily understandable comprehensive outline of the subject covered in somewhat greater detail than could be assimilated by merely listening to the lectures.

H. A. FREDIANI

Isotopic Carbon. Techniques in Its Measurement and Chemical Manipulation. By MELVIN CALVIN, Professor of Chemistry, CHARLES HEIDELBERGER, JAMES C. REID, BERT M. TOLBERT, and PETER F. YANKWICH, Instructor in Chemistry. All members of the Scientific Staff of the Radiation Laboratory, University of California, Berkeley. John Wiley and Sons, Inc., 440–4th Avenue, New York 16, N. Y., 1949. xiii + 376 pp. 107 figs. 15 × 24 cm. Price, $5.50.

In this book are collected the personal and vicarious experiences of Professor Calvin and his associates at the University of California with the carbon isotopes. Also included is an exhaustive digest of the literature on methods of synthesis of labelled molecules and techniques of measurement of these isotopes. The dust jacket offers this book as "A complete manual . . . for those who wish to use the isotopes of carbon as tracers in chemistry and biology. . .," and while the book could hardly be expected to fulfil such a broad claim, it will be of great value to anyone involved in problems of measurement of any of the low energy activities such as that of C-14, or in problems of synthesis of labelled molecules from the available chemical forms of the carbon isotopes. The table of contents shows the topics treated: Chap. 1. Production and Properties of Isotopic Carbon; 2. Measurement of Carbon-13; 3. Characteristics of Carbon Tracer Radiations; 4. Instruments for Radioactivity Measurement; 5. Detectors for Radioactivity Measurement; 6. Sample Preparation I; 7. Sample Preparation II; 8. Vacuum Techniques in Organic Chemistry; 9. Synthesis of Carbon Labelled Compounds; 10. Criteria of Purity; 11. Degradation Procedures; 12. Biosynthetic Methods; Appendix I. Isotope Dilution Methods; II. Statistical Treatment of Counting Data; III. Determination of Coincidence Corrections; IV. Determination of Counter Efficiency; V. Self Absorption Data; VI. Numerical Examples; VII. Flow in Vacuum Systems; VIII. Vacuum Gauges and Manometers; IX. Induction Stirrer for Use with Vacuum or Closed Systems.

Because the authors are personally familiar with a large fraction of the experimental procedures, many of them having been developed in their own laboratories, the book offers a wealth of detail which is usually omitted in journal publications. This value is lacking in those sections which merely reprint the literature without comment. Chapters 3 to 7 and Appendices II, III and V treat in considerable detail the procedures for preparing and measuring sample of C-14. Many of these minor, but quite important, points of technique are either new or have been available only as hearsay. Much of this material is directly applicable to other low energy β activities such as S^{35}. Chapter 9 presents all, apparently, of the methods that have been used in the synthesis of carbon labelled compounds.

Stable tracer carbon has been here treated as a stepchild. Syntheses with C-13 are presented along with those with C-14, and justifiably, since the problems are almost identical. But while there are more than one hundred pages devoted to the various problems associated with measuring the radioactive isotopes, the measurement of C-13 is reviewed in less than six. This ratio is not a measure either of the relative importance or of the relative complexity of handling stable and radioactive carbon. The authors do not examine the factors that determine the unique applicability of one method or the other to certain types of problems nor do they emphasize the complementary function, so nicely demonstrable with the carbon isotopes, of stable and radioactive tracer methods.

The authors might well have included a discussion of the various experimental conditions that must be considered in designing an experiment involving the use of carbon tracers. These conditions determine the particular isotope, the method of measurement and the necessary pre-

cision, and the isotopic concentration of the labelled compounds. This last determines the scale of the synthesis of the compounds. Particularly when a micromole scale is demanded to maintain a high tracer concentration the synthesis may be the most difficult hurdle met.

The exposition is generally clear and lucid and considering the large number of authors the style is quite uniform. The errors introduced are few and those are not seriously misleading. The book is well made but the price is high for one with such a rapid rate of obsolescence. Had the extraneous material, such as the chapters on vacuum methods and some of the introductory and survey material, been left out, the book could have been published in pamphlet form under the title "Techniques in the Use of Radioactive Carbon" without appreciably impairing its value which, on the topics appropriate to that title, is quite considerable.

WARREN W. MILLER

Advances in Carbohydrate Chemistry. Vol. 3. Edited by W. W. PIGMAN, The Institute of Paper Chemistry, Appleton, Wisconsin, and M. L. WOLFROM, The Ohio State University, Columbus, Ohio. Academic Press, Inc., Publishers, 125 East 23rd Street, New York 10, N. Y. 1948. xxiii + 424 pp. 15 × 23 cm. Price, $8.50.

The third volume of the "Advances" appeared in 1948, and by now will be found on the desks, on the shelves, in the mountains and at the beaches, wherever carbohydrate chemists are at work or play throughout the world. For those chemists who are not yet familiar with the excellent historical and critical up-to-date reviews comprising this series, a brief glance at the contents of the new volume will show the wide range of topics and indicate their appeal especially to the teacher and the research chemist in the many fields in which carbohydrates play major roles.

The book opens with a short obituary of Dr. R. Max Goepp, Jr., a former member of the Executive Committee of the "Advances."

The titles and authors of the reviews are as follows.

"Historical Aspects of Emil Fischer's Fundamental Conventions for Writing Stereo-Formulas in a Plane," (22 pp.), by C. S. Hudson, National Institutes of Health, U. S. Public Health Service, Bethesda, Maryland.

"The Structure and Reactivity of the Hydrazone and Osazone Derivatives of the Sugars," (22 pp.), by E. G. V. Percival, The University of Edinburgh, Scotland.

"The Chemistry and Configuration of the Cyclitols," (33 pp.), by Hewitt G. Fletcher, Jr., National Institutes of Health, U. S. Public Health Service, Bethesda, Maryland.

"Trityl Ethers of Carbohydrates," (33 pp.), by Burckhardt Helferich, Chemisches Institut der Universität, Bonn am Rhein, Germany.

"Glutose and the Unfermentable Reducing Substances in Cane Molasses," (16 pp.), by Louis Sattler, Department of Chemistry, Brooklyn College, Brooklyn, N. Y., and the New York Sugar Trade Laboratory, New York, N. Y.

"The Halogen Oxidation of Simple Carbohydrates, Excluding the Action of Periodic Acid," (56 pp.), by John W. Green, The Institute of Paper Chemistry, Appleton, Wisconsin.

"The Molecular Constitution of Cellulose," (44 pp.), by Jack Compton, Viscose Research Department, Celanese Corporation of America, Rome, Georgia.

"Isotopic Tracers in the Study of Carbohydrate Metabolism," (22 pp.), by Samuel Gurin, Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

"Products of the Enzymic Degradation of Starch and Glycogen," (60 pp.), by Karl Myrbäck, Biokemiska Institutet, Stockholms Högskola, Stockholm, Sweden.

"The Polysaccharides of *Mycobacterium tuberculosis*," (26 pp.), by M. Stacey and P. W. Kent, Chemistry Department, The University, Birmingham, England.

"The Chemistry of Streptomycin," (48 pp.), by R. U. Lemieux and M. L. Wolfrom, The Ohio State University, Columbus, Ohio.

NELSON K. RICHTMYER

Some Aspects of the Luminescence of Solids. By F. A. KROGER, Natuurkundig Laboratorium, N. V. Philips Gloeilampenfabrieken, Eindhoven (Netherlands). Elsevier Publishing Company, Inc., 215 Fourth Avenue, New York 3, N. Y., 1948. xi + 310 pp. Illustrated. 15.5 × 21 cm. Price $5.50.

This monograph on inorganic luminescent solids, based on experimental work by Kroger and associates at the Philips Lamp Company in Holland, does not pretend to give a comprehensive account of the present status of solid-state luminescence, nor does it present a general survey.

The emphasis is largely on luminescent efficiency, absorption, excitation and emission phenomena, and their temperature dependence. After an elementary, descriptive presentation of the theoretical basis for luminescence in solids, the properties of aluminate, molybdate, silicate and tungstate phosphors, and of manganese, titanium and uranium as activators are discussed in detail. Much of the work is reported for the first time. The experimental data are largely semi-quantitative with no indication of probable errors, and the correlations, in many cases, are only qualitative, *e.g.*, the correlation of absorption edge and the maximum of emission. The relevant published researches of other investigators are briefly mentioned. A tabulation, complete with emission color and original references, of 949 different phosphors according to 43 activators is extremely useful for reference purposes.

Kroger has an easy and enthusiastic style of presentation that occasionally reverts to the first person. A few odd expressions such as "cheap transition" denoting the transition requiring the least energy indicate that English is not the native language of the author and in general add to the charm of the presentation.

Investigators in luminescence can most painlessly become familiar with the work of one of the currently most active groups in phosphor research by reading this book.

FERD E. WILLIAMS

Max Planck in seinen Akademie-Ansprachen. Erinnerungsschrift der Deutschen Akademie der Wissenschaften zu Berlin, Akademie-Verlag, Berlin, 1948. 204 pp. 1 illustration. 15 × 24 cm. Price, DM 8.75.

Max Planck was a member of the German Academy of Sciences in Berlin from 1894 to his death in 1947 and its permanent secretary for mathematics and the natural sciences from 1912 to 1938. As a memorial to him the Academy has published this little book containing some of the addresses he made to the Academy, whether upon his admission or upon some festive or memorial occasion or when welcoming newly elected members in response to their remarks at the time of their admission; and when necessary to make Planck's response intelligible to the reader, the address of the newly elected member is also reproduced.

In his acceptance speech on admission Planck made clear his own philosophy of the rôle of the theoretical as contrasted with the experimental physicist, and not the least interesting of his later responses to new members are those in which the member expressed a different philosophy, as in the case of Einstein. The last essay was a Leibniz-day address of 1935. The little volume begins with a picture of Planck and closes with a list of 235 titles of his articles published between 1879 and 1948 (a seventy-year span) assembled by Max von Laue.

EDWIN B. WILSON

BOOKS RECEIVED

September 10, 1949—October 10, 1949

JOHN LEO ABERNETHY. "Principles of Organic Chemistry." W. B. Saunders Company, Philadelphia, Pennsylvania and London. 1941. 317 pp. $4.00.

ROGER ADAMS, Editor-in-Chief. "Organic Reactions." Vol. V. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1949. 446 pp. $6.00.

ROGER ADAMS AND JOHN R. JOHNSON. "Laboratory Experiments in Organic Chemistry." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 1949. 525 pp. $3.25.

G. BRYANT BACHMAN. "Organic Chemistry." (International Chemical Series.) McGraw-Hill Book Company, 330 West 42nd Street, New York 18, N. Y. 1949. 432 pp. $4.25.

JELKS BARKSDALE. "Titanium, its Occurrence, Chemistry and Technology." The Ronald Press Company, 15 East 26th Street, New York 10, N. Y. 1949. 591 pp. $10.00.

R. S. BURDON. "Surface Tension and the Spreading of Liquids." Second Edition. Cambridge University Press (American Branch), 51 Madison Avenue, New York 10, N. Y. 1949. 92 pp. $3.00.

GEORGE L. CLARK, LEONARD K. NASH AND ROBERT B. FISCHER. "A Basic Course in the Theory and Practice of Quantitative Chemical Analysis." W. B. Saunders Company, Philadelphia, Pennsylvania, and London. 1949. 448 pp. $4.25.

JACKSON W. FOSTER. "Chemical Activities of Fungi." Academic Press, Inc., 125 East 23rd Street, New York, N. Y. 1949. 648 pp. $9.50.

STANFORD GOLDMAN. "Transformation Calculus and Electrical Transients." Prentice-Hall, Inc., 70 Fifth Avenue, New York 11, N. Y. 1949. 439 pp. $8.35.

C. A. JACOBSON, Editor and Compiler. "Encyclopedia of Chemical Reactions." Vol. III. Reinhold Publishing Corporation, 330 West 42nd Street, New York, N. Y. 1949. 842 pp. $12.00.

MAURICE LECAT. "Tables Azéotropiques. Azéotropes binaires orthobares." Vol. I, Second Edition. Chez l'Auteur, Uccle-Bruxelles, 29, Rue Auguste Danse. 1949. 406 pp. Prix, mille frs. belges.

HOWARD J. LUCAS AND DAVID PRESSMAN. "Principles and Practice in Organic Chemistry." John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, N. Y. 1949. 557 pp. $6.00.

A. R. MILLER. "The Adsorption of Gases on Solids." Cambridge University Press (American Branch), 51 Madison Avenue, New York 10, N. Y. 1949. 133 pp. $2.50.

CHARLES E. O'HARA AND JAMES W. OSTERBURG. "An Introduction to Criminalistics. The Application of the Physical Sciences to the Detection of Crime." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 1949. 705 pp. $10.00.

FRANK A. PATTY, Editor. "Industrial Hygiene and Toxicology." Vol. II. Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y. 1949. 1138 pp. $15.00.

H. M. RANDALL, R. G. FOWLER, NELSON FUSON AND J. R. DANGL. "Infrared Determination of Organic Structures." D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 1949. 239 pp. $10.00.

F. J. W. ROUGHTON AND J. C. KENDREW, Editors. "Haemoglobin. A Symposium based on a Conference held at Cambridge in June 1948 in memory of Sir Joseph Barcroft." Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y., and London. 1949. 317 pp. $8.50.

WILLIAM E. SIRI, with Contributions by Ellsworth C. Dougherty, Cornelius A. Tobias, James S. Robertson, Rayburn W. Dunn and Patricia P. Weymouth. "Isotopic Tracers and Nuclear Radiations with Applications to Biology and Medicine." McGraw-Hill Book Company, 330 West 42nd Street, New York 18, N. Y. 1949. 653 pp. $12.50.

G. W. WHELAND. "Advanced Organic Chemistry." Second Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1949. 799 pp. $8.00.

"Cosmic Radiation." Colston Papers based on a Symposium promoted by the Colston Research Society and the University of Bristol in September, 1948, now published as a Special Supplement to "Research," a Journal of Science and its Applications. (Butterworths Scientific Publications, London.) Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y. 1949. 189 pp. $5.50.

"Proceedings of the International Congress on Rheology. Holland, 1948." Edited by the Organising Committee. (North-Holland Publishing Company Amsterdam.) Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y. 1949. 641 pp. $11.00.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in Stereochemistry. I. The Stereospecific Wagner–Meerwein Rearrangement of the Isomers of 3-Phenyl-2-butanol[1]

BY DONALD J. CRAM[2]

A considerable amount of our more intimate knowledge of the mechanisms of molecular rearrangements rests on the use of stereochemical relationships which exist between particular groups of carbon atoms in reactants and products of a given reaction. Thus Wallis and co-workers[3] and others have unequivocally demonstrated in their fundamental researches on the subject that in the Curtius, Hofmann, Lossen and Wolff rearrangements the migrating species when asymmetric is capable of maintaining optical configuration throughout the course of the reaction. There is good reason to expect that this stereospecificity with regard to the migrating group can be equally well applied to the pinacol and Wagner–Meerwein rearrangements.

Bartlett and Pöckel[4] called attention to evidence that in the Wagner–Meerwein rearrangement the carbon atom where replacement occurs undergoes a Walden inversion. Bernstein and Whitmore[5] in their elegant study of the semipinacolic deamination reaction of optically active 1,1-diphenyl-2-amino-1-propanol have demonstrated that a Walden inversion of the carbon atom originally bearing the amino group accompanies the reaction.

The Wagner–Meerwein reaction is unique, in that the stereochemistry of all three of the carbon atoms involved in the bond-making and breaking processes can be examined through the use of the proper systems. This rearrangement has been studied extensively in bicyclic systems with the use of such reactions as the conversion of camphene hydrochloride to isobornyl chloride,[4,6,7,8] and the reverse reaction of the conversion of isobornyl chloride to camphene hydrate.[9] In these and other examples investigated that involve asymmetric carbon atoms at both sites of reaction (the carbon atoms *from which* and *to which* migration of a methylene group occurs), the complete stereochemical structures of both starting material and product were not known.[10] In every case the starting materials as well as the products are bicyclic compounds, and the reactions are limited to the methylene group as the migrating species.

Wallis, *et al.*,[11] have studied the migration of a phenyl group in optically active 2-methyl-2-phenyl-1-butanol when this compound is treated with thionyl chloride. These authors have suggested on the basis of changes in sign of rotatory power during rearrangement that inversion occurred at the carbon atom originally bearing the phenyl group. They also considered the existence of any true carbonium ions during the course of the reaction to be very doubtful, and looked upon their reaction as taking place by a concerted mechanism in which all bond-making and bond-breaking processes occurred at the same time, once the thionyl chloride derivative of the starting carbinol

(1) This paper was presented in part before the Organic Division of the American Chemical Society, San Francisco Meeting, March, 1949.

(2) American Chemical Society Postdoctoral Fellow, 1947–1948.

(3) A summary of the vast literature on this subject, as well as a generalized mechanism for a number of intramolecular rearrangements, was published by Lane and Wallis, THIS JOURNAL, **63**, 1674 (1942).

(4) Bartlett and Pöckel, *ibid.*, **59**, 820 (1937); **60**, 1585 (1938).

(5) Bernstein and Whitmore, *ibid.*, **61**, 1324 (1939).

(6) Meerwein and van Emster, *Ber.*, **53**, 1815 (1920); **55**, 2500 (1922).

(7) Asahina, Ishidate and Sans, *ibid.*, **69**, 343 (1936).

(8) Nevell, Salas and Wilson, *J. Chem. Soc.*, 1188 (1939).

(9) Meerwein, *Ann.*, **453**, 16 (1927).

(10) The configurations of the carbon atom bearing the chlorine atom in camphene hydrochloride and the carbon atom bearing the hydroxyl in camphene hydrate have not been determined.

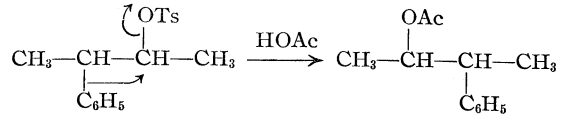
(11) Wallis and Bowman, *J. Org. Chem.*, **1**, 383–392 (1936).

was formed. This work, however, represents the only attempt to study the stereochemistry of the Wagner–Meerwein rearrangement in an acyclic system.

Among others, Wilson, *et al.*,[8] have postulated an ionic intermediate in the Wagner–Meerwein rearrangement, but more concrete evidence for an ionic intermediate is found in the work of Winstein, *et al.*,[12] on the *i*-cholesteryl system which involves a pair of electrons as the migrating species.

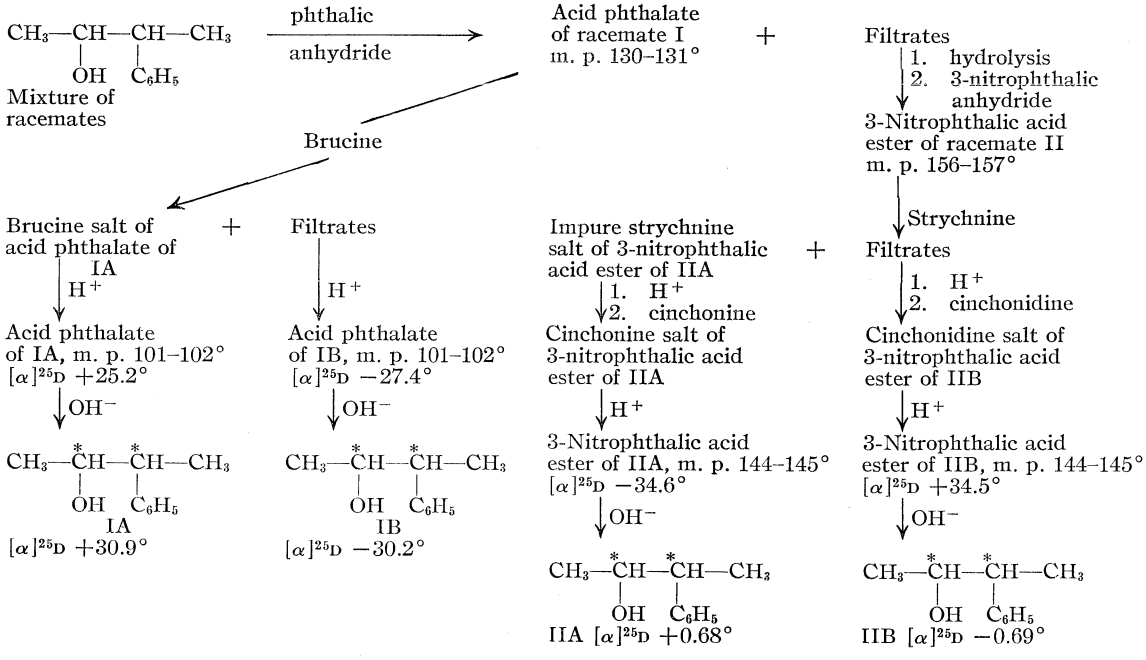
In contrast to the findings of the above authors, the present investigation (see papers I, II, III and IV in this series) will unequivocally demonstrate for the first time the existence of a *discrete molecular species*, a carbocyclic three-membered carbonium ion as an intermediate in a Wagner–Meerwein rearrangement in an acyclic system.[13] It should be stated, however, that the results of this work are in a sense not unlike the demonstration of the existence of a bromonium ion by Winstein and Lucas,[14] whose work has served as an inspiring model in the present investigation.

Paper I in the present series is devoted to an investigation of the mechanism of the Wagner–Meerwein reaction which takes place during the acetolysis of the *p*-toluenesulfonates of the stereoisomers of 3-phenyl-2-butanol. When rearrangement occurs in the molecule, the product is a derivative of an alcohol of the same structural formula as is the reactant, but not necessarily the same stereochemical formula. This fact simplifies the procedures of isolation and identification of products as well as giving some information in regard to the possible existence of symmetrical intermediates. This system also allows a study at the same time of the stereochemical transformations that occur at both the carbon atoms *from which* and *to which* migration takes place; these carbon atoms are free to rotate, and the substituents attached to them are not held in a definite position in space with respect to each other.



Preparation and Resolution of 3-Phenyl-2-butanol

A mixture of the two racemates of 3-phenyl-2-butanol[15] was obtained by the treatment of 2-phenylpropionaldehyde (this compound was prepared by the procedure of Claisen[16]) with the methyl Grignard reagent. The resolution of this carbinol into the four optically pure stereoisomers was accomplished according to the scheme indicated. The four alcohols are designated as IA, IB, IIA and IIB, the numerals referring to the racemate series and the letters to the enantiomorphs within the series.



The acid phthalates of II, IIA and IIB were prepared as well as the 3-nitrophthalic acid esters of I, IA and IB, and in each case where an enanti-

(12) Winstein and Adams, THIS JOURNAL, **70**, 838 (1948); Winstein and Schlesinger, *ibid.*, **70**, 3528 (1948).

(13) Such an intermediate represents not a transition state (maximum in a potential energy curve) but an actual intermediate ion containing a three-membered ring and situated at a minimum in the curve of potential energy *vs.* reaction coördinate. The experiments leading to the previously discussed three-membered cycle of Lane and Wallis were not such as to distinguish between these possibilities.

(14) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939).

(15) The preparation of this alcohol was first carried out by Geissman and Akawie (unpublished work) and will be reported by these authors at a future date.

(16) Claisen, *Ber.*, **38**, 705 (1905).

TABLE I

PHYSICAL DATA PERTAINING TO THE STEREOISOMERS OF 3-PHENYL-2-BUTANOL AND DERIVATIVES

Compound alcohols	Yield, %	B. p. °C.	Mm.	$[\alpha]^{25}D$ Pure liq.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I[a]	90	108	10	.....	$C_{10}H_{14}O$	79.95	9.39	79.58	9.47
II[b]	84	105	10	.....	$C_{10}H_{14}O$	79.95	9.39	79.91	9.55
IA	93	118	25	+30.9	$C_{10}H_{14}O$	79.95	9.39	80.08	9.29
IB	89	118	25	−30.2	$C_{10}H_{14}O$	79.95	9.39	79.64	9.67
IIA	87	119	30	+ 0.68	$C_{10}H_{14}O$	79.95	9.39	79.73	9.40
IIB	85	119	30	− 0.69	$C_{10}H_{14}O$	79.95	9.39	80.02	9.57
Acid phthalates		**M. p., °C.**		**In ethanol $c \cong 3\%$**					
I[c]	27	130–131		.....	$C_{18}H_{18}O_4$	72.41	6.08	72.60	6.30
II[d]	86	83–84		.....	$C_{18}H_{18}O_4$	72.41	6.08	72.50	6.25
IA[d]	42	101–102		+25.2	$C_{18}H_{18}O_4$	72.41	6.08	72.69	6.26
IB[d]	29	101–102		−27.4	$C_{18}H_{18}O_4$	72.41	6.08	72.09	6.16
IIA[e]	82	101–102		−63.7	$C_{18}H_{18}O_4$	72.41	6.08	72.63	6.26
IIB[e]	86	102–103		+64.1	$C_{18}H_{18}O_4$	72.41	6.08	72.53	6.33
3-Nitrophthalic acid esters									
I[f]	90	143–144		.....	$C_{18}H_{17}NO_6$	62.97	5.00	63.28	5.05
II[f]	52	156–157		.....	$C_{18}H_{17}NO_6$	62.97	5.00	63.25	5.06
IA[f]	84	150–151		+34.2	$C_{18}H_{17}NO_6$	62.97	5.00	63.16	5.11
IB[f]	87	148–149		−33.4	$C_{18}H_{17}NO_6$	62.97	5.00	63.32	5.37
IIA[f]	34	144–145		−34.6	$C_{18}H_{17}NO_6$	62.97	5.00	62.97	5.03
IIB[f]	40.5	144–145		+34.5	$C_{18}H_{17}NO_6$	62.97	5.00	63.25	5.23
***p*-Toluenesulfonates**									
IA[f]	84	62–63		.....	$C_{17}H_{20}SO_3$	67.08	6.62	66.97	7.79
IB[e]	78	35–36		.....	$C_{17}H_{20}SO_3$	67.08	6.62	66.96	6.74

[a] $n^{25}D$ 1.5159. [b] $n^{25}D$ 1.5167. [c] Rod-shaped crystals. [d] Clusters of thick square plates. [e] Flat irregular needles [f] Fine needles.

omorphic pair was obtained, the magnitude of the rotation of the one is in good agreement with that of the other. The melting points of the solid derivatives also coincide. These data indicate that complete resolution was accomplished. The *p*-toluenesulfonates of IA and IIA were prepared by treating the corresponding alcohols with *p*-toluenesulfonyl chloride in a pyridine solution. Table I records the physical constants, analytical data and yields pertaining to these compounds.

Acetolysis of the *p*-Toluenesulfonates of the Stereoisomers of 3-Phenyl-2-butanol

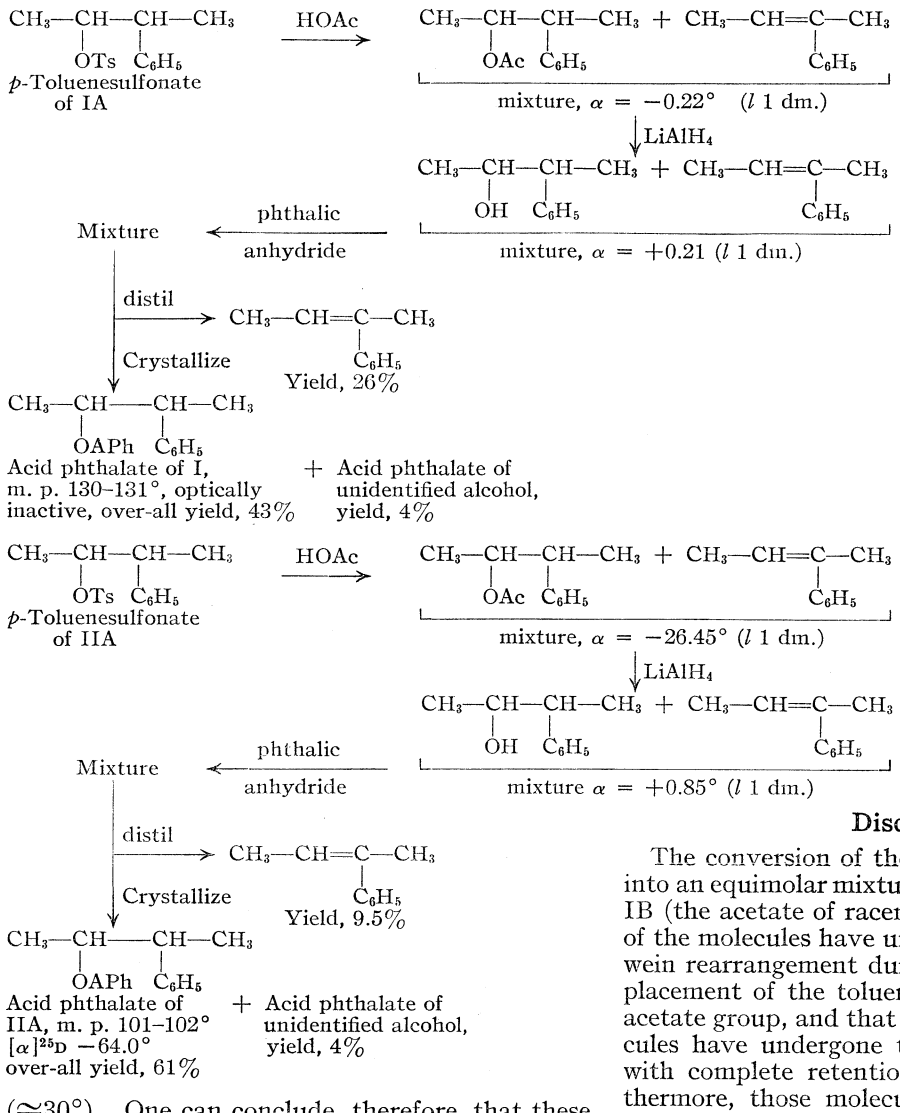
The *p*-toluenesulfonates of IA and IIA were prepared and heated at 70° for thirty hours[17] in a solution of glacial acetic acid which contained 1% of acetic anhydride and enough potassium acetate to neutralize the toluenesulfonic acid produced in the reaction.[18] The following formulations indicate the procedures used for isolation of the products, the yields and rotations. The alcohol IIA was isolated as the acid phthalate because this derivative possesses more desirable crystallization properties than the corresponding 3-nitrophthalic acid ester.

The observed rotation of the liquid acetate–olefin mixture obtained from the acetolysis of the *p*-toluenesulfonate of IA is very small (−0.22°) indicating that almost complete racemization took place. Had simple inversion of the carbon atom bearing the *p*-toluenesulfonate group occurred to any extent, one would have expected a corresponding increase in this rotation since the magnitude of the rotation of the acetate of IIA or IIB is quite high (>26°). The magnitude of the rotation obtained by the reduction of this mixture is also very low (+0.21°) indicating that there is little, if any, predominance of the amount of IA over IB, or *vice versa*.

The observed rotation of the liquid acetate–olefin mixture obtained from the acetolysis of the *p*-toluenesulfonate of IIA is quite large (−26.45°), which indicates that there is a considerable amount of optically active compound present. When reduced to the carbinol–olefin mixture, however, the rotation drops to +0.85°, a fact consistent with the large amount of IIA alcohol ($[\alpha]^{25}D$ +0.68°) present in this mixture There can be little if any of either IA or IB present, however, (products of simple inversion), because these alcohols have a high magnitude of rotation

(17) This period of heating is equal to about six half-lives of the starting material under these conditions, as calculated from the kinetic data obtained for acetolysis of these compounds by S. Winstein and B. Friess[23] (unpublished work).

(18) Experiments run without the potassium acetate gave a slightly lower yield of product and more tar.



(≅30°). One can conclude, therefore, that these acetolysis reactions proceeded with little, if any, *simple inversion* of the carbon atom bearing the *p*-toluenesulfonate group.

Another interesting point that should be noted is that the sum of the yields of the final carbinol derivative and the olefin in the I series (≅70%) is just about equal to the sum of the yields of the carbinol derivative and the olefin obtained in the II series, even though the relative amounts of olefin and carbinol differ.

Walden Inversion of the *p*-Toluenesulfonate of IIA

It seemed desirable to relate the configurations of the two asymmetric carbon atoms of one of the enantiomorphs of racemate I to those of one of the enantiomorphs of racemate II. This relationship could be established if a simple inversion without rearrangement could be performed on the carbon atom bearing the oxygen of one of the stereoisomers of 3-phenyl-2-butanol or a derivative. Accordingly, one of the diastereoisomers would be converted into another without altering the stereochemistry of the carbon atom bearing the phenyl group. Simple inversion was accomplished through the use of the method that Phillips[19] employed for the inversion of the *p*-toluenesulfonate of 1-phenylpropanol-2. Treatment of the *p*-toluenesulfonate of IA with a solution of a large amount of potassium acetate dissolved in absolute ethanol produced a small amount of the acetate of IIA (most of the *p*-toluenesulfonate was converted to the ethyl ether). This acetate was converted to the acid phthalate for identification purposes.

Discussion

The conversion of the *p*-toluenesulfonate of IA into an equimolar mixture of the acetates of IA and IB (the acetate of racemate I) indicates that half of the molecules have undergone a Wagner–Meerwein rearrangement during the course of the displacement of the toluenesulfonate groups by the acetate group, and that the other half of the molecules have undergone the displacement reaction with complete retention of configuration. Furthermore, those molecules that have undergone rearrangement have done so in a highly stereospecific manner.[20] In the acetolysis of IIA there is no concrete proof that any rearrangement has taken place, but it would seem highly probable that since rearrangement took place in the I series, the same occurred in the II series. If the analogy between systems I and II is maintained, half of the molecules of *p*-toluenesulfonate of IIA must rearrange to IIA acetate, and half of the molecules produce IIA acetate without rearrangement.[21]

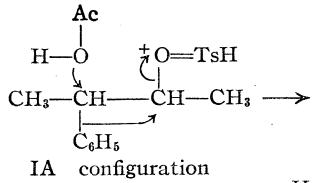
The isolation of the acetates of IA and IB in equimolar proportion from the acetolysis with

(19) Phillips, *J. Chem. Soc.*, **123**, 44 (1923).

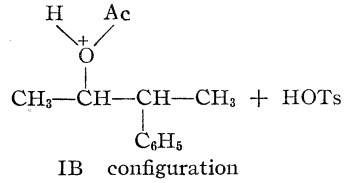
(20) The reaction giving rise to the acetates was at least 90% stereospecific since the ratio of the yield of the acid phthalate of racemate I to the yield of the acid phthalates of other alcohols was ten to one. Stereospecificity of even a higher degree was found in the II series.

(21) Strong evidence for this suggestion is found in paper III of this series. The *p*-toluenesulfonates of the two racemates series of 3-phenyl-2-pentanol were submitted to acetolysis, and in both cases the product was a mixture of the acetate of starting material and the acetate of rearranged material (2-phenyl-3-pentanol acetate).

glacial acetic acid of the *p*-toluenesulfonate of IA is strong evidence that both products arose from a symmetrical intermediate ion, and that the reaction was *not* completely concerted. Had the latter been the case, only rearranged product (IB) would have been obtained. The acetate group would have entered the molecule at the same time that the phenyl group migrated and the *p*-toluenesulfonate group left.[22]



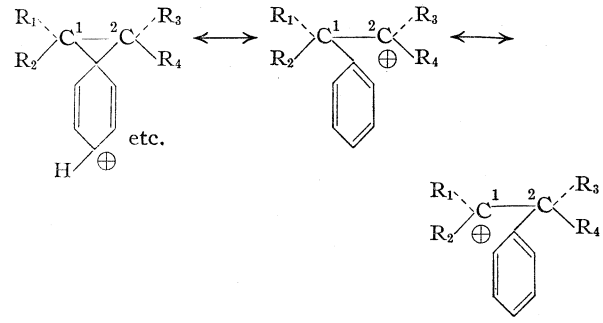
IA configuration



IB configuration

In the acetolysis experiments with glacial acetic acid the lack of products belonging to the II racemate series when the starting materials belong to the I racemate series and *vice versa* indicates that any intermediate ions formed during the reaction are capable of maintaining their optical integrity. Furthermore, very little, if any, simple bimolecular displacement of the *p*-toluenesulfonate group by acetic acid molecules could have taken place under these conditions. When the reaction was conducted in ethanol containing acetate ion, simple bimolecular displacement was the only reaction encountered exclusive of the reaction with ethanol, the nature which was not examined.

These facts can be rationalized in the following manner. The first step in the rearrangement is probably the transfer of a proton from a glacial acetic acid molecule to one of the two negative oxygens of the *p*-toluenesulfonate group placing a positive charge on the sulfur that can be distributed through resonance on the oxygen bearing the carbon. The carbon–oxygen bond is thus weakened and the second step is the departure of a molecule of *p*-toluenesulfonic acid, leaving a carbonium ion that must in some way be capable of maintaining optical and hence tetrahedral character. A cyclic ion existing as a resonance hybrid as shown below fulfills this requirement and offers an attractive hypothesis for explaining the racemization of the *p*-toluenesulfonate of IA on the one hand, and the maintenance of configuration of the same derivative of IIA on the other, during acetolysis with acetic acid. If R_1 and R_3 are methyl groups and R_2 and R_4 are hydrogens, this intermediate possesses a plane of symmetry, and the cycle could be opened by an acetic acid molecule

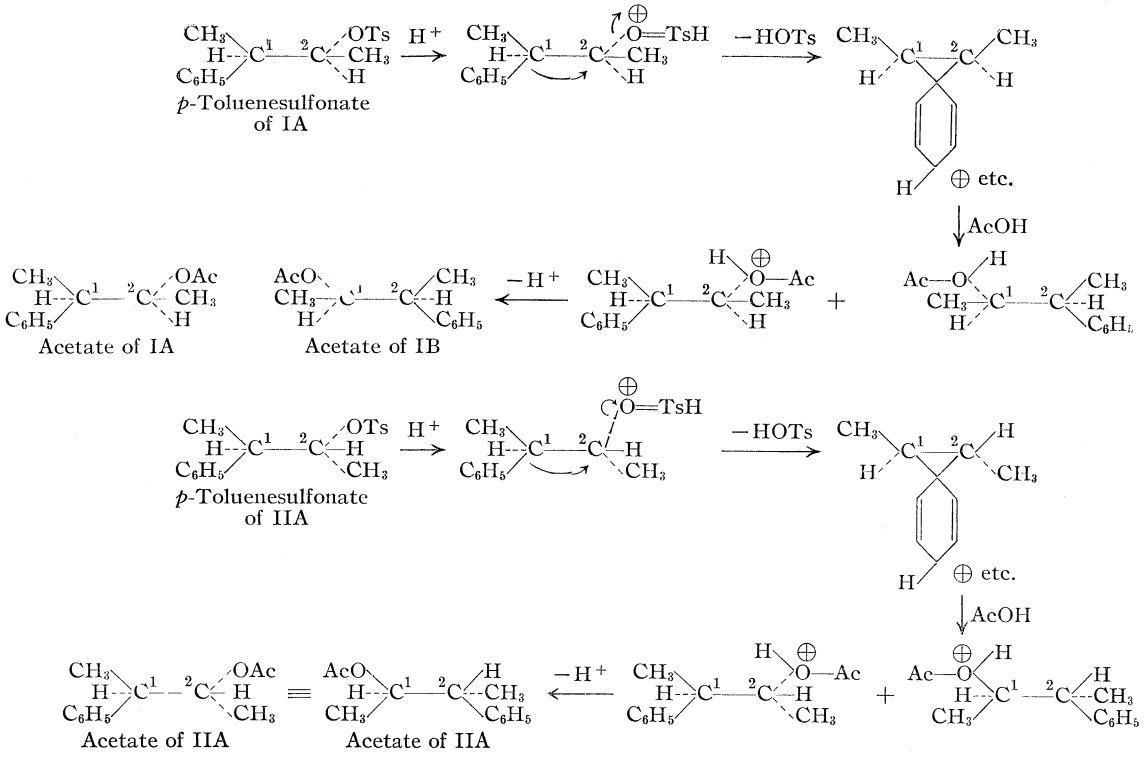


at either carbon atoms 1 or 2 (with equal probability), giving rise to racemic acetate after the departure of a proton from the molecule. If R_1 and R_4 are methyl groups and R_2 and R_3 are hydrogens, the intermediate is asymmetric, and when the cycle is opened at either carbon atoms 1 or 2 (with equal probability), optically active product is obtained. Since there are no cases known of simple front-side displacement unattended by the possibility of reaction by a cyclic mechanism, it is logical to assume that the cycle was formed with inversion of the carbon atom bearing the *p*-toluenesulfonate group, and that when the cycle is opened, the carbon atom hit by the acetic acid molecule is inverted. The latter reaction is probably bimolecular. The question as to whether the cycle is formed by a concerted displacement of the *p*-toluenesulfonate by the phenyl group is difficult to settle. The stereospecificity of the reaction would seem to demand that this step is concerted. On the other hand, kinetic determinations[23] of the comparative rates of the liberation of *p*-toluenesulfonic acid from the *p*-toluenesulfonates of I, II and 2-butanol in glacial acetic acid showed that these reactions all take place with very little difference in rate. Since the butanol derivative does not and the derivatives of I and II do rearrange, the breaking of the carbon–oxygen bond in the latter molecules cannot be much aided energetically by the formation of a new carbon–carbon bond in a cycle, or there would be divergence in the activation energies and hence the rates of the reactions in the two types of molecules. These data suggest that either intermediate ions of other than a cyclic nature exist, or that the loss of the *p*-toluenesulfonate group and the formation of the intermediate cycle take place in concert with one another, but that the energy gained by the formation of a new carbon–carbon bond of the cycle approximately cancels the energy needed to compensate for the decrease of resonance energy and for the energy needed to distort the bond angles into a three-membered ring. The latter explanation is preferred because the stereochemistry of the reaction is not compatible with the existence of intermediates of a non-cyclic character.

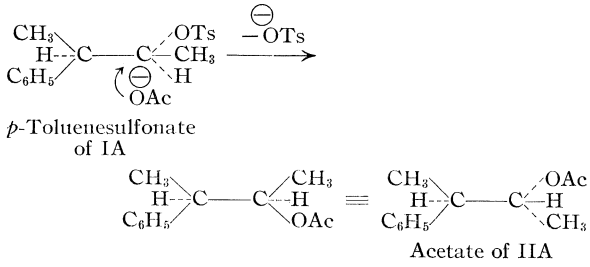
The hypothesis favored for the mechanism is summarized in the formulations.

(22) This evidence is in accord with the suggestion of C. G. Swain [THIS JOURNAL, **70**, 1126 (1948); **70**, 2989 (1948)] that Wagner-Meerwein rearrangements are concerted processes as far as the carbonium ion intermediates.

(23) Private communication from S. Winstein and B. Friess of work carried out in connection with a general investigation of the Wagner–Meerwein rearrangement.



In presenting this mechanism, IA has been assumed to have a certain stereochemical configuration. This assumption was made because it leads to a symmetrical intermediate cyclic ion which in turn gives equal molecular amounts of IA and IB acetates. The assignment of IA to the configuration shown and not to that assumed for IB was purely arbitrary. Having assigned the configuration of IA, the configuration of IIA is determined through the conversion of the *p*-toluenesulfonate of IA to the acetate of IIA by acetate ion through simple inversion of the carbon atom bearing the oxygen bond. The configurations of IB and IIB



become fixed through their enantiomorphic relationship to IA and IIA, respectively. The configurations of IIA and IIB are such that each would give rise to an asymmetric cyclic intermediate, these two intermediates being enantiomorphic in relationship. This type of intermediate for the II series is just what the results of the acetolysis experiments demand. Thus this series of experiments not only provides a certain insight into the mechanism of the Wagner–Meerwein rearrangement, but also presents a unique method of determining the stereochemical structure of this type of compound. The results of an independent determination of the stereochemical structure of each of these four isomers is presented in the fourth paper in this series, and the results are in full agreement with the above assignments. A discussion of the mechanism of the formation and the configuration of the olefin formed in the acetolysis experiments will also be found in the fourth paper of this series.

It is interesting to note in regard to the studies of the inversion by acetate ion in ethanol of the *p*-toluenesulfonates of 1-phenyl-2-propanol[19] and 3-phenyl-2-butanol that the yields of acetate product decreased respectively and that the yields of ether increased. Since the rate-determining step in the reaction with acetate ion is in each case bimolecular, the rate is more sensitive to steric hindrance than is the rate of the reaction with the ethanol, which probably proceeds by a different mechanism.

Experimental

Separation of the Mixture of Isomers of 3-Phenyl-2-butanol into Racemates I and II.—The mixture of the isomers of 3-phenyl-2-butanol[15] (112 g.) obtained from the action of methylmagnesium bromide on 2-phenylpropionaldehyde was heated to 100° for one hour with 112 g. of phthalic anhydride and 125 g. of pyridine. The resulting mixture was cooled, dissolved in benzene, extracted twice with excess dilute sulfuric acid, washed with water, dried, evaporated, dissolved in two volumes of ethyl acetate, and low-boiling petroleum ether added until the solution became slightly turbid. The product that crystallized was recrystallized from ethyl acetate and petroleum ether to give 35.5 g. of pure phthalic acid ester of racemate I, m. p. 130–131° (white flat needles).

The filtrates from the crystallization and purification of the above substance were combined, evaporated to an oil, and brought to reflux for fifteen hours in a solution of 80 g. of sodium hydroxide dissolved in 400 ml. of water. The mixture was then cooled, extracted with petroleum ether, and the organic layer was separated, washed with water, dried, evaporated to an oil and distilled. This alcohol (90.0 g.) was mixed with 116 g. of 3-nitrophthalic anhydride and 120 g. of pyridine and heated to 100° for one hour. The mixture was then cooled, dissolved in benzene, and this solution was extracted with excess dilute sulfuric acid, washed with water, dried and evaporated to an oil. This oil was dissolved in two volumes of ethyl acetate and low-boiling petroleum ether added until the solution became turbid. On standing, a solid separated which, when recrystallized from ethyl acetate and petroleum ether, produced 91 g. of the 3-nitrophthalic acid ester of racemate II, m. p. 156–157° (fine white needles).

The filtrates from the above crystallizations were combined, evaporated, and hydrolyzed to the alcohol in the same manner as described above, weight 46 g. This mixture of racemates was submitted to the same cycle as described above to produce 25 g. of additional acid phthalate of racemate I (m. p. 130–131°) and 28 g. of additional 3-nitrophthalic acid ester of racemate II (m. p. 156–157°).

Resolution of the Phthalic Acid Ester of Racemate I.—A mixture of 52 g. of the acid phthalate of racemate I, 40 g. of brucine and 900 ml. of acetone was brought to boiling, filtered and allowed to cool. The needles that separated were recrystallized from acetone to give 70.5 g. of salt which was shaken with ether and excess 2 *N* sulfuric acid. The ether layer was washed with water, dried and evaporated to an oil, and this oil crystallized from ethyl acetate and petroleum ether to give 18.2 g. of white square plates of the acid phthalate of IA, m. p. 101–102°, which was depressed by admixture with a small amount of the acid phthalate of racemate I.

The filtrates from the crystallizations of the above brucine salt were combined and shaken with excess 2 *N* sulfuric acid and ether, the ether layer washed several times with water, dried and evaporated to an oil. This oil was taken up in two volumes of ethyl acetate and a slight turbidity produced by the addition of petroleum ether. The mixture was carefully seeded with the acid phthalate of racemate I and allowed to crystallize until an estimated one-third of the total amount of solid in the solution had crystallized. The mixture was filtered, 10.4 g., m. p. 128–131°. This material when submitted to the procedure recorded above produced an additional 3.8 g. (m. p. 130–131°) of the acid phthalate of IA, m. p. 101–102°.

The combined filtrates from the crystallization of racemate I were diluted with low-boiling petroleum ether, and when allowed to stand, 17.5 g. of square plates were deposited. This material was recrystallized from ethyl acetate and petroleum ether and the product collected in two crops, the first amounting to 4.2 g. (m. p. 103–106°) and the second to 11.7 g., m. p. 101–102° (square plates) of the acid phthalate of IB. An additional 3.3 g. (m. p. 101–102°) of pure acid phthalate of IB was obtained by fractional recrystallization of the other fractions of impure material.

Resolution of the 3-Nitrophthalic Acid Ester of Racemate II.—A solution of 90 g. of the 3-nitrophthalic acid ester of racemate II, 53 g. of strychnine, 300 ml. of chloroform and 100 ml. of acetone was allowed to stand overnight and the solid deposited was collected. The filtrate was shaken with a mixture of excess 2 *N* hydrochloric acid solution and ether. The ether layer was washed with water, dried, evaporated to an oil and mixed with 43 g. of cinchonidine and 300 ml. of acetone. The clear solution deposited fine white needles on standing, which were collected and recrystallized twice from acetone to give 58 g. of salt. This material was shaken with a mixture of ether and excess 2 *N* sulfuric acid, the ether layer was washed with water, dried, and evaporated to an oil, and the 3-nitrophthalic acid ester of IIB was crystallized and recrystallized from an ethyl acetate–petroleum ether mixture to give 28 g. of white needles, m. p. 144–145°, of pure 3-nitrophthalic acid ester of IIB.

The filtrates from the crystallization of the cinchonidine salt were combined with the strychnine salt and shaken with excess 2 *N* hydrochloric acid and ether, the ether layer was separated, washed with water, dried and evaporated to an oil. This oil was dissolved in 350 ml. of acetone and mixed with 43 g. of cinchonine and the resulting solution cooled. After standing for two days at 0°, the white needles that separated were collected and recrystallized twice from acetone to give 55 g. of cinchonine salt. This material was shaken with an excess of 2 *N* hydrochloric acid and ether, the ether layer was separated, washed with water, dried and evaporated to an oil which crystallized from ethyl acetate and petroleum ether. This compound (white needles) when recrystallized from ethyl acetate and petroleum ether amounted to 24.2 g., m. p. 144–145°, of pure 3-nitrophthalic acid ester of IIA.

The filtrates from the crystallization of the cinchonine salt were converted to a mixture of 3-nitrophthalic acid esters, which, when submitted to the same resolution procedure, produced 8.5 g. (m. p. 144–145°) of additional ester of IIB and 6.3 g. (m. p. 144–145°) of additional ester of IIA.

Conversion of the Phthalic Acid Esters of I, IA and IB and the 3-Nitrophthalic Acid Esters of II, IIA and IIB into the Corresponding Alcohols.—The procedure for the hydrolysis of the above esters to the corresponding alcohols is illustrated by the conversion of the acid phthalate of IA to IA. A mixture of 22 g. of this ester, 8 g. of sodium hydroxide, 8 g. of potassium hydroxide and 80 ml. of water was refluxed for sixteen hours, cooled and extracted twice with low boiling petroleum ether. The extracts were combined, washed once with water, dried, evaporated to an oil, and the oil distilled to produce 10.3 g. of IA, b. p. 118° (25 mm.).

Conversion of I, IA and IB to the Corresponding 3-Nitrophthalic Acid Esters and the Conversion of II, IIA and IIB to the Corresponding Phthalic Acid Esters.—The procedures for the above introconversions is illustrated by the preparation of the 3-nitrophthalic acid ester of IA. A mixture of 2.2 g. of IA, 2.83 g. of 3-nitrophthalic anhydride and 5 ml. of pyridine was heated to 100° for one hour, cooled and shaken with a mixture of ether and excess 2 *N* sulfuric acid. The ether layer was washed with water, dried and evaporated to an oil. This material was crystallized from one volume of ethyl acetate and two volumes of low-boiling petroleum and the product recrystallized from the same solvents to give 4.3 g. of fine white needles, m. p. 150–151°.

Preparation of the *p*-Toluenesulfonates of IA and IIA.—The procedure for the above preparations is illustrated by the conversion of IA to the *p*-toluenesulfonate of IA. A mixture of 10.3 g. of IA, 12.8 g. of pure *p*-toluenesulfonyl chloride and 20 ml. of pure pyridine was allowed to stand at room temperature for twenty-four hours. The mixture was then shaken with a cold mixture of excess 2 *N* sulfuric acid, ether and petroleum ether. The organic layer was separated, washed with water, with a dilute alkaline solution, and again with water. The solution was then dried, evaporated to an oil under reduced pressure and crystallized and recrystallized from a mixture of one volume of benzene and five volumes of low boiling petroleum ether to give 17.5 g. of white needles, m. p. 62–63°.

Acetolysis of the *p*-Toluenesulfonate of IA.—The *p*-toluenesulfonate of IA (5.0 g.) was dissolved in 100 ml. of a mixture of 1 ml. of acetic anhydride, 100 ml. of dry glacial acetic acid and 1.96 g. of freshly fused potassium acetate. The resulting solution was held at 70° for thirty hours, cooled, and shaken with a mixture of 300 ml. of low boiling petroleum ether and one liter of water. The layers were separated, the organic layer washed with water, with a dilute alkaline solution, again with water, and dried, evaporated to an oil and the oil distilled; weight 2.70 g., observed rotation on the liquid ($l = 1$, $\lambda = D$), $-0.22°$. This distillate was added dropwise to a solution of 3 g. of lithium aluminum hydride in ether, the excess reagent was decomposed with ethanol and the mixture shaken with a mixture of petroleum ether and dilute sulfuric acid. The organic layer was washed with water, dried, evaporated to

an oil and the oil distilled, weight 2.05 g., observed rotation on the liquid (l = 1, λ = D), +0.21°. This liquid was mixed with 2.05 g. of phthalic anhydride and 3 g. of pyridine and heated to 100° for one hour, cooled, and shaken with a mixture of benzene and excess 2 *N* sulfuric acid. The benzene layer was washed with water, dried, evaporated to an oil, and this oil distilled at 130° at 20 mm. of pressure. The olefin that distilled amounted to 0.55 g. The residue was crystallized from ethyl acetate and low boiling petroleum ether and the product recrystallized from the same solvents to give 2.10 g. of the acid phthalate of racemate I, m. p. 130–131°, not depressed by admixture with an authentic sample of racemate I acid phthalate, $[\alpha]^{25}D$ 0° (c = 3.12) in absolute ethanol. The filtrates were combined and evaporated to give 0.11 g. of residue.

Acetolysis of the *p*-Toluenesulfonate of IIA.—This reaction was carried out in exactly the same manner as described above for the acetolysis of the *p*-toluenesulfonate of IA. From 2.9 g. of the *p*-toluenesulfonate of IIA was obtained 1.67 g. of a mixture of acetate and olefin, observed rotation (l = 1, λ = D), −26.5°. Reduction with lithium aluminum hydride produced 1.26 g. of a mixture of alcohol and olefin, observed rotation (l = 1, λ = D), +0.85°. Treatment of this liquid with phthalic anhydride gave a mixture from which was isolated 0.12 g. of olefin and 1.33 g. of the acid phthalate of IIA, m. p. 101–102°, m. m. p. with an authentic sample, 101–102°, $[\alpha]^{25}D$ −64.0°. The filtrates from the crystallizations were combined, evaporated and fractionated on a small column of acid-washed alumina. The material was absorbed from a benzene solution, and the column was developed with a 30% acetone–70% benzene mixture. From the 1st fraction coming through the column was isolated 0.4 g. more of the acid phthalate of IIA, m. p. 101–102°, m. m. p. with an authentic sample, 101–102°. No crystalline compounds were obtained from the other fractions. The column was flushed with methanol and all residues combined to give 0.11 g. of unidentified material.

Inversion of the *p*-Toluenesulfonate of IA with Acetate Ion to Produce the Acetate of IIA.—A mixture of 1.0 g. of the *p*-toluenesulfonate of IA, 5 ml. of absolute ethanol and 0.70 g. of freshly fused potassium acetate was heated to reflux for twenty-four hours. The material was then cooled and shaken with a mixture of water and petroleum ether, the layers separated and the organic layer was washed twice with water, dried, evaporated to an oil and distilled; 0.42 g. This oil was added dropwise to a solution of 0.5 g. of lithium aluminum hydride dissolved in dry ether, and at the end of the addition the excess hydride was decomposed with ethanol. The resulting mixture was shaken with petroleum ether and dilute sulfuric acid, the organic layer was washed with water, dried, evaporated to an oil and distilled; 0.35 g. This mixture of alcohol and ether was heated at 100° with 0.35 g. of phthalic anhydride and 1 ml. of pyridine. This resulting mixture was cooled, shaken with benzene and excess 2 *N* sulfuric acid, and the organic layer was washed with water, dried and evaporated. The resulting oil was distilled at 1 mm. and 130°, the ether distilling first and the excess phthalic anhydride coming over last. The residue was crystallized from ethyl acetate and low-boiling petroleum ether, and two recrystallizations of the product from the same solvents produced 120 mg. of the acid phthalate of IIA, m. p. 100–101°, m. p. with an authentic sample, 101–102°. This melting point was depressed 25° by the acid phthalates of either IA or IB. Crystallization of the above product with an equal amount of the acid phthalate of IIB produced the acid phthalate of racemic II, m. p. 83–84°, not depressed by admixture with an authentic sample.

Acknowledgments.—It is a pleasure to express appreciation to Drs. S. Winstein, T. A. Geissman and G. Hammond for their many important and helpful suggestions regarding the work presented in this paper. The author is indebted to Mr. Welton Burney for the analytical data.

Summary

1. The compound 3-phenyl-2-butanol has been completely resolved into its four optically pure stereoisomers, IA, IB, IIA and IIB, and a series of derivatives of the isomers prepared.

2. When the *p*-toluenesulfonate of IA was submitted to acetolysis, the acetate of racemic I was obtained whereas when the *p*-toluenesulfonate of IIA was submitted to acetolysis, the acetate of IIA was obtained. These results are interpreted as evidence for an intermediate cyclic carbonium ion in a Wagner–Meerwein rearrangement, this ion being symmetrical in the I series and asymmetrical in the II series. The carbon atom bearing the bond to oxygen is inverted when the cycle is formed and another inversion takes place on the carbon atom whose bond is broken when the cycle is opened.

3. These reactions provide a unique proof of stereochemical structure with respect to the configuration of racemate I and racemate II.

4. The configuration of IA has been related to IIA by the simple inversion by acetate ion of the carbon atom bearing the oxygen in the *p*-toluenesulfonate of IA.

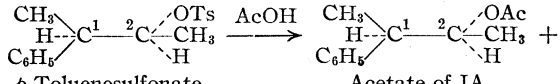
LOS ANGELES, CALIFORNIA RECEIVED MARCH 14, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

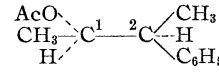
Studies in Stereochemistry. II. The Preparation and Complete Resolution of 3-Phenyl-2-pentanol and 2-Phenyl-3-pentanol

BY DONALD J. CRAM AND ROBERT DAVIS[1]

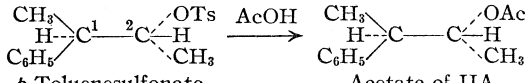
The first paper of this series reported the stereospecific Wagner–Meerwein rearrangement of the *p*-toluenesulfonates of the stereoisomers of 3-phenyl-2-butanol during acetolysis. Good evidence was provided that the *p*-toluenesulfonate of IA rearranged to I acetate; however, since the *p*-toluenesulfonate of IIA gave the acetate of IIA, there was no concrete proof of any disturbance of the carbon chain even though rearrangement was very probable.



p-Toluenesulfonate of IA — Acetate of IA

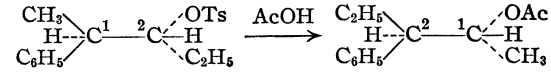


Acetate of IB



p-Toluenesulfonate of IIA — Acetate of IIA

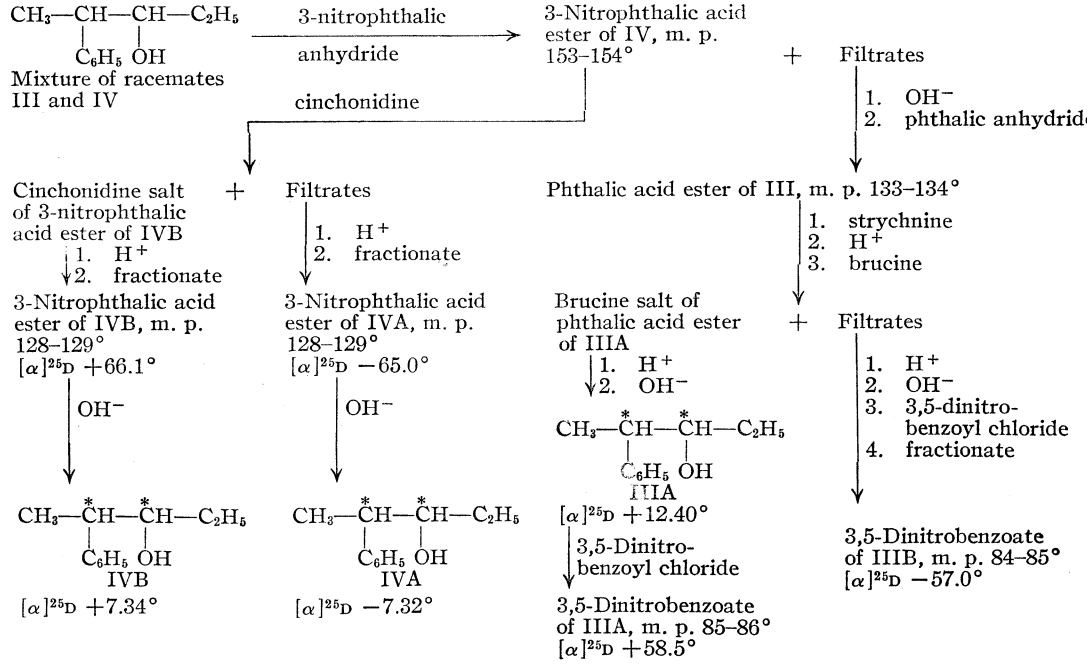
In the similar treatment of the *p*-toluenesulfonate of the isomer of 2-phenyl-3-pentanol that is sterically analogous to IIA, if rearrangement occurs, the relative positions of the methyl and ethyl groups in the product will be reversed, and the substance will be a derivative of 3-phenyl-2-pentanol. This system should also provide additional facts concerning the postulated existence of a cyclic intermediate carbonium ion.



This paper deals with the preparation and resolution of 2-phenyl-3-pentanol and 3-phenyl-2-pentanol into the eight stereoisomers of these two structural isomers, and with a correlation of the probable configuration of these isomers with their physical properties and modes of resolution. Paper III in this series will report the results of the rearrangement studies to which these isomers were submitted.

Results

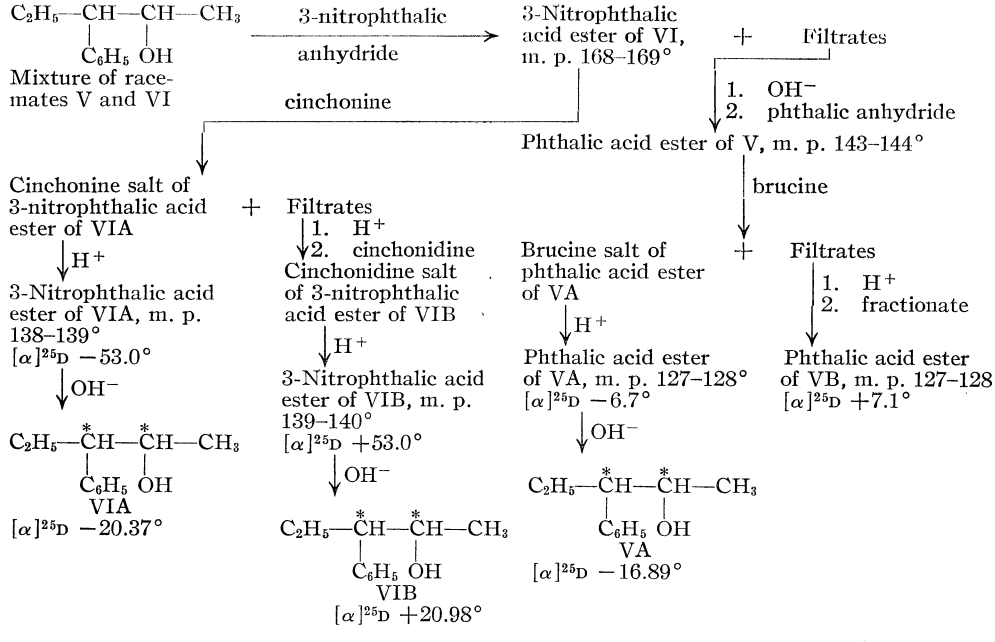
A mixture of the two racemates of 2-phenyl-3-pentanol was prepared by the treatment of 2-phenylpropionaldehyde[2] with ethylmagnesium bromide. The method used for the resolution is outlined below.



(1) Present address: Medical School, University of California, Los Angeles 24, California.

(2) This compound was prepared by the method that Dutta [*J. Indian Chem. Soc.*, **18**, 233 (1941)] used for the preparation of 2-*p*-tolylpropionaldehyde. Claisen [*Ber.*, **38**, 705 (1905)] prepared 2-phenylpropionaldehyde previously by a different method.

The compound 2-phenylbutyraldehyde[3] was prepared by a method analogous to that used for the preparation of 2-phenylpropionaldehyde.[2] The former substance was treated with methylmagnesium bromide to give a mixture of the two racemates of 3-phenyl-2-pentanol. Resolution of this mixture was affected by the following method.



The magnitude of the rotations and the melting points of the enantiomorphically related substances in the two series are in agreement, which indicates that optical purity was obtained in each case. The acid phthalates of IIIA and IIIB were never obtained in a crystalline condition, and therefore the 3,5-dinitrobenzoate derivative was prepared for identification purposes.

Table I records the physical properties and the yields of the above compounds.

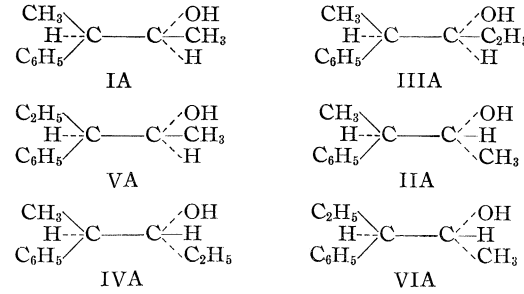
Discussion

The analogy between the methods used for the resolution of 3-phenyl-2-butanol[4] and the resolutions of 2-phenyl-3-pentanol and 3-phenyl-2-pentanol is so clear cut as to provide a clue to the relative configuration of the isomers of the two latter compounds. In all three cases the two racemates were split through the preparation of the acid phthalate and 3-nitrophthalic acid ester derivatives. In each case the latter derivative was obtained in greater quantity. The racemic mixtures of the acid phthalates of I, III and V were each resolved through the brucine salt, giving in each case a crystalline salt of only one of the enantiomorphs. The racemic mixtures of the 3-nitrophthalic acid esters of II, IV and VI were each resolved through the cinchonidine salts, and in each case one of the enantiomorphic pair formed a crystalline cinchonidine salt, and in two of the three cases the other member of the enantiomorphic pair formed a crystalline cinchonine salt.[5]

A comparison of the melting points of the derivatives of the above alcohols also points to analogous configurational relationships along the lines suggested above. Thus the acid phthalates of racemates I, III and V melt at 130–131°, 133–134°, 143–144°, and the 3-nitrophthalic acid esters of racemates II, IV and VI melt at 156–157°, 153–154° and 168–169°, respectively.

Finally, comparisons of the specific rotations of the stereoisomers themselves strengthen the analogy. Thus the specific rotation of IA is more positive than that of IIA, IIIA more positive than IVA, and VA is more positive than VIA.

The above argument provides a basis for the following assignments of relative configurations for the stereoisomers of 3-phenyl-2-butanol, 2-phenyl-3-pentanol and 3-phenyl-2-pentanol. Since



(3) This substance has been reported by Stoermer, *Ber.*, **39**, 2300 (1906).

(4) See paper I in this series.

(5) Attempts to form crystalline brucine salts of the acid phthalates of IB, IIIB and VB failed; attempts to form crystalline cinchonine salts of the 3-nitrophthalic acid esters of IIB and VIB failed; attempts to form crystalline cinchonidine salts of IIA and VIA failed. Crystalline cinchonine salts of IVA and IVB and crystalline cinchonidine salts of IVA and IVB were obtained.

TABLE I

PHYSICAL DATA PERTAINING TO THE STEREOISOMERS OF 2-PHENYL-3-PENTANOL, 3-PHENYL-2-PENTANOL AND DERIVATIVES

Compound alcohols	B. p., °C.	Mm.	$[\alpha]^{25}D$ Pure liq.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Yields, %
III[a]	127	23	.....	$C_{11}H_{16}O$	80.44	9.82	80.49	10.00	93
IV[b]	128	26	.....	$C_{11}H_{16}O$	80.44	9.82	80.23	9.97	94
V[c]	125	22	.....	$C_{11}H_{16}O$	80.44	9.82	80.09	9.94	94
VI[d]	128	25	.....	$C_{11}H_{16}O$	80.44	9.82	80.42	10.00	95
IIIA	125	23	+12.40	$C_{11}H_{16}O$	80.44	9.82	80.07	9.99	32[e]
IVA	123	18	− 7.32	$C_{11}H_{16}O$	80.44	9.82	80.14	10.01	90
IVB	123	18	+ 7.34	$C_{11}H_{16}O$	80.44	9.82	80.31	10.10	93
VA	120	17	−16.89	$C_{11}H_{16}O$	80.44	9.82	80.53	9.94	96
VIA	121	17	−20.37	$C_{11}H_{16}O$	80.44	9.82	80.65	9.91	96
VIB	121	17	+20.98	$C_{11}H_{16}O$	80.44	9.82	80.08	9.98	93
Acid phthalates	**M. p., °C.**		**$[\alpha]^{25}D$ ($c \cong 3\%$ in ethanol)**						
III[f]	133–134		.....	$C_{19}H_{20}O$	73.06	6.45	72.83	6.79	14
V[g]	143–144		.....	$C_{19}H_{20}O$	73.06	6.45	73.06	6.74	18
VA[g]	127–128		− 6.7	$C_{19}H_{20}O$	73.06	6.45	72.90	6.76	36
VB[g]	127–128		+ 7.1	$C_{19}H_{20}O$	73.06	6.45	73.09	6.62	15
3-Nitrophthalic acid esters									
IV[g]	153–154		.....	$C_{19}H_{19}NO_6$	63.85	5.36	63.67	5.48	36
VI[h]	168–169		.....	$C_{19}H_{19}NO_6$	63.85	5.36	63.86	5.53	42
IVA[h]	128–129		−65.0	$C_{19}H_{19}NO_6$	63.85	5.36	64.02	5.26	14
IVB[h]	128–129		+66.1	$C_{19}H_{19}NO_6$	63.85	5.36	63.64	5.39	32
VIA[h]	138–139		−53.0	$C_{19}H_{19}NO_6$	63.85	5.36	63.88	5.53	43
VIB[h]	139–140		+53.0	$C_{19}H_{19}NO_6$	63.85	5.36	63.76	5.47	36
3,5-Dinitrobenzoates									
III[h]	83–84		.....	$C_{18}H_{18}N_2O_6$	60.33	5.06	60.20	4.90	91
IIIA[h]	85–86		+58.5[i]	$C_{18}H_{18}N_2O_6$	60.33	5.06	60.58	5.22	93
IIIB[h]	84–85		−57.0[i]	$C_{18}H_{18}N_2O_6$	60.33	5.06	60.33	5.39	0.3[e]

[a] $n^{25}D$ 1.5113. [b] $n^{25}D$ 1.5121. [c] $n^{25}D$ 1.5097. [d] $n^{25}D$ 1.5106. [e] This yield is based on the acid phthalate of racemic III. [f] Irregular flat needles. [g] Irregular prisms. [h] Fine needles. [i] Rotations taken chloroform ($c \cong 3\%$).

the structures of IA and IIA were determined in the first paper of this series, the following assignments can be made. The respective enantiomorphic relationships of the above compounds to IB, IIB, IIIB, IVB, VB and VIB determines the structures of the B series.[6]

The above configurational assignments are consistent with further evidence that is presented in papers III and IV in this series.

Experimental

Preparation and Separation of the Racemates of 2-Phenyl-3-pentanol.—A mixture of 126 g. of 2-phenylpropionaldehyde[7] and 500 ml. of dry ether was added over a period of an hour to a cooled stirred solution of ethylmagnesium bromide (made from 24.1 g. of magnesium and 110 g. of ethyl bromide) dissolved in 1000 ml. of dry ether. After warming the mixture for one hour, the flask was cooled and the product decomposed by pouring into a mixture of ice and excess 2 *N* sulfuric acid. The two layers that resulted were separated, the organic layer washed with water, dried, and the product distilled to give 130 g. of alcohol, b. p. 123–125° at 18 mm. pressure.

A mixture of this alcohol (130 g.), 155 g. of 3-nitrophthalic anhydride and 150 g. of pyridine was heated at 100° for one hour, cooled and shaken with a mixture of excess of 2 *N* sulfuric acid and benzene. The layers were separated and the organic layer was washed with water, dried, evaporated to an oil, and this oil was crystallized from a mixture of three volumes of ethyl acetate and enough low-boiling petroleum ether to make the solution turbid. The crystalline product that separated was recrystallized from ethyl acetate and petroleum ether to give 68 g. of 3-nitrophthalic acid ester of racemate IV, m. p. 153–154° (fine needles).

The combined filtrates were evaporated and hydrolyzed by heating at reflux with a solution of 102 g. of potassium hydroxide in 500 ml. of water for fifteen hours. At the end of this time the mixture was cooled, extracted with petroleum ether, and the organic layer was washed with water, dried, evaporated and the resulting oil distilled, 75 g.

This alcohol (70 g.) was heated at 100° with a mixture of 64 g. of phthalic anhydride and 75 g. of pyridine for one hour. This mixture was then cooled, shaken with a mixture of excess 2 *N* sulfuric acid and benzene, the layers separated and the organic layer washed with water, dried, and evaporated to an oil. This oil was crystallized from two volumes of ethyl acetate and enough petroleum ether to make the solution slightly turbid. The solid that deposited was recrystallized from ethyl acetate and petroleum ether to give 24.7 g. of the acid phthalate of racemate III, m. p. 133–134° (wedge-shaped needles).

The filtrates from the above crystallizations were combined and put through the same cycle as that described above to give 33 g. of additional 3-nitrophthalic acid ester of racemate II, m. p. 153–154°, and 10.5 g. of additional

(6) This type of nomenclature has been adopted until the configuration of one of the two asymmetric carbon atoms of one of these isomers has been related to *d*-glyceraldehyde.

(7) This aldehyde[2] was prepared by the same procedure described further on for the preparation of 2-phenylbutyraldehyde.

phthalic acid ester of racemate I, m. p. 133–134°. A total of 19 g. of unresolved 2-phenyl-3-pentanol was recovered from these operations.

Preparation of 2-Phenylbutyraldehyde.[2]—A mixture of 87.2 g. of sodium and 872 ml. of absolute ethanol was refluxed until the sodium disappeared. The solution was cooled and 872 ml. of dry low-boiling petroleum ether was added and the mixture cooled in an ice-bath. To this mixture was added a cooled solution of 410 g. of ethyl chloroacetate and 448 g. of propiophenone, the resulting mixture was stirred to break up all the lumps and then allowed to stand for twenty hours in an ice-bath. At the end of this time the dark solution was brought to reflux and the petroleum ether allowed to gradually escape through the partial condenser over a period of eight hours (this material was collected through the use of a second condenser). The contents of the flask were diluted with sufficient water, ice and ethyl ether to produce two layers which were separated; the water layer was extracted with ether and discarded. The two organic solutions were combined, washed five times with a 1 *N* sodium hydroxide solution, three times with water, dried, and evaporated to an oil which was distilled under reduced pressure. The first fraction, 203.6 g., distilled at about 90° (8 mm.), and the product (a glycidic ester) was collected at 127–133° (5 mm.), weight 314.5 g.

This material was added to a solution of 34.4 g. of sodium which had been decomposed in 560 ml. of 95% ethanol. The mixture formed a red homogeneous solution which was allowed to stand about twenty hours. A white solid formed at first but dissolved when more water was added. This solution was acidified with 330 ml. of 6 *N* hydrochloric acid at a temperature below 10°, and the oil that separated was extracted with ether. The extract was dried, the ether evaporated, and the resulting oil was added to a mixture of 1300 ml. of 6 *N* sulfuric acid and 1300 g. of ice. After standing overnight the mixture was steam distilled until about 2 l. of distillate was obtained. The oily aldehyde was extracted with ether, the resulting solution was washed twice with 3 *N* sodium carbonate solution and twice with water, dried, evaporated to an oil which was distilled to give 165.5 g. of 2-phenylbutyraldehyde, b. p. 97–99° (15 mm.).

Preparation and Separation of the Racemates of 3-Phenyl-2-pentanol.—To a Grignard solution prepared from 30 g. of magnesium, 177 g. of methyl iodide and 500 ml. of ether was added slowly 165.5 g. of 2-phenylbutyraldehyde. The mixture was then refluxed for an hour, cooled, and decomposed on a mixture of ice and excess 2 *N* sulfuric acid. The oil that separated was extracted with ether, the extract was washed with water, dried and evaporated to an oil and distilled to give 142 g. of 3-phenyl-2-pentanol, b. p. 128–131° (30 mm.).

A mixture of 142 g. of this carbinol, 168 g. of 3-nitrophthalic anhydride and 190 g. of dry pyridine was warmed to 100° for one hour, cooled and shaken in a mixture of benzene and excess 2 *N* sulfuric acid. The organic layer was washed first with 2 *N* sulfuric acid, then with water, dried and the benzene was evaporated. The oil crystallized from a mixture of ethyl acetate and petroleum ether and recrystallization of the product from the same solvents gave 96 g. of fine white needles (m. p. 167–168°) of the 3-nitrophthalic acid ester of VI.

The filtrates were combined, the solvent evaporated and the oil held at reflux for twelve hours in a mixture of 40 g. of sodium hydroxide, 40 g. of potassium hydroxide and 400 ml. of water. The resulting mixture was cooled, extracted with petroleum ether and the extract was washed with water, dried, evaporated and the oil distilled to give 70 g. of alcohol. This material was heated to 100° for one hour with 63 g. of phthalic anhydride and 85 ml. of pyridine, cooled, and shaken with a mixture of benzene and excess *N* sulfuric acid. The organic layer was washed, first with 2 *N* sulfuric acid, then with water, the solution was dried, evaporated and the oil crystallized from ethyl acetate and petroleum ether. Recrystallization of the product from the same solvents produced 39 g. of the phthalic acid ester of V, m. p. 143–144° (heavy prisms).

A second cycle similar to that described above produced 33 additional grams of 3-nitrophthalic acid ester of VI, m. p. 167–168°, and 9 additional grams of the phthalic acid ester of V, m. p. 143–144°. A total of 12.5 g. of unresolved alcohol was recovered.

Resolution of the Phthalic Acid Ester of III.—A solution of 13.5 g. of the racemic ester and 10 g. of strychnine in 100 ml. of acetone was brought to boiling and slowly cooled. The solid that separated was collected and shaken with a mixture of ether and excess 2 *N* hydrochloric acid. The organic layer was washed with water, dried, evaporated and the resulting oil was mixed with 7 g. of brucine and 50 ml. of acetone. The material that separated was collected and recrystallized from acetone to give 7.0 g. of salt. The combined filtrates from all the above crystallizations were concentrated and shaken with ether and 2 *N* hydrochloric acid. The organic layer was washed with water, dried, evaporated and crystallized from ethyl acetate and petroleum ether to give 5 g. of racemic starting material. This material was put through the same cycle of operations and an additional 4 g. of recrystallized brucine salt obtained. The combined 11 g. of brucine salt was shaken with excess 2 *N* sulfuric acid and ether, the organic layer washed with water, dried and evaporated to an oil. This oil (4.5 g.) could not be crystallized and was hydrolyzed directly to IIIA by heating at reflux for twelve hours with 3.5 g. of sodium hydroxide and 20 ml. of water. The resulting oil was extracted with petroleum ether, the organic layer was washed with water, dried, evaporated and distilled to give 2.27 g. of IIIA, b. p. 125° (23 mm.).

A small sample of this alcohol was converted to the 3,5-dinitrobenzoate in the usual manner, m. p. 85–86° (needles from ether and petroleum ether).

The combined filtrates from the crystallizations of the brucine salt were concentrated and converted to the acid phthalate of impure IIIB. Crystallization of this oil from ethyl acetate and petroleum ether produced 2.0 g. of the acid phthalate of racemic III. The filtrate from this crystallization was hydrolyzed in the usual manner and the alcohol converted to the 3,5-dinitrobenzoate. Five crystallizations of this material from an ether–petroleum ether mixture produced 400 mg. of the 3,5-dinitrobenzoate of IIIB, m. p. 84–85° (needles from an ether–petroleum ether mixture).

Resolution of the 3-Nitrophthalic Acid Ester of IV.—A mixture of 50 g. of the 3-nitrophthalic acid ester of IV, 41 g. of cinchonidine and 400 ml. of 95% ethanol was heated to reflux temperature and slowly cooled. The material that separated was recrystallized twice from 95% ethanol to give 18 g. of salt which was converted to the 3-nitrophthalic acid ester of IVB by the usual method; weight 8.5 g., m. p. 128–129°, rosettes from ethyl acetate and petroleum ether.[8]

The combined filtrates were concentrated and converted to the 3-nitrophthalic acid ester which crystallized slowly from ethyl acetate and petroleum ether when seeded with racemic 3-nitrophthalic acid ester of IV. A first crop was harvested when about half of the material had crystallized, weight 26 g. (racemic material). This substance was put through the same resolution cycle and an additional 7.5 g. of 3-nitrophthalic acid ester of IVB was obtained, m. p. 128–129°.

The combined filtrates were concentrated and converted to the acid ester and this material was submitted to fractional crystallization (four cycles) from ethyl acetate and petroleum ether, in each case the derivative of IVA crystallizing last. A total of 7.2 g. of the 3-nitrophthalic acid ester of IVA was obtained, m. p. 128–129° (rosettes)[8] from ethyl acetate and petroleum ether.

Resolution of the Phthalic Acid Ester of V.—A mixture of 30 g. of the phthalic acid ester of V, 25 g. of brucine and 200 ml. of acetone was brought to boiling and cooled slowly. The plates that separated were collected and recrystallized from acetone and the 23 g. obtained was con-

(8) This substance crystallizes in two different forms, needles, which if heated rapidly partially melt at 117°, resolidify and melt at 128–129°, and rosettes, m. p. 128–129°.

verted to the phthalic acid ester of VA; weight 9.2 g., m. p. 127–128° (flakes from ethyl acetate and petroleum ether). The filtrates were combined, concentrated and converted to the acid ester which was allowed to crystallize from ethyl acetate and petroleum ether until about half of the material had appeared. This substance was collected (weight 5 g.) and submitted to the resolution procedure described above to give 1.5 additional grams of acid phthalate of VA.

The combined filtrates were concentrated and converted to the free acid ester which was submitted to a four-cycle fractional crystallization procedure with ethyl acetate and petroleum ether as solvent. In each case the material that first crystallized was rich in racemate. A total of 4.5 g. of the phthalic acid ester of VB was obtained, m. p. 127–128° (flakes).

Resolution of the 3-Nitrophthalic Acid Ester of VI.—A mixture of 100 g. of the 3-nitrophthalic acid ester of VI, 65 g. of cinchonine and 500 ml. of acetone was heated to the boiling point and slowly cooled. The needles that separated were collected and twice recrystallized from a mixture of chloroform and acetone. The salt (55 g.) was converted to the 3-nitrophthalic acid ester of VIA; weight 30 g., m. p. 138–139° (needles from ethyl ether and petroleum ether).

The filtrates were combined, concentrated and converted to the acid ester which was mixed with 50 g. of cinchonidine and 300 ml. of acetone. The needles that separated were recrystallized twice from acetone to give 25 g. of salt which was converted to 13 g. of white needles (from ether and petroleum ether) of the 3-nitrophthalic acid ester of VIB, m. p. 139–140°.

The filtrates were combined, concentrated and converted to the acid ester which was subjected to the resolution procedure described above to produce 9 additional grams of the 3-nitrophthalic acid ester of VIA (m. p. 139–140°) and 13 additional grams of the 3-nitrophthalic acid ester of VIB, m. p. 139–140°.

Hydrolysis of the Phthalic Acid Esters of III, V and VA to III, V and VA, Respectively, and the 3-Nitrophthalic Acid Esters of IV, VI, IVA, IVB, VIA, and VIB to IV, VI, IVA, IVB, VIA and VIB, Respectively.—The procedure used for the above introconversions is illustrated by the hydrolysis of the 3-nitrophthalic acid ester of VIA to VIA alcohol. A mixture of 36 g. of the ester, 10 g. of potassium hydroxide, 10 g. of sodium hydroxide and 100 ml. of water was heated at reflux for twelve hours. The mixture was then cooled, extracted twice with petroleum ether, the extracts combined and washed with water, dried and evaporated to an oil. This oil was distilled to give 15.6 g. of VIA, b. p. 121° (17 mm.).

Acknowledgment.—The author wishes to express his thanks to Welton Burney, who performed the analysis of the compounds reported in this paper.

Summary

1. The compounds 2-phenyl-3-pentanol and 3-phenyl-2-pentanol have been prepared and completely resolved into the eight optically pure stereoisomers.

2. Tentative stereochemical structures have been assigned to each isomer.

LOS ANGELES, CALIFORNIA RECEIVED MARCH 14, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in Stereochemistry. III. The Wagner–Meerwein Rearrangement in the 2-Phenyl-3-pentanol and 3-Phenyl-2-pentanol Systems[1]

BY DONALD J. CRAM

Paper II[2] of this series reported the primary resolutions of 2-phenyl-3-pentanol into racemates III[3] and IV followed by the secondary resolution of each of these racemates into IIIA, IIIB and IVA and IVB, respectively. The structural isomer, 3-phenyl-2-pentanol, was also resolved to give racemates V and VI, and subsequently VA, VB and VIA and VIB, respectively. Tentative assignments of configuration for each of these isomers were suggested. This paper reports the results of an investigation of the acetolyses of the *p*-toluenesulfonates of III, IV, V, VI, IIIA, IVA, VA and VIA.

Results

Table I records the physical properties, analyses and yields of the *p*-toluenesulfonates of III, IV, V, VI, IIIA, IVA, IVB, VA, VIA and VIB. In each case the acetolysis of these substances was conducted at 70° and for thirty hours in anhydrous glacial acetic acid containing enough potassium acetate to neutralize the *p*-toluenesulfonic acid as it formed. The mixtures of acetate products were hydrolyzed to the corresponding mix-

TABLE I

PHYSICAL AND ANALYTICAL DATA PERTAINING TO THE *p*-TOLUENESULFONATES OF THE ISOMERS OF 2-PHENYL-3-PENTANOL AND 3-PHENYL-2-PENTANOL

Isomer	M. p., °C.	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
III	90–91[a]	67	$C_{18}H_{22}SO_3$	67.89	6.97	67.82	7.17
IV	67–68	68	$C_{18}H_{22}SO_3$	67.89	6.97	67.73	7.18
V	40–41	63	$C_{18}H_{22}SO_3$	67.89	6.97	67.98	7.18
VI	Oil[b]	45	$C_{18}H_{22}SO_3$	67.89	6.97	68.02	7.22
IIIA	100–101	71	$C_{18}H_{22}SO_3$	67.89	6.97	67.92	7.18
IVA	86–87	66	$C_{18}H_{22}SO_3$	67.89	6.97	68.12	7.06
IVB	86–87	75	$C_{18}H_{22}SO_3$	67.89	6.97	67.82	7.17
VA	71–72	85	$C_{18}H_{22}SO_3$	67.89	6.97	67.75	6.78
VIA	41–42	69	$C_{18}H_{22}SO_3$	67.89	6.97	67.86	7.18
VIB	41–42	68	$C_{18}H_{22}SO_3$	67.89	6.97	67.76	7.25

[a] All of the compounds except VI crystallized as needles from low-boiling petroleum ether. [b] This compound was never obtained in a crystalline state. Purification was accomplished through repeated precipitation of the substance from low-boiling petroleum ether at Dry Ice temperature followed by high vacuum drying of the oil at room temperature.

(1) This paper was presented in part before the Organic Division of the American Chemical Society, San Francisco Meeting, March, 1949.

(2) Cram, THIS JOURNAL, **71**, 3871 (1949).

(3) The numbering system has been maintained from paper to paper in this investigation.

TABLE II

DATA ON ACETOLYSIS OF *p*-TOLUENESULFONATES OF THE RACEMATES OF 2-PHENYL-3-PENTANOL AND 3-PHENYL-2-PENTANOL

p-Toluenesulfonate	Yield,[a] of olefin, %	Solid deriv. product	M. p., °C. solid deriv.	Yield[a] solid deriv., %	Composition of known mixt.	M. p., °C. known mixt.	M. m. p. known mixt. and solid derivative, °C.
III	31	P. A. E.[b]	129–131[c]	30	32% P. A. E.[b] III 68% P. A. E.[b] V	129–131	129–131
V	29	P. A. E.[b]	128–130	33	33% P. A. E.[b] III 67% P. A. E.[b] V	128–130	128–130
IV	14	N. P. A. E.[d]	147–149[e]	34	31% N. P. A. E.[d] IV 69% N. P. A. E.[d] VI	147–149	147–149
VI	11	N. P. A. E.[d]	148–150	36	29% N. P. A. E.[d] IV 71% N. P. A. E.[d] VI	148–150	148–150

[a] This yield is based on the *p*-toluenesulfonate of the respective alcohol. [b] P. A. E. stands for phthalic acid ester. [c] A mixed melting point determination of this substance with the phthalic acid ester obtained from the acetolysis of the *p*-toluenesulfonate of V produced no depression. [d] N. P. A. E. stands for 3-nitrophthalic acid ester. [e] A mixed melting point determination of this substance with the 3-nitrophthalic acid ester obtained from the acetolysis of the *p*-toluenesulfonate of VI produced no depression.

tures of alcohols which were converted to mixtures of solid derivatives.

Table II records the yields and compositions of the products of the acetolysis experiments performed on the racemic *p*-toluenesulfonates of III, V, IV and VI. The products were identified in the first two experiments (III and V) by conversion to the phthalic acid ester mixtures, which melted at 129–131° and 128–130°, respectively (mixed melting point, 128–130°). Figure 1 records the plot of composition against melting point of known mixtures of phthalic acid esters of III and V, and mixed melting point determinations of the unknown and known mixtures served to identify the unknown mixture from both a qualitative and quantitative point of view.

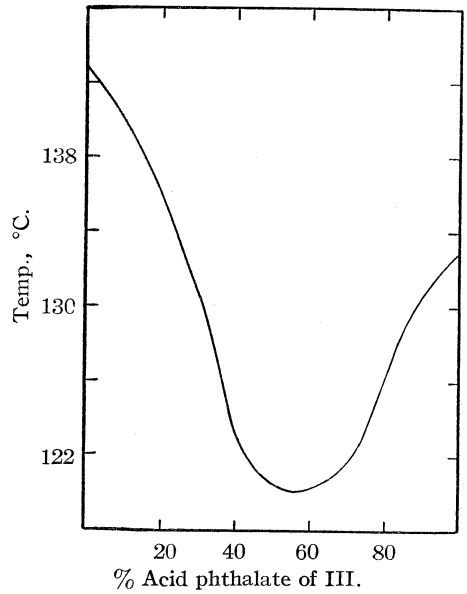


Fig. 1.—Melting point–composition diagram of the acid phthalates of III and V.

The products of the acetolysis experiments performed on the racemic *p*-toluenesulfonates of IV and VI were converted to mixtures of 3-nitrophthalic acid esters which melted at 147–149° and 148–150°, respectively (mixed melting point, 148–150°). Figure 2 records the plot of composition against melting point of known mixtures of the 3-nitrophthalic acid esters of IV and VI, and mixed melting point determinations of the unknown mixtures served to identify both quantitatively and qualitatively the compositions of the unknowns.

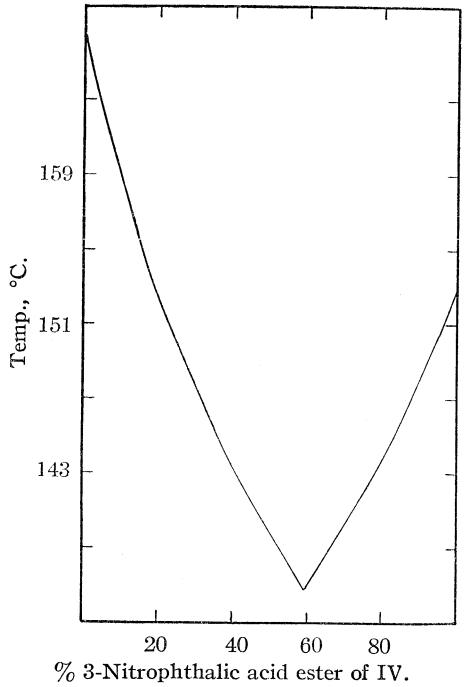
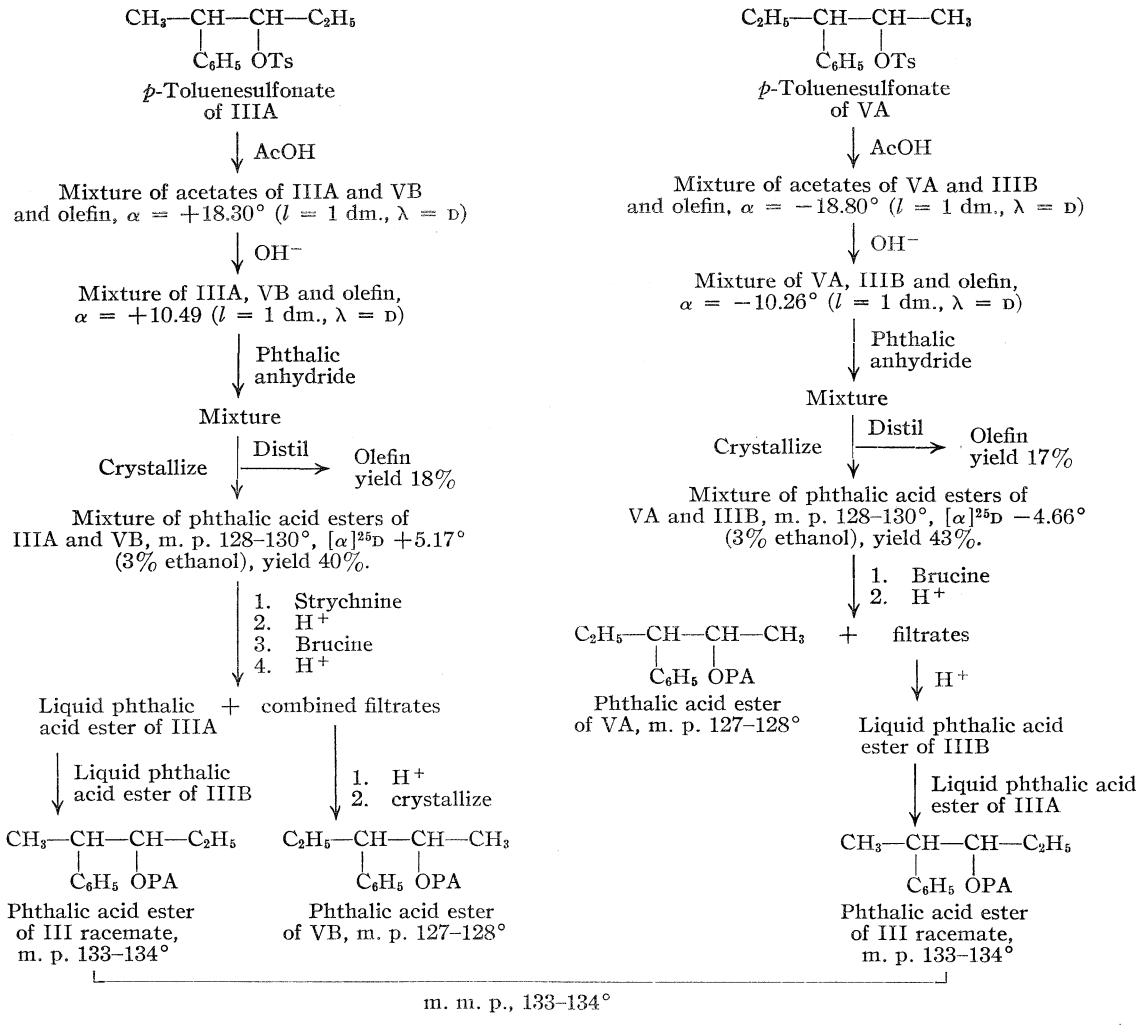


Fig. 2.—Melting point–composition diagram of the 3-nitrophthalic acid esters of IV and VI.

The methods employed for the determination of the products of the acetolysis experiments performed on the *p*-toluenesulfonates of IIIA and VA are outlined below. Special isolation procedures had to be used to demonstrate the qualitative composition of the products of each reaction, because the phthalic acid esters of IIIA and IIIB are liquids and hence a melting point–composition plot of mixtures of this derivative of IIIA and VB on the one hand and VA and IIIB on the other was impossible.



The procedure used for the determination of the compositions of the products of the acetolysis experiments performed on the *p*-toluenesulfonates of IVA and VIA is outlined in the following scheme. Figure 3 plots the variation of melting point with composition of mixtures of the 3-nitrophthalic acid esters of IVA and VIA. The qualitative and quantitative determinations of the compositions of the unknown mixtures were made through the use of mixed melting point determinations between the known and unknown mixtures.

For purposes of relating the configurations of VIA to VA, the *p*-toluenesulfonate of VIA was subjected to the action of potassium acetate[4] dissolved in absolute ethyl alcohol. The product (mixture of acetate and ether) was hydrolyzed and converted to the phthalic acid ester which proved to be the ester of VA.

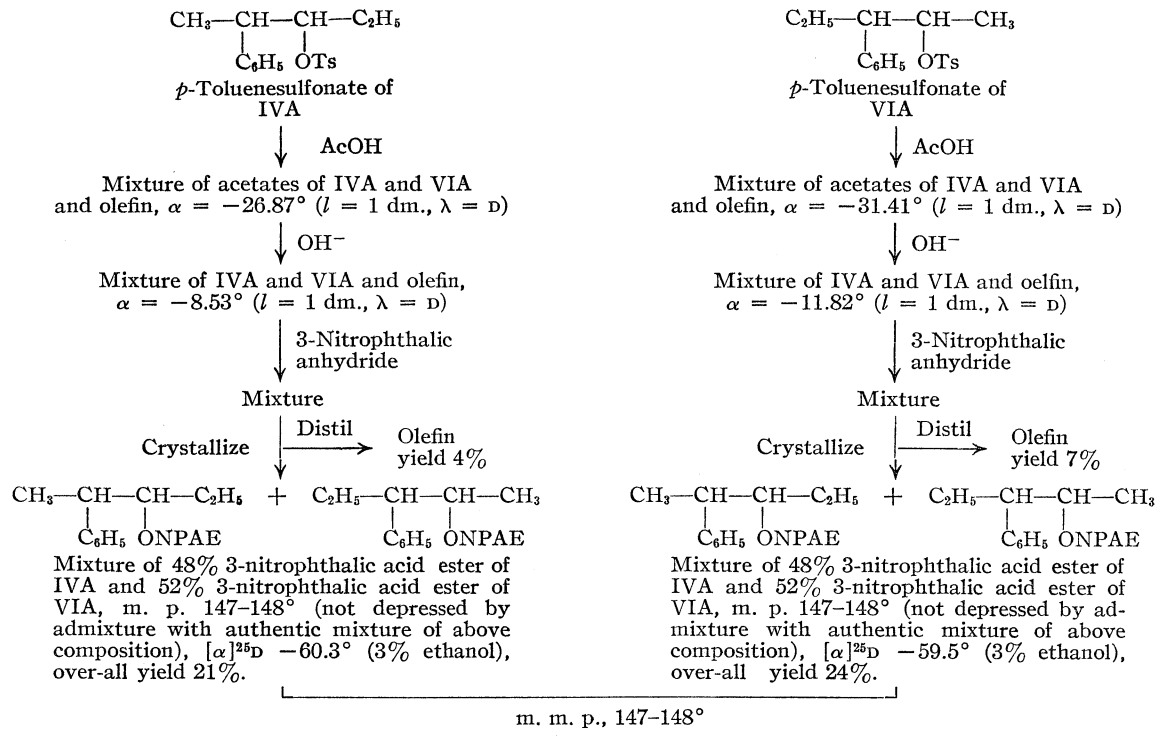
Discussion

The above results clearly indicate that a partial rearrangement of the carbon skeleton has taken place during the acetolysis of the *p*-toluenesulfonates of the isomers of 2-phenyl-3-pentanol and 3-phenyl-2-pentanol (p. 3879).

This rearrangement appears to be stereospecific, at least as far as the main products of the reaction are concerned. The material that did not rearrange underwent a displacement reaction with complete retention of configuration. Thus in each case a mixture of rearranged and unrearranged acetate was obtained. These results are in complete agreement with what would be predicted from the interpretation given to the behavior of the analogous 3-phenyl-2-butanol system reported in paper I of this series.[5] The fact that rearrangement was found in both racemate series of the 2-phenyl-3-pentanol and 3-phenyl-2-pentanol systems provides strong evidence that rearrangement also took place in *both* racemate series of the 3-phenyl-2-butanol system. The *p*-toluenesulfonate of IIA must then have given acetate of IIA by two routes, one involving rearrangement, and the other not, even though there is no way of distin-

(4) This reaction results in simple inversion of the carbon atom bearing the oxygen and is analogous to the reaction reported in paper I (THIS JOURNAL, **71**, 3863 (1949)) of this series in which the *p*-toluenesulfonate of IA was converted to the acetate of IIA.

(5) Cram, THIS JOURNAL, **71**, 3863 (1949).



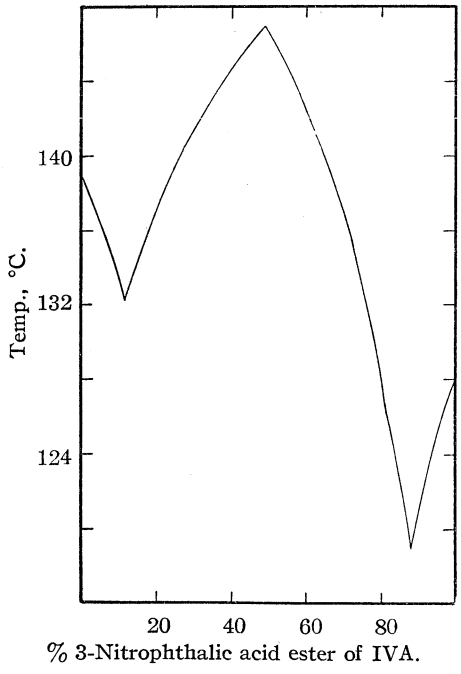
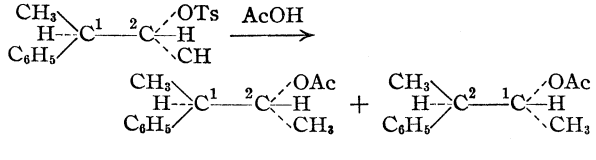


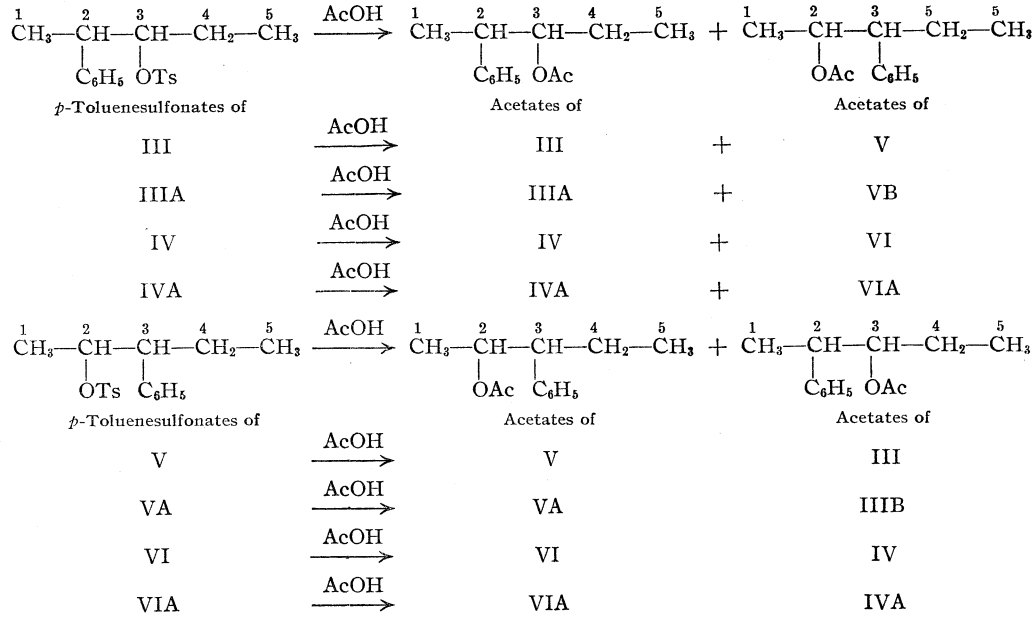
Fig. 3.—Melting point–composition diagram of the 3-nitrophthalic acid esters of IVA and VIA.

guishing between the products coming from the two paths.



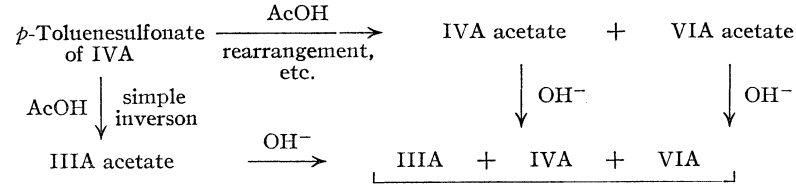
From an experimental point of view, the 3-phenyl-2-pentanol and 2-phenyl-3-pentanol systems are much more difficult to study because the products of the reactions are mixtures of two structural isomers whose properties are very similar. As a result, the products were identified as mixtures of solid derivatives, and in only two cases were the two components separated. This method of analysis served well for a qualitative determination of the isomeric products, but is indicative in only a crude way of the relative amounts of each isomer produced in the reaction. Thus from the acetolysis of the *p*-toluenesulfonates of racemates III, IV, V and VI was ultimately obtained in each case approximately a seven to three ratio of 3-phenyl-2-pentanol derivative to 2-phenyl-3-pentanol derivative. When IVA and VIA esters were employed, however, the ratio was about one to one. This discrepancy is probably due to the interesting fact that the 3-nitrophthalic acid esters of IVA and VIA form a molecular compound in a one to one ratio (see Fig. 3), and that this molecular compound is more insoluble in the crystallization solvent than the VIA component (the melting point of the molecular compound is higher than either pure component). Hence the molecular compound crystallized preferentially.

The good agreement between the relative amounts of each isomer produced (see Table II) from the reactions of the III, V, IV, and VI esters, however, was probably not fortuitous, and can safely be interpreted as meaning that the 3-phenyl-2-pentanol isomer was produced in somewhat larger quantities than was the 2-phenyl-3-pentanol isomer, regardless of which series the starting mate-

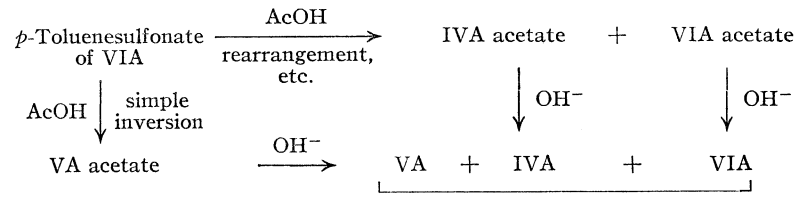


rial belonged to. The striking fact about the data is that the *p*-toluenesulfonates of the structural isomers, III and V, produced the same products in the same ratios, and that the *p*-toluenesulfonates of the structural isomers IV and VI gave analogous results. When the optically active *p*-toluenesulfonates of IIIA and VA were used, the rotations of the whole samples of the acetate products were taken and the values proved to be of almost equal magnitude but of opposite sign (+18.30 and −18.80°, respectively). This relationship of the rotations was maintained through the conversions of the acetates to the alcohols, and the subsequent conversions to the phthalic acid esters. These data are excellent evidence that in these two runs the products were qualitatively and quantitatively the same but of opposite configurations.

The data obtained for the acetolysis of the *p*-toluenesulfonates of the optically active isomers, IVA and VIA, are not as conclusive. The yields of the solid derivatives are only about half of the yields obtained in the runs involving the esters of IIIA and VA as starting materials. Undoubtedly more material was lost during the purification of the solid derivatives in the former cases due to the formation of a molecular compound between the two components. However, the poor agreement between the rotations of the impure acetate products of the IVA and VIA runs suggests that small amounts of side reactions interfered. A plausible explanation for the direction which the rotations took is to assume that a small amount of direct displacement took place with simple inversion at the carbon atom bearing the oxygen during the acetolysis of the *p*-toluenesulfonates of IVA and VIA. Thus the ester of IVA would give small amounts of acetate of IIIA and subsequently the alcohol, IIIA, and the ester of VIA would give small amounts of acetate of VA and subsequently the alcohol, VA.



mixture, $\alpha = -8.53$, $l = 1$ dm. (λ = D)
(IIIA, $[\alpha]^{25}D$ +12.40°; IVA, $[\alpha]^{25}D$ −7.32°; VIA, $[\alpha]^{25}D$ −20.37°)[6]



mixture, $\alpha = -11.82°$, $l = 1$ dm. (λ = D)
(VA), $[\alpha]^{25}D$ −16.89°; IVA, $[\alpha]^{25}D$ −7.32°; VIA, $[\alpha]^{25}D$ −20.37°)[6]

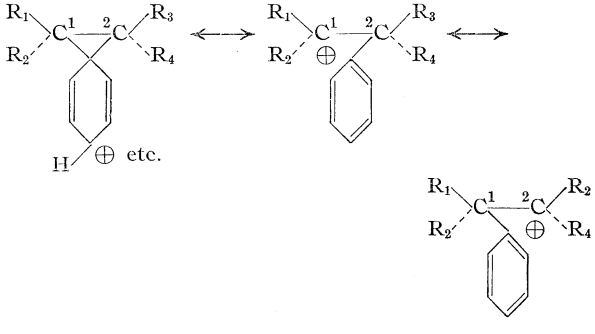
The positive rotation of IIIA would tend to cancel some of the negative rotation of the mixture of IVA and VIA, whereas the negative rotation of VA would not affect very much the negative rotation of the mixture of IVA and VIA.

The relative yields of olefin obtained from the acetolysis reactions are consistent with the con-

(6) These rotations of the pure alcohols were reported in paper II of this series (THIS JOURNAL, **71**, 3871 (1949)).

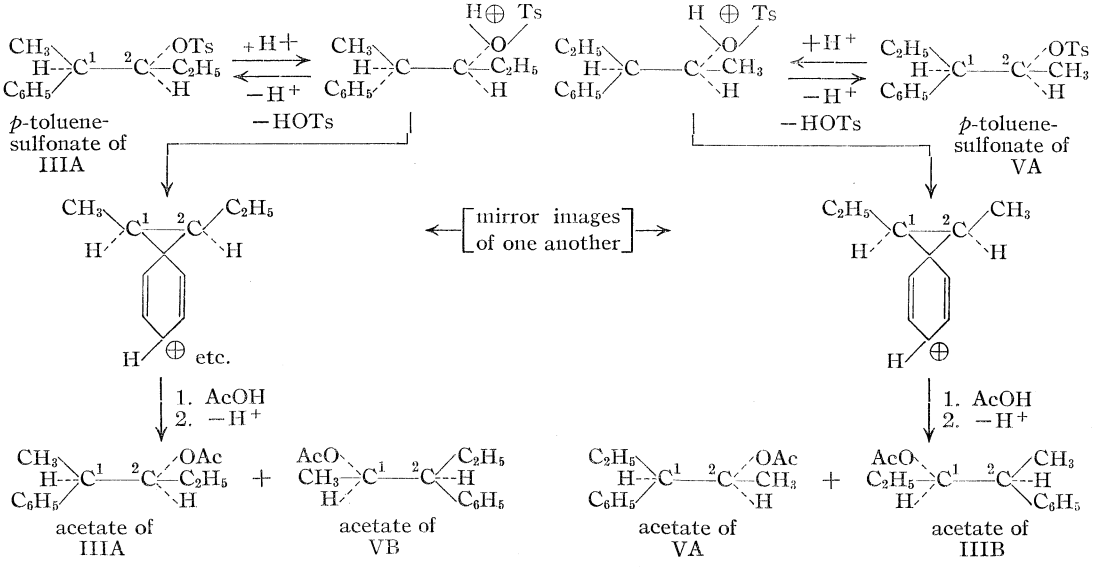
figurational assignments of III, IV, V, and VI (racemic alcohols) made in part II[2] of this series. The yield of olefin obtained from the acetolysis of the *p*-toluenesulfonate of IA (see paper I[5] of this series) was 26% as compared to a yield of 9.5% obtained from the *p*-toluenesulfonate of IIA. Since the *p*-toluenesulfonates of III and V gave yields of olefin amounting to 31 and 29%, respectively, and the *p*-toluenesulfonates of IV and VI, yields of 14 and 11%, respectively, it seems probable that the configurations of III and V are analogous to I on the one hand, and the configurations of IV and VI are analogous to II on the other. Further evidence for this analogy is found in paper IV of this series, along with definite proof that IVA possesses a configuration analogous to that of IIA.

Enough information is now at hand to rationalize the experimental results and the deductions based on these results in terms of a mechanistic interpretation of the acetolysis reaction of the *p*-toluenesulfonates of IIIA, IVA, VA and VIA. In the generalized cyclic ionic species shown, if R_1 and R_3 are methyl groups and R_2 and R_4 are hydrogens, the cycle possesses a plane of symmetry.

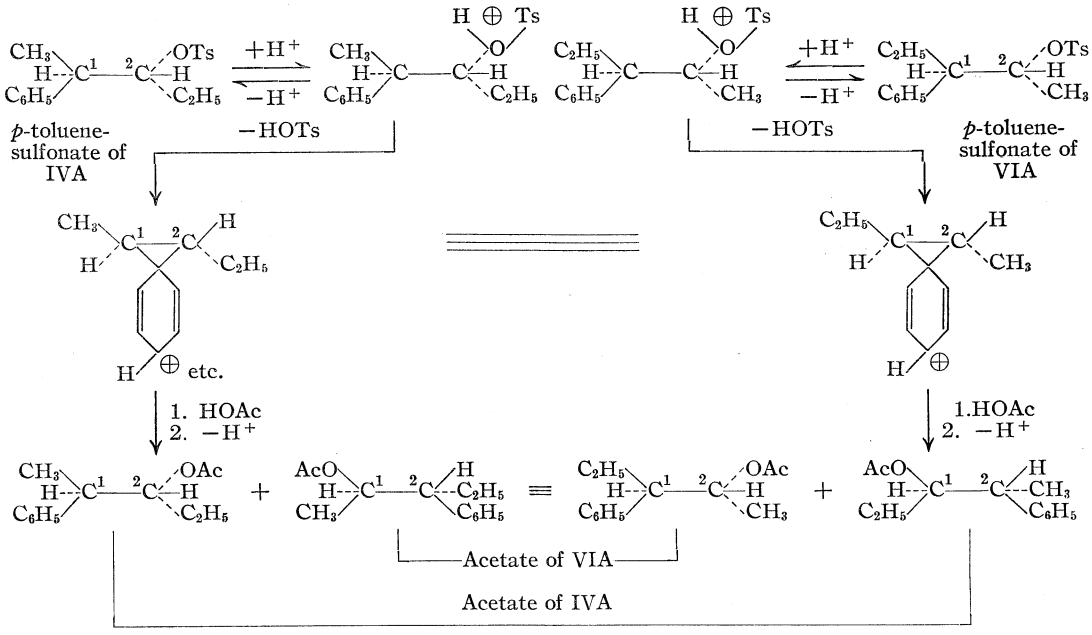


This intermediate was postulated as being formed during the acetolysis of the *p*-toluenesulfonates of either IA or IB.[5] Opening of the cycle at carbon atoms 1 or 2 (with equal probability) leads to racemic I acetate.[7] If R_1 and R_4 are methyl groups and R_2 and R_3 are hydrogens, the cycle is asymmetric, and can be formed only from the *p*-toluenesulfonate of IIA. When such a cycle is opened, the same product (acetate of IIA) is obtained whether the cycle is opened at carbon atoms 1 or 2. Such an intermediate was postulated in the acetolysis of the *p*-toluenesulfonate of IIA. If R_1 is a methyl group, R_3 an ethyl group, and R_2 and R_4 are hydrogens, the cycle is asymmetric, and would be formed from the *p*-toluenesulfonates of either IIIA or VB, these two structural isomers possessing a pseudo-enantiomorphic configurational relationship to one another. Furthermore, when the cycle is opened at carbon atom 2, acetate of IIIA would be obtained, and when the cycle is opened at carbon atom 1, acetate of VB is produced. If both reactions occur, a mixture would be obtained. The composition of the mixture would be independent of whether the starting material was one or the other isomer (IIIA or VB configuration) if no competing side reactions interfered. If R_1 is a methyl group, R_4 an ethyl group and R_2 and R_3 are hydrogens, the cycle is asymmetric, and would be formed from the *p*-toluenesulfonates of either IVA or VIA, these two structural isomers possessing an analogous configurational relationship to one another. When this cycle is opened at carbon atom 2, the acetate of IVA is obtained, and when opened at carbon atom 1, the acetate of VIA is produced. When both reactions occur, a mixture would result, the composition of which would be independent of which of the two starting materials the cycle came from.

The following scheme summarizes the argument.

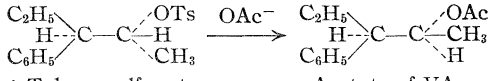


(7) The reasonable assumption has been made that inversion occurs at the carbon atom bearing the oxygen when the cycle closes, and that a second inversion occurs at the point where the cycle is opened.



The interesting fact that a small excess of 3-phenyl-2-pentanol derivative over 2-phenyl-3-pentanol derivative was obtained in each case (see Table II) independent of which racemate series was involved is explainable on the hypothesis that the cyclic intermediate ions are always asymmetric. The cycle is opened by a collision with an acetic acid molecule more often at the carbon atom bearing a methyl group than at the carbon atom bearing an ethyl group because of the slightly greater steric hindrance an ethyl group offers over that of a methyl group in the nucleophylic bimolecular displacement reaction.

The assignments of relative configurations of VA and VIA were substantiated by the inversion of the carbon bearing the oxygen bond of the *p*-toluenesulfonate of VIA by acetate ion in absolute ethanol. Although ether of undetermined configuration was the main product of the reaction, a small amount of solid derivative of VA was isolated.



p-Toluenesulfonate of VIA — Acetate of VA

Although any one experimental observation in the series of investigations reported in the first three papers of this series does not substantiate the general hypothesis of a carbocyclic ionic intermediate, the long sequence of facts become coherent only in terms of such a hypothesis. The formulation of the fundamental ideas early in the work was of great help not only in designing systems to broaden the experimental evidence but also in predicting products of reactions and thereby aiding in the experimental work. However, there has been no evidence obtained that the mechanism presented above applies to Wagner–Meerwein rearrangements in systems that are not closely similar to the one at hand. Since, in a sense, the reactions studied above amount to an aromatic substitution of an alkyl group for an alkyl group in a benzene ring, the results of this study should be relevant to the general question of the mechanism of aromatic substitution.

Experimental

Syntheses of the *p*-Toluenesulfonates of III, IV, V, VI, IIIA, IVA, IVB, VA, VIA and VIB.—The procedure used for the above syntheses is illustrated by the conversion of III to the *p*-toluenesulfonate of III. A mixture of 3.85 g. of III, 4.46 g. of pure *p*-toluenesulfonyl chloride and 10 ml. of pure dry pyridine was allowed to stand at room temperature for twenty-four hours. The mixture was then shaken with a cooled mixture of benzene and excess 2 *N* sulfuric acid, and the organic layer was washed successively with 2 *N* sulfuric acid, water, dilute alkaline solution and water. The organic layer was then dried, the solvent was evaporated under reduced pressure and at room temperature, and the resulting oil was crystallized and recrystallized from a low boiling petroleum ether and benzene mixture to give 5.0 g. of ester, m. p. 90–91° (white needles).

Acetolysis of the *p*-Toluenesulfonates of III, V, IV, VI, IVA, VIA, IIIA and VA.—The same procedure was used for the acetolyses of the *p*-toluenesulfonates of all of the above isomers. The acetates produced were hydrolyzed to the respective alcohols and solid derivatives were prepared by completely analogous methods. The following procedure is representative.

The *p*-toluenesulfonate of III (3.45 g.), 79 ml. of glacial acetic acid, 0.79 ml. of acetic anhydride and 1.5 g. of freshly fused potassium acetate was heated at 70° for thirty hours, cooled, and shaken with a mixture of petroleum ether and a large volume of water. The organic layer was separated, washed first with water, then with dilute alkaline solution and again with water. The solvent was evaporated and distilled to give 1.91 g. of mixture of acetate and olefin. This mixture was hydrolyzed by heating at reflux temperature for twenty-four hours in a mixture of 10 ml. of water and 1.91 g. of potassium hydroxide. The mixture was then cooled, extracted with

petroleum ether, the extract was washed with water, dried, evaporated and distilled. The 1.50 g. of the mixture of alcohols and olefin obtained was heated at 100° for one hour with 1.50 g. of phthalic anhydride and 2 ml. of pyridine. This mixture was cooled, shaken with a mixture of ethyl ether and excess of 2 *N* sulfuric acid, the ether layer was washed with water, dried and evaporated to an oil. This oil was crystallized from ethyl acetate and petroleum ether and recrystallized from these same solvents to produce 1.00 g. of acid phthalate, m. p. 129–131°, m. m. p. with a mixture of 32% acid phthalate of III and 68% acid phthalate of V (m. p. 129–132°), 129–132°, m. m. p. with an equal weight of the acid phthalate of III, 121–127°, m. m. p. with an equal weight of the acid phthalate of V, 137–142°.

The combined filtrates were evaporated to an oil and this oil was subjected to distillation under 18 mm. of pressure to give 0.50 g. of olefin.

When the *p*-toluenesulfonate of V (6.8 g.) was subjected to the above procedures, 3.8 g. of a mixture of acetate and olefin was obtained which was converted to 3.0 g. of a mixture of olefin and alcohol. Conversion of the mixture to the acid phthalate gave 2.22 g. of a recrystallized mixture of acid esters, m. p. 128–130°, m. m. p. with a mixture of 33% acid phthalate of III and 67% acid phthalate of V (m. p. 128–130°), 128–130°, m. m. p. with an equal weight of the acid phthalate of III, 121–126°, m. m. p. with an equal weight of acid phthalate of V, 136–141°. Olefin (0.90 g.) was recovered from the filtrates.

Acetolysis of the *p*-toluenesulfonate of IV (3.71 g.) produced 2.0 g. of a mixture of acetate and olefin which on hydrolysis gave 1.55 g. of a mixture of alcohol and olefin. Treatment of this mixture with 3-nitrophthalic acid ester produced 1.40 g. of a recrystallized mixture of acid esters, m. p. 147–149°, m. m. p. with a mixture of 31% 3-nitrophthalic acid ester of IV and 69% 3-nitrophthalic acid ester of VI (m. p. 147–149°) 147–149°, m. m. p. with an equal weight of the 3-nitrophthalic acid ester of IV, 139–145°, m. m. p. with an equal weight of the 3-nitrophthalic acid ester of VI, 152–161°. A total of 0.24 g. of olefin was recovered from the filtrates.

Acetolysis of the *p*-toluenesulfonate of VI (3.90 g.) produced 2.45 g. of a mixture of acetates and olefin which upon hydrolysis gave 1.75 g. of a mixture of alcohols and olefin. Conversion of the mixture of the 3-nitrophthalic acid ester produced 1.55 g. of recrystallized material, m. p. 148–150°, m. m. p. with a mixture of 29% 3-nitrophthalic acid ester of IV and 71% of the same derivative of VI (m. p. 148–150°), 148–150°, m. m. p. with an equal weight of the 3-nitrophthalic acid ester of IV, 139–146°, m. m. p. with an equal weight of the same derivative of VI, 154–163°. A total of 0.20 g. of olefin was obtained from the filtrates.

When the *p*-toluenesulfonate of IVA (2.4 g.) was subjected to acetolysis, 1.32 g. of a mixture of acetate and olefin was obtained, $\alpha = -26.87°$ ($l = 1$ dm.) and hydrolysis of the mixture produced 0.88 g. of a mixture of olefin and alcohol, $\alpha = -8.53°$ ($l = 1$ dm.). Conversion of this material to the 3-nitrophthalic acid ester produced 0.58 g. of recrystallized product, m. p. 147–148°, $[\alpha]^{25}D$ −60.3° (3% in ethanol), m. m. p. with a mixture of 48% of the 3-nitrophthalic acid ester of IVA and 52% of the 3-nitrophthalic acid ester of VIA (m. p. 147–148°), 147–148°, m. m. p. with an equal weight of IVA, 134–141°, m. m. p. with an equal weight of VIA, 138–142°. From the filtrates was isolated 0.05 g. of olefin.

Acetolysis of the *p*-toluenesulfonate of VIA (5.0 g.) produced 2.90 g. of a mixture of alcohol and olefin, $\alpha = -31.41°$ ($l = 1$ dm.), which when hydrolyzed gave 2.20 g. of a mixture of alcohol and olefin, $\alpha = -11.82°$ ($l = 1$ dm.). This material was converted to the 3-nitrophthalic acid ester derivative to give 1.33 g. of recrystallized material, m. p. 147–148°, $[\alpha]^{25}D$ −59.5° (3% in ethanol), m. m. p. with a mixture of 48% 3-nitrophthalic acid ester of IVA and 52% 3-nitrophthalic acid ester of VIA (m. p. 147–148°), 147–148°, m. m. p. with an equal weight of 3-nitrophthalic acid ester, of IVA, 131–136°, m. m. p. with an equal weight of the same derivative of VIA, 137–142°. A total of 0.15 g. of olefin was obtained from the filtrate.

Acetolysis of the *p*-toluenesulfonate of IIIA (2.4 g.) produced 1.26 g. of a mixture of acetate and olefin, $\alpha = +18.30°$ ($l = 1$ dm.) which when hydrolyzed gave 0.94 g. of a mixture of alcohol and olefin, $\alpha = +10.49°$ ($l = 1$ dm.). Conversion of this material to the acid phthalate gave 0.96 g. of recrystallized derivative, m. p. 128–130°, $[\alpha]^{25}D$ +5.17° (3% in ethanol). Olefin (0.19 g.) was obtained in the usual way from the filtrates.

A mixture of 0.80 g. of the above mixture, 0.70 g. of strychnine and 10 ml. of acetone was allowed to stand and the material that separated was recrystallized from acetone and shaken with a mixture of ethyl ether and excess dilute sulfuric acid. The organic layer was washed with water, dried, the solvent was evaporated and the resulting oil mixed with 0.50 g. of brucine and 5 ml. of acetone. The material that separated was recrystallized from acetone and shaken with a mixture of ether and excess dilute sulfuric acid, the organic layer was washed with water, dried and evaporated to an oil, weight, 155 mg. This material was mixed with 155 mg. of the acid phthalate of IIIB (this material is an oil and was prepared by hydrolysis of the pure 3,5-dinitrobenzoate of IIIB[2] with subsequent esterification of the alcohol obtained). When dissolved in an equal volume of ethyl acetate and a small amount of petroleum ether added, the oil crystallized to give 250 mg. of the acid phthalate of III, m. p. 133–134°, mixed melting point with an authentic sample, 133–134°.

The filtrates from the crystallizations of the strychnine and brucine salts were evaporated to dryness, shaken with an excess of dilute sulfuric acid and ether, the ether layer was washed with water, dried and evaporated to an oil. Crystallization of this material from ethyl acetate and petroleum ether and recrystallization of the product from the same solvents gave 0.54 g. of the acid phthalate of VB, m. p. 127–128°, m. m. p. with an authentic sample, 127–128°. A sample of this material was mixed with an equal weight of the acid phthalate of VA and the mixture recrystallized from ethyl acetate and petroleum ether, m. p. 143–144°, m. m. p. with an authentic sample of the acid phthalate of V, 143–144°.

Acetolysis of the *p*-toluenesulfonate of VA (5.0 g.) produced 2.80 g. of a mixture of acetate and olefin, $\alpha = -18.80°$ ($l = 1$ dm.), which on hydrolysis gave 2.17 g. of a mixture of olefin and alcohol, $\alpha = -10.26°$ ($l = 1$ dm.). Conversion of this material to the acid phthalate gave 2.11 g. of recrystallized material, m. p. 128–130°, $[\alpha]^{25}D$ −4.66° (3% in ethanol). Olefin (0.40 g.) was obtained from the filtrate in the usual way.

A solution of 1.5 g. of the above material and 1.8 g. of brucine dissolved in 10 ml. of acetone was allowed to stand and the salt that separated was recrystallized and converted back to the phthalic acid ester; weight 0.70, m. p. 128–129°, m. m. p. with an authentic sample of the acid phthalate of VA, 128–129°. A small amount of this material was mixed with an equal weight of the same derivative of VB and recrystallized from ethyl acetate and petroleum ether, m. p. 143–144°, m. m. p. with an authentic sample of the acid phthalate of V, 143–144°.

The filtrates from the crystallization of the salt were concentrated and shaken with a mixture of excess dilute sulfuric acid solution and ether, the organic layer was washed with water, dried, and evaporated to an oil, weight 0.52 g. A small amount of this oil (50 mg.) was mixed with an equal amount of the oil obtained by treatment of IIIA with phthalic anhydride (the non-crystalline phthalic acid ester of IIIA), and the mixture was crystallized and recrystallized from ethyl acetate and petroleum ether; weight 55 mg., m. p. 133–134°, m. m. p. with an authentic sample of the phthalic acid ester of III, 133–134°.

Inversion of the *p*-Toluenesulfonate of VIB to Produce the Acetate of VB.—A solution of 10 ml. of absolute ethanol, 1.0 g. of *p*-toluenesulfonate of VIB and 3.0 g. of freshly fused potassium acetate was held at reflux for fifteen hours. The mixture was then cooled and shaken with a mixture of water and petroleum ether (low boiling).

The organic layer was washed three times with water, dried, evaporated to an oil and distilled to give 0.40 g. of oil. This material was treated with 0.20 g. of phthalic anhydride and 2 ml. of pyridine at 100° for one hour, cooled and shaken with a mixture of benzene and dilute sulfuric acid (excess). The organic layer was washed with water, dried, evaporated and the oil submitted to distillation; weight of ether 0.27 g.

The material that did not distil was crystallized and recrystallized three times from a mixture of ethyl acetate and petroleum ether to give 32 mg. of acid phthalate of VB; m. p. 126–128°, m. m. p. with an authentic sample, 127–129°.

A sample of this material was mixed with an equal weight of the acid phthalate of VA and the mixture crystallized from ethyl acetate and petroleum ether; m. p. 143–144°, m. m. p. with an authentic sample, 143–144°.

Acknowledgment.—The author wishes to thank Welton Burney for the analyses reported in this paper.

Summary

1. The *p*-toluenesulfonates of the isomers of 3-phenyl-2-pentanol and 2-phenyl-3-pentanol (III, IV, V, VI, IIIA, IVA, VA and VIA) were prepared and submitted to acetolysis, and the mixtures of acetates obtained were hydrolyzed to the respective mixtures of alcohols, of which solid derivatives were prepared. From the *p*-toluenesulfonate of either III or V was obtained a mixture of III and V derivatives, from the *p*-toluenesulfonate of either IV or VI was obtained a mixture of derivatives of IV and VI, from the *p*-toluenesulfonate of either IVA or VIA was obtained a mixture of derivatives of IVA and VIA, from the *p*-toluenesulfonate of IIIA was obtained a mixture of derivatives of IIIA and VB, and from the *p*-toluenesulfonate of VA was obtained a mixture of derivatives of IIIB and VA. These results have been interpreted as constituting evidence that a Wagner–Meerwein rearrangement takes place in each system and in a highly stereospecific manner, and that the stereochemistry of these reactions can be explained only on the basis of carbocyclic, asymmetric ionic intermediates.

2. Additional evidence has been obtained for the relative configurations of the above isomers.

LOS ANGELES, CALIFORNIA RECEIVED MARCH 14, 1949

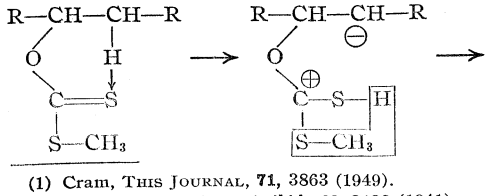
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in Stereochemistry. IV. The Chugaev Reaction in the Determination of Configuration of Certain Alcohols

BY DONALD J. CRAM

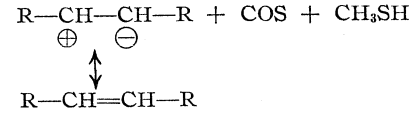
The results of rearrangement studies of the *p*-toluenesulfonates of the isomers of 3-phenyl-2-butanol led in paper I[1] of this series to an assignment of relative configurations to the four stereoisomers. The determination of the relative configurations by an independent method is desirable, and the use of the Chugaev reaction offers not only an attractive and unique method of accomplishing this end, but also offers a means of extending our knowledge of the steric course and mechanism of the Chugaev reaction itself. Since these two problems are completely interdependent, the purpose of this investigation is to show consistency between what is already known about the configurations of the starting material, and what is already known about the stereochemistry of the Chugaev reaction.

Stevens and Richmond[2] have suggested that the lack of rearranged olefins as products of this reaction can be explained by assuming that intramolecular hydrogen bonding prior to the proton elimination takes place, and that the reaction can be pictured as follows.



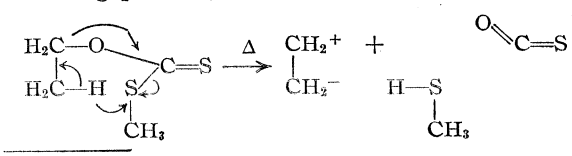
(1) Cram, THIS JOURNAL, **71**, 3863 (1949).

(2) Stevens and Richmond, *ibid.*, **63**, 3132 (1941).



These authors did not state whether the proton was pulled from the carbon before or during the breaking of the carbon oxygen bond, but the diagram implies the former.

Hückel, *et al.*,[3] found that decomposition of the xanthate of *l*-menthol produced about 30% Δ^2-menthene and 70% Δ^3-menthene, and the xanthate of *d*-neomenthol decomposed to give 80% Δ^2-menthene and 20% Δ^3-menthene. Since the hydrogen, loss of which leads to Δ^3-menthene, lies *cis* to the carbon–oxygen bond in the xanthate of *l*-menthol, and *trans* in the xanthate of *d*-neomenthol, the 70% Δ^3-menthene produced by the xanthate of *l*-menthol represents in effect a *cis* elimination reaction, and the 20% Δ^3-menthene obtained from the xanthate of *d*-neomenthol a *trans* elimination reaction. The stereochemistry of the reactions that produced Δ^2-menthene are not clear. These authors interpret the reaction as taking place by a completely concerted proc-



(3) Hückel, Tapp and Legutke, *Ann.*, **543**, 191 (1940).

ess, in which the sulfur bearing the methyl group plucks a proton from the carbon atom adjacent to the carbon atom bearing the oxygen at the same time that the carbon–oxygen and carbon–sulfur bonds break. Such a mechanism can, of course, only apply to a *cis* elimination reaction.

In the present investigation, each of the two racemate series of 3-phenyl-2-butanol when submitted to the Chugaev reaction should give a different geometric isomer of 2-phenyl-2-butene, determination of the structures of which should provide evidence for the relative configurations of the starting carbinols.

Discussion

Preparation, Identification and Characterization of the Isomers of 2-Phenyl-2-butene.—A mixture of the two geometric isomers[4] of 2-phenyl-2-butene was produced by the acid-catalyzed dehydration of 2-phenyl-2-butanol, and the large difference in boiling points permitted separation of the isomers by fractional distillation. If a small amount of *p*-toluenesulfonic acid is added to the pot during fractional distillation, pure *trans* compound[5] can be obtained.

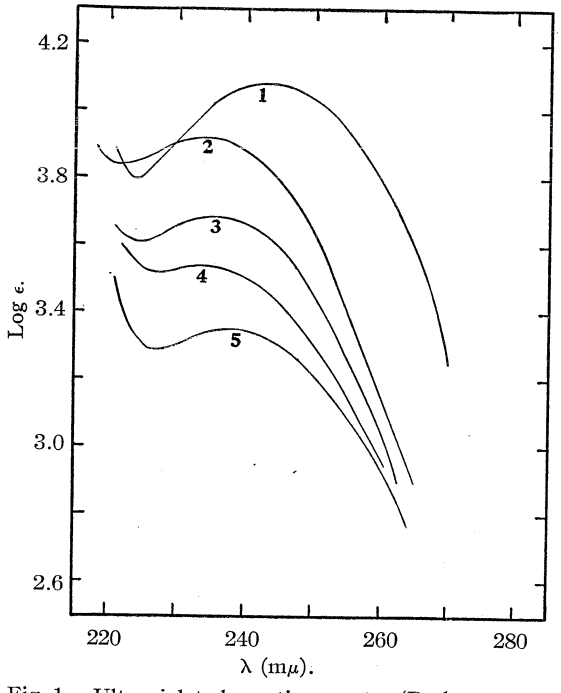


Fig. 1.—Ultraviolet absorption spectra (Beckman quartz spectrophotometer) run in cyclohexane: curve 1, *cis*-2-phenyl-2-butene; curve 2, *trans*-2-phenyl-2-butene; curve 3, fraction A of olefin obtained from xanthate of II; curve 4, fraction A of olefin obtained from xanthate of IV; curve 5, fraction A of olefin obtained from xanthate of I.

(4) If one assumes that the index of refraction of mixtures of these two components is a linear function of the composition, the ratio of the *cis* to *trans* isomer is 4 to 1. This value is roughly verified by the yield data.

(5) This substance, which is the lower boiling isomer, can be distilled from the continually equilibrating mixture.

The molecular structure of each olefin was confirmed by ozonolysis experiments, and the assignment of relative configuration was made on the basis of a comparison of the difference in the ultraviolet absorption spectra (see Fig. 1), and the difference in steric requirements for resonance involving the double bond and the benzene ring that exists between the two substances. Examination of Fisher–Hirschfelder models of each isomer indicates that when the benzene ring and methyl group are on the same side of the double bond (*trans* isomer), rotation of the benzene ring through the position corresponding to coplanarity with the double bond is resisted by interference between the methyl group and the hydrogen at the *o*-position of the ring. When the methyl group is on the opposite side of the double bond (*cis* isomer), this particular resistance to coplanarity is absent. Therefore, a certain amount of steric inhibition of resonance must exist in the *trans* isomer that would not be found in the *cis* compound, and this difference should lead to a divergence in the physical properties of the two substances. Thus the *cis* compound would be expected to be more polar (there should be a greater contribution to the resonance hybrid of dipolar forms in the *cis* than *trans* forms), to boil higher, to have a higher index of refraction and to absorb light at a longer wave length and at higher intensities.[6] Examination of the physical properties (see Experimental) of the two olefins obtained would indicate that the higher boiling substance corresponds to a *cis* (the two methyl groups *cis* to each other) and the lower boiling to a *trans* configuration. The presence of a much higher concentration of the *cis* isomer in an acid equilibrated mixture is consistent with the greater resonance of stabilization expected for the *cis* over the *trans* structure. The difference in free energy amounts to about 520 cal. based on the amounts of each obtained from an equilibrated mixture (the same mixture was obtained from each pure component).

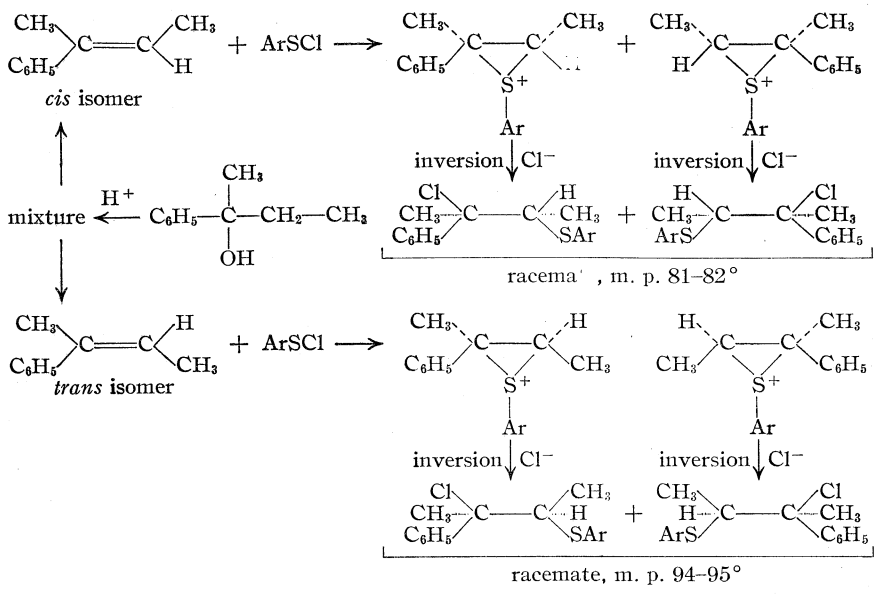
The addition of 2,4-dinitrobenzenesulfenyl chloride[7] to each isomer produced different crystalline derivatives (presumably different racemates), indicating that the addition reaction proceeds in a stereospecific manner. N. Kharasch and Buess[8] have demonstrated that the addition proceeds predominantly according to Markownikoff's rule when conducted in glacial acetic acid, and these authors have suggested a three-membered cyclic cation as an intermediate in the reaction, formed by the addition of 2,4-dinitrobenzenesulfenyl cation to the double bond. The stereospecificity of the reaction found in the present investi-

(6) An example of the effect of steric inhibitions of resonance on absorption spectrum is found in the study of the spectra of *cis*- and *trans*-stilbene by Smakula and Wassermann, *Z. physik. Chem.*, **A155**, 353 (1931).

(7) This reagent, directions for its use and suggestions as to its mode of addition were kindly supplied by Dr. N. Kharasch, University of Southern California.

(8) Kharasch and Buess, THIS JOURNAL, **71**, 2724 (1949).

gation would support this hypothesis, and the course of the reaction can be tentatively formulated as



action which gives rise to 3-phenyl-1-butene. If one assumes on the basis of the findings of Hückel, *et al.*,[3] that the Chugaev reaction is predominantly a *cis* elimination, the above results are substantial proof of the correctness of the configurational assignments of racemates I and II. If one assumes that the configurations of racemates I and II were previously demonstrated by the rearrangement studies (see paper I of this series), then the above results demonstrate that the Chugaev reaction goes predominantly by a *cis* elimination mechanism. In any case, these experiments have linked the two chains of stereochemical evidence together in an internally consistent manner, thereby strengthening each argument.

The Products of the Chugaev Reaction.—The xanthates of racemate I[9] (rich in IB), racemate II (rich in IIA), and racemate IV (rich in IVA) were prepared and decomposed to produce mixtures of olefins, the compositions of which are summarized in Table I. The methods of analysis of the olefins are indicated in the footnotes of Table I and in the experimental section.

It is clear from these results that each reaction produced three products. The xanthates of the isomers of 3-phenyl-2-butanol each gave *cis*- and *trans*-2-phenyl-2-butene and 3-phenyl-1-butene. The presence of the last compound in the olefinic products was demonstrated in each case by the optical activity of the mixtures, and by the preparation and isolation of the racemic crystalline 2,4-dinitrobenzenesulfenyl chloride addition compound of this olefin. The production of this olefin from the two xanthates is to be expected, since a hydrogen can be lost from either carbon atom 1 or carbon atom 3 of the xanthate. The estimated amount of 3-phenyl-1-butene present in the mixture came to 30–40% in each case.

The relative amounts of *cis* and *trans* isomers obtained from the two xanthates indicate that the Chugaev reaction proceeds for the most part but not completely in a stereospecific manner. Thus 36% of the purified olefin mixture obtained from the xanthate of I proved to be *cis*-2-phenyl-2-butene, whereas 11–14% of the *trans* isomer was found. From the xanthate of II was obtained hydrocarbon of which 49–52% proved to be *trans*-2-phenyl-2-butene and only a trace of the *cis* isomer was detected. There is no way of determining the stereochemistry of the re-

(9) The numbering system has been maintained throughout papers I, II, III and IV of this series.

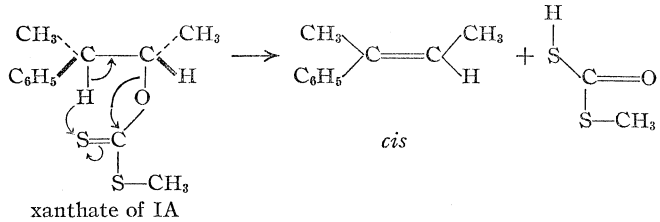
TABLE I

PRODUCTS OF THE CHUGAEV REACTION

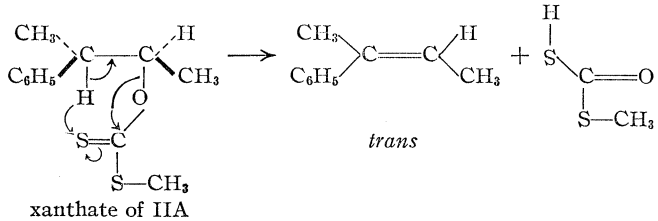
Compos., start. alc., %		Yields, % Xanthate	Tot. olef.[b]	Compn. of olef. mix., % Cis isom.	Trans. isom.	Struct. isom.	Obs. rot., Olef. fract.[d]	deg. Ald. mix.
80	IB				11[e]	40[f]		
20	IA	80	76	36	11[g]	37[h]	−2.02	+75.80
72	IIA				52[e]	32[f]		
28	IIB	85	91	5	49[g]	35[h]	+1.10	−24.78
68	IVA				52[e]	42[f]		
32	IVB	75	67	6	40[g]	55[h]	+6.01	−26.51

[a] The relative amounts of each isomer were estimated from the rotation of the mixture. [b] This yield is based in each case on the sum of the olefin fractions obtained by fractional distillation. [c] Sum of the fractions obtained by fractional distillation = 100%. [d] l = 1 dm. [e] The mixture of the *trans* isomer and the structural isomer (the olefin whose double bond is not in conjugation with the benzene ring) were never separated. Estimates of the amounts of *trans* isomer obtained were made from the amounts of acetophenone isolated from the ozonolysis mixtures (these values were corrected for the small manipulative losses found in a control experiment involving the separation of acetophenone from 2-phenylpropionaldehyde, the other ozonolysis product). [f] These values were obtained by difference, utilizing the estimates of the amounts of the *trans* olefin which were based on the isolation of acetophenone. [g] This estimate is based on the molar extinction coefficients of the spectrum of this mixture (see Fig. 1) at λ = max. The absorption of the olefin whose double bond is not in conjugation with the benzene ring is negligible in this region. A pure sample of 3-phenyl-1-butene was never obtained; however, the spectrum of this substance should simulate that of toluene, which exhibits very weak absorption ($\epsilon > 50$) in the region of 230–240 mμ and should not interfere (see Jones, *Chem. Revs.*, **32**, 1 (1943), and Braude, *et al.*, *J. Chem. Soc.*, 1087 (1947), and Murry, *et al.*, THIS JOURNAL, **70**, 3867 (1948)). [h] These values were obtained by difference, using the estimates of the amounts of *trans* olefin in the mixture, which estimates were based on spectral data.

The Chugaev reaction is considered in the present investigation to go predominantly by the following mechanism. The elimination reaction

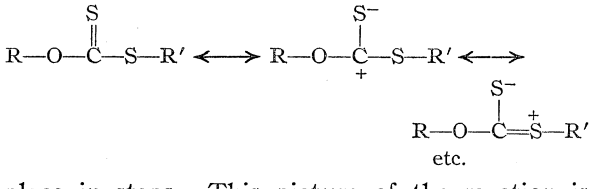


xanthate of IA



xanthate of IIA

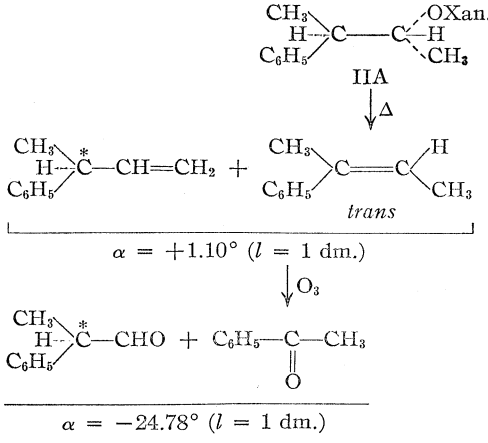
is pictured as being completely concerted, the hydrogen–carbon and the carbon–oxygen bonds breaking at the same time. The decomposition of the thiomethyl carbonate product is considered to be a second and independent reaction, the course of which is not pertinent. The above mechanism differs from that of Stevens and Richmond[2] only insofar as the reaction is thought to be completely concerted, rather than as taking

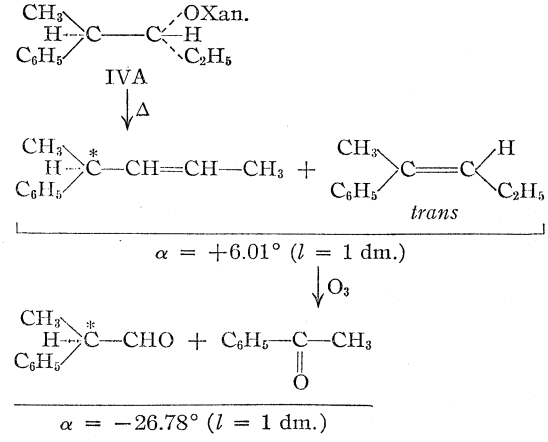


place in steps. This picture of the reaction is preferred over that of Hückel's[3] because the resonance inherent in the xanthate group would tend to increase the nucleophilic character of the sulfur of the thiocarbonyl group over that of the sulfide group. Furthermore, the steric requirements for the attack of the thiocarbonyl group on the hydrogen are less than those of the sulfur bearing a methyl group. The small amount of olefin that arises as a result of a *trans* elimination reaction is considered to be produced by an independent intermolecular mechanism.

The preparation and decomposition of the xanthate of IV (rich in IVA) was carried out for purposes of establishing the configuration of IVA relative to that of the I and II series of alcohols. Production of a large predominance of the *trans* (40–52%) over that of *cis* product (6%) is proof that IV possesses a configuration analogous to that of II.[10] Furthermore, the ozonolysis experiments, the results of which are outlined below, establish that IVA possesses a configuration analogous to IIA. The use of starting materials containing considerable amounts of the corresponding enantiomorphs (IIB and IVB, respectively) in no way modifies the argument. The opposite directions of the rotations of the olefin mixtures obtained from IIA and IB as well as of their respective ozonolysis products (see Table I) confirms the configurational assignments given to these isomeric alcohols in paper I[1] of this series, which were made on the basis of the simple inversion of the *p*-toluenesulfonate of IA by acetate ion to produce the acetate of IIA. The above experiment has demonstrated that the configurations about carbon atom 3 of IB and IIA are enantiomorphically related, and hence the configurations about that carbon atom in IA and IIB must be similarly related, in conformity with the previous argument.

Enough evidence is now available to place the configurational relationships of the four stereoisomers of 3-phenyl-2-butanol and the eight isomers of 2-phenyl-3-pentanol and 3-phenyl-2-pentanol on a secure basis. The configurations of I and II have been established through re-





(10) In making the estimate based on spectral data of the amount of *trans*-2-phenyl-2-pentene obtained from the xanthate of IV (see Table I), the assumption has been made that the spectrum of this substance should be very similar to that of *trans* 2-phenyl-2-butene. The positions of $\lambda_{max.}$ for the curve of the latter compound and the curve of the mixture of *trans* 2-phenyl-2-pentane and 4-phenyl-2-pentene (see Fig. 1) would tend to make this assumption valid.

arrangement studies and through the Chugaev reaction. If one assumes an absolute configuration for IA (this is the only assumption that has to be made), the structures of IB, IIA and IIB become fixed. The structure of IV was related to that of II through the Chugaev reaction, and the configurations of IVA and IIA related to one another by the degradative experiments, thereby fixing the structure of IVB. The *p*-toluenesulfonate of IVA was rearranged (acetolysis) in a stereospecific and predictable fashion to give acetate VIA, thereby fixing the structures of VIA and VIB. The structure of VIA was related to that of VA through simple inversion of the *p*-toluensulfonate of VIA by acetate ion to give acetate of VA, thereby fixing the structure of VA and VB. The *p*-toluenesulfonate of VA upon acetolysis produced IIIB acetate in a stereospecific and predictable manner thereby fixing the structure of IIIA and IIIB. Thus the assignments of configuration made earlier in the work and based for the most part on analogies between physical properties have been substantiated through the use of chemical introconversions and degradative experiments.

The olefinic products of the acetolysis of the *p*-toluenesulfonates of IA and IIA reported in paper I of this series were identified through the preparation of their addition compounds with 2,4-dinitrobenzenesulfenyl chloride. In each case the product obtained proved to be the derivative of *cis*-2-phenyl-2-butene. This fact suggests that the olefin arises from a non-asymmetric intermediate, possibly a free carbonium ion. Such an ion could be formed while the relative rotational positions of the two asymmetric carbon atoms with respect to each other was not conducive to the ring closure that leads to the acetate product.

Experimental

Preparation of *cis*- and *trans*-2-Phenyl-2-butene.—Methylethylphenylcarbinol (260 g.) was prepared according to the method of Klages,[11] and this material was held at reflux temperature mixed with 750 ml. of 4 *N* sulfuric acid. The olefin produced was isolated and distilled in the usual manner; weight 208 g., b. p. 80–84° (18 mm.), $n^{25}D$ 1.5347. This material was submitted to fractionation on a center rod column (55 theoretical plates at the highest operating efficiency) at 29.5 mm. of pressure and three fractions were taken: 1st, wt. 52 g., b. p. 82–88°; 2nd, wt. 85 g., b. p. 88–93.8°; 3rd, wt. 48 g., b. p. 93.8–94.0°. The second fraction was submitted to the same procedure to give 25 g. of material boiling below 93.8° and 58 g., b. p. 93.8–94.0°. All the fractions boiling below 88° were combined and treated by the same procedure to produce 22 g. of olefin, b. p. 77–78°, 45 g., b. p. 78–83°, and 30 g., b. p. 83–94°. Several refractionations of the middle boiling portions finally produced a total of 33 g. of material, b. p. 77–78°, and 128 g. of material, b. p. 93.8–94°. Careful redistillation of the higher boiling olefin gave 124 g. of pure *cis* isomer, b. p. 93.9–94.0° (p = 29.5 mm.), b. p. 194° (p = 1 atm.), $n^{25}D$ 1.5393, d^{25}_4 0.9799, MR_D 45.08, $\lambda_{max.}$ 243 mμ, log ε 4.082. The physical properties of this substance were unaltered by distillation at atmospheric pressure.

(11) Klages, *Ber.*, **35**, 3507 (1902).

Anal. Calcd. for $C_{10}H_{12}$: C, 90.84; H, 9.15. Found: C, 90.92; H, 9.39.

Careful redistillation of the lower boiling olefin produced 29 g. of pure *trans* isomer, b. p. 77.0–77.1° (p = 29.5 mm.), b. p. 174° (p = 1 atm.), $n^{25}D$ 1.5192, d^{25}_4 0.9191, MR_D 45.01, $\lambda_{max.}$ 235 mμ, log ε 3.912. The physical properties of this substance were unchanged by distillation at atmospheric pressure.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.84; H, 9.15. Found: C, 90.72; H, 9.18.

The *cis* isomer (13.5 g.) was mixed with 0.10 g. of pure toluenesulfonic acid and the mixture submitted to slow fractionation at 29.5 mm. to produce 11.4 g. of *trans* isomer, b. p. 77–79° (slight fluctuation), $n^{25}D$ 1.5197.

Equilibration of *cis* and *trans* 2-Phenyl-2-butene.—Pure *cis* isomer (5.0 g.) was heated to 100° with 0.05 g. of *p*-toluenesulfonic acid for three hours, the mixture cooled, shaken with a mixture of petroleum ether and water. The organic layer was washed with alkali, with water, dried, evaporated and distilled; wt. 4.1 g., $n^{25}D$ 1.5334.

Pure *trans* isomer (5.0 g.) when submitted to the same procedure gave 3.6 g. of product, $n^{25}D$ 1.5320.

2,4-Dinitrobenzenesulfenyl Chloride Addition Compounds of *cis*- and *trans*-2-Phenyl-2-butene.—A mixture of 0.50 g. of *cis*-2-phenyl-2-butene, 0.875 g. of 2,4-dinitrobenzenesulfenyl chloride and 2 ml. of glacial acetic acid was stirred until homogeneous and allowed to stand overnight. The heavy prisms that separated were recrystallized from a small amount of glacial acetic acid and petroleum ether; wt., 0.94 g., m. p. 81–82° (rich yellow prisms),[12] mixed m. p. with 2,4-dinitrobenzenesulfenyl chloride, 55–76°.

Anal. Calcd. for $C_{16}H_{15}SN_2O_4Cl$: C, 52.38; H, 4.12. Found: C, 52.27; H, 4.37.

Using the procedure described above, 0.50 g. of *trans*-2-phenyl-2-butene was converted into its addition compound with 2,4-dinitrobenzenesulfenyl chloride to give 0.97 g. of yellow rectangular plates (material recrystallized from ethyl acetate and petroleum ether), m. p. 94–95°, mixed m. p. with same derivative of the *cis* isomer, 59–73°, mixed m. p. with 2,4-dinitrobenzenesulfenyl chloride, 61–81°.

Anal. Calcd. for $C_{16}H_{15}SN_2O_4Cl$: C, 52.38; H, 4.12. Found: C, 52.21; H, 4.12.

Ozonolysis of *cis*- and *trans*-2-Phenyl-2-butene.—Ozone was passed into a mixture of 0.50 g. of *cis* isomer and 10 ml. of ethyl acetate at 0° until no more ozone was absorbed (twenty minutes). The resulting solution was added dropwise to a stirred boiling mixture of 50 ml. of water, 1.0 g. of zinc dust, a trace of silver nitrate and a trace of hydroquinone. After the addition was complete the mixture was cooled and extracted three times with ether, the combined extracts were washed with water, dried and evaporated to an oil, and the oil distilled to give 350 mg. of acetophenone, b. p. (micro) 202.5°. A small sample was converted to the oxime, m. p. 57–58°, mixture m. p. with an authentic sample 58–59°. Another sample was converted to the 2,4-dinitrophenylhydrazone, m. p. 248–249°, mixed m. p. with an authentic sample 248–249°.

From 0.50 g. of the *trans* isomer was obtained by the same procedure 310 mg. of acetophenone, b. p. (micro) 202°. Oxime was prepared from this material, m. p. 57–58°, mixed m. p. with an authentic sample, 58–59°. The 2,4-dinitrophenylhydrazone melted at 248–249°, mixed m. p. with an authentic sample, 248–249°.

Xanthates of I (rich in IB), II (rich in IIA) and IV (rich in IVA).—A mixture of 14.8 g. of II rich in IIA ($[\alpha]^{25}D$ +0.29), 3.85 g. of potassium and 60 ml. of dry toluene were heated at reflux for sixteen hours, cooled and the

(12) The melting point of this substance is sensitive to the rate of heating of the melting point bath; the substance melts at 81–82° if the rate of increase is normal, at 85–86° if very slow. If the substance is recrystallized from ethyl acetate and petroleum ether, the melting point decreases. Material recrystallized after having been melted shows the same characteristics.

small lump of potassium removed with a wire. A large excess (20 ml.) of carbon disulfide was added and the resulting mixture stirred at reflux temperature overnight. The mixture was again cooled and 12 ml. of methyl iodide added, the mixture was held at reflux temperature for four hours, cooled and shaken with a mixture of ether and water. The organic layer was washed with water, dried and the solvent evaporated to a low volume on a steam-bath, and the resulting concentrated solution was submitted to distillation at 15 mm. to remove the toluene. The remaining oil was distilled to give 20.2 g. of xanthate (yellow oil), b. p. 134–135° (p = 3 mm.), $n^{25}D$ 1.5746.

Anal. Calcd. for $C_{12}H_{16}OS_2$: C, 59.96; H, 6.71. Found: C, 60.23; H, 6.83.

The xanthate of I (rich in IB) was prepared by the procedure described above. From 22.0 g. of I rich in IB ($[\alpha]^{25}D$ −18.9°) was obtained 28.8 g. of yellow oil, b. p. 122–123° (p = 1 mm.), $n^{25}D$ 1.5749.

Anal. Calcd. for $C_{12}H_{16}OS_2$: C, 59.96; H, 6.71. Found: C, 60.18; H, 6.81.

The same procedure was used for the preparation of the xanthate of IV (rich in IVA). From 9.5 g. of IV (rich in IVA) ($[\alpha]^{25}D$ −2.64°) was obtained 11.0 g. of xanthate (yellow oil), b. p. 131–132° (p = 2 mm.), $n^{25}D$ 1.5680.

Anal. Calcd. for $C_{13}H_{18}OS_2$: C, 61.37; H, 7.13. Found: C, 61.73; H, 7.45.

Decomposition of the Xanthate of I.—The xanthate of I (rich in IB) (28.8 g.) was heated at 180° in a Wood's metal bath, and the olefin formed was collected as it distilled from the mixture, wt. 16.9 g. of crude yellow material. This material was distilled at reduced pressure (20 mm.) to get rid of low boiling impurities and undecomposed xanthate, wt. 13.7 g. Fractional distillation of this mixture of olefins through a center rod column (55 theoretical plates at the highest operating efficiency) at 29.5 mm. gave three fractions: fraction A, wt. 6.12 g., $n^{25}D$ 1.5093, d^{25}_4 0.8841, MR_D 44.67, b. p. 79.5–80.5°, α −2.01 (l = 1 dm., λ = D); fraction B, wt. 1.55 g., b. p. 80.5–93.8°; and fraction C, wt. 4.32 g., b. p. 93.8–94.0°, $n^{25}D$ 1.5387. Fraction A was analyzed, and Fig. 1 records the ultraviolet absorption spectrum of this mixture.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.84; H, 9.15. Found: C, 90.82; H, 9.38.

Fraction A (1.40 g.) was submitted to ozonolysis (the procedure described earlier for the ozonolysis of *cis*-2-phenyl-2-butene was employed) to produce 0.91 g. of a mixture of acetophenone and 2-phenylpropionaldehyde, α +75.80° (l = 1 dm., λ = D). This mixture (0.50 g.) was dissolved in 5 ml. of ethyl alcohol and added to a suspension of silver oxide in 10 ml. of water (this reagent was prepared just before use by dissolving 1.5 g. of silver nitrate in 10 ml. of water and adding a dilute alkaline solution until no more precipitate formed). The resulting mixture was heated at reflux temperature for half-an-hour, cooled and extracted three times with ether, the extracts were combined, washed with dilute alkaline solution and then with water, dried, evaporated to an oil, and the oil was distilled to give 90 mg. of acetophenone, b. p. (micro) 200°. The 2,4-dinitrophenylhydrazone was prepared, m. p. 248–249°, mixed m. p. with an authentic sample 248–249°.

A known mixture of 250 mg. of acetophenone and 250 mg. 2-phenylpropionaldehyde[1] was submitted to the procedure described above and 230 mg. of acetophenone was obtained, b. p. (micro) 201°, m. p. of the 2,4-dinitrophenylhydrazone, 248–249°, mixed m. p. with an authentic sample, 248–249°.

A mixture of fraction A (325 mg.), 560 mg. of 2,4-dinitrobenzenesulfenyl chloride and 1 ml. of glacial acetic acid was allowed to stand overnight and the resulting oil was dissolved in 3 ml. of benzene and submitted to chromatographic absorption on a small alumina column. The first band to filter through (benzene was used to develop the column) was collected, evaporated under reduced pressure and crystallized and recrystallized from ethyl acetate and petroleum ether to give 110 mg. of optically inactive yellow needles, m. p. 123–124°, depressed by admixture with the 2,4-dinitrobenzenesulfenyl chloride addition products of either *cis*- or *trans*-2-phenyl-2-butene. No other crystalline products could be isolated.

Anal. Calcd. for $C_{16}H_{15}SN_2O_4Cl$: C, 52.38; H, 4.12. Found: C, 52.59; H, 4.39.

Fraction B from the original distillation was discarded. Fraction C (200 mg.) was mixed with 350 mg. of 2,4-dinitrobenzenesulfenyl chloride and 0.5 ml. of glacial acetic acid. The addition compound was isolated and purified in the usual manner; wt. 330 mg., m. p. 81–82°, mixed m. p. with the authentic derivative of *cis*-2-phenyl-2-butene, 81–82°.

Decomposition of the Xanthate of II.—The xanthate of II (rich in IIA) (20.2 g.) was decomposed by the procedure described above to give 12.89 g. of crude olefin, distillation of which produced 11.2 g. of material which was submitted to fractional distillation at 29.5 mm. to give two fractions: fraction A, wt. 8.72 g., b. p. 79–80°, $n^{25}D$ 1.5120, d^{25}_4 0.8831, MR_D 44.92, α +1.10° (l = 1 dm., λ = D); and fraction B, wt. 1.54 g., b. p. 80–84°. Fraction A was analyzed, and Fig. 1 records its ultraviolet absorption spectrum.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.84; H, 9.15. Found: C, 90.42; H, 9.30.

Fraction A (500 mg.) was treated with 2,4-dinitrobenzenesulfenyl chloride in the usual manner and 350 mg. of recrystallized derivative was obtained, m. p. 94–95°, mixed m. p. with an authentic sample of the addition product of 2,4-dinitrobenzenesulfenyl chloride with *trans*-2-phenyl-2-butene, 94–95°. The filtrates from the crystallization and recrystallization of the above substance were concentrated, dissolved in a small amount of benzene, and submitted to chromatographic absorption on a small column of alumina. The column was developed with benzene and the first band to filter through the column was collected, concentrated and the resulting oil crystallized and recrystallized from ethyl acetate and petroleum ether to give 20 mg. of yellow needles, m. p. 124–125°, not depressed by admixture with the corresponding derivative prepared from fraction A obtained from the decomposition of the xanthate of I.

Fraction A (4.4 g.) was submitted to ozonolysis to give 2.7 g. of a mixture of acetophenone and 2-phenylpropionaldehyde, α −24.78° (l = 1 dm., λ = D). This mixture (500 mg.) was oxidized with silver oxide, and the acetophenone was isolated in the usual manner (see above), wt. 302 mg., b. p. 202° (micro), m. p. of the 2,4-dinitrophenylhydrazone, 248–249°.

Fraction B was submitted to fractional distillation, and the material that boiled above 85° (p = 29.5 mm.) and the material held in the column at the end were combined (total wt., 450 mg.) and converted to the 2,4-dinitrobenzenesulfenyl chloride addition product, wt. 640 mg., m. p. 81–82°, not depressed by admixture with an authentic sample of the addition product of 2,4-dinitrobenzenesulfenyl chloride with *cis*-2-phenyl-2-butene.

Decomposition of the Xanthate of IV.—The xanthate of IV (rich in IVA) (10.5 g.) when pyrolyzed at 200° gave crude olefin (5.9 g.) which on distillation produced 4.7 g. of material. This mixture was submitted to fractional distillation at 29.5 mm. and two fractions were taken: fraction A, wt. 3.8 g., b. p. 94.4–98.0°, α +6.01 (l = 1 dm., λ = D); and fraction B, wt. 0.23 g., b. p. 98–101°. Fraction A was analyzed, and Fig. 1 records its ultraviolet absorption spectrum.

Anal. Calcd. for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.18; H, 9.91.

Fraction A (1.5 g.) was submitted to ozonolysis to produce 0.83 g. of a mixture of acetophenone and 2-phenylpropionaldehyde, α −26.51° (l = 1 dm., λ = D). This mixture (500 mg.) was oxidized with silver oxide by the procedure reported above and 240 mg. of acetophenone was isolated, b. p. 201° (micro). The 2,4-dinitrophenylhydrazone of this substance melted at 248–249°, not depressed by admixture with an authentic sample.

Identification of Olefin from Rearrangement Studies.—The olefin (0.55 g.) obtained from the acetolysis of the *p*-toluenesulfonate of IA (see paper I of this series) was treated in the usual manner with 2,4-dinitrobenzenesulfenyl chloride, and 0.65 g. of recrystallized product obtained, m. p. 81–82°, not depressed by admixture with the same derivative of an authentic sample of *cis*-2-phenyl-2-butene.

In the same way the olefin (0.12 g.) obtained from the acetolysis of the *p*-toluenesulfonate of IIA (see paper I of this series) was converted to the 2,4-dinitrobenzenesulfenyl chloride addition compound, wt. 90 mg. (recrystallized material), m. p. 81–82°, not depressed by admixture with an authentic sample of the same derivative of *cis*-2-phenyl-2-butene.

Acknowledgments.—The author wishes to thank Welton Burney for the analyses reported in this paper. The use of the reagent, 2,4-dinitrobenzenesulfenyl chloride was made possible through the kindness of N. Kharasch, who provided a sample of the substance and directions for its use, and who also made information available as to the direction of addition of the reagent to the carbon–carbon double bond.

Summary

1. The geometric isomers of 2-phenyl-2-butene have been prepared, configurational assignments have been made on the basis of physical properties, and solid derivatives have been prepared.

2. Evidence has been adduced for the stereospecific addition of 2,4-dinitrobenzenesulfenyl chloride to the carbon–carbon double bond.

3. The Chugaev reaction has been shown to be predominantly a *cis* elimination reaction in an acyclic system.

4. Evidence has been obtained for the relative configurations of all the stereoisomers of 3-phenyl-2-butanol, 2-phenyl-3-pentanol and 3-phenyl-2-pentanol.

5. The formation of olefin during the acetolysis of the *p*-toluenesulfonates of IA and IIA has been shown to be a non-stereospecific reaction.

LOS ANGELES, CALIFORNIA RECEIVED MARCH 14, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Phellandral[1,2]

BY ROBERT L. FRANK, ROBERT E. BERRY AND ODETTE L. SHOTWELL

Most of the evidence concerning the structure of the terpene phellandral has indicated that this naturally occurring aldehyde is best represented by Structure X.[3,4,5] Cooke, Macbeth and Swanson[5b] have established the structure of the carbon skeleton by hydrogenation of phellandric acid to the known *cis*- and *trans*-hexahydrocuminic acids, and ultraviolet absorption spectra have located the double bond in the position α,β to the carbonyl group.[5a,6] This structure has now been confirmed by the synthesis of *dl*-phellandral through *dl*-phellandric acid, and the resolution of the racemic acid to the *d*-form corresponding to the acid obtained by oxidation of *d*-phellandral. The steps to the aldehyde are represented by Structures I–X.

The starting material, *p*-isopropylphenol (I), was best prepared by sulfonation of cumene, followed by alkali fusion. Methods involving nitration, reduction and diazotization or the alkylation of phenol resulted in mixtures of *o*- and *p*-isopropylphenols.

The hydrogenation and oxidation steps (I–II–III) were straightforward and gave yields of 96 and 82%, respectively.

In the preparation of the cyanohydrin acetate of 4-isopropylcyclohexanone (V) it was expected that treatment of the ketone with acetic anhydride and aqueous potassium cyanide[7] would lead directly to the cyanohydrin acetate. The reaction was tried on cyclohexanone as a model compound, and it was found to yield not the acetate but the cyanohydrin itself. The latter is resistant to acetylation by acetic anhydride, giving only 19% acetylation even in an excess of the reagent. Subsequent experiments showed that if one adds a trace of acetyl chloride to the acetic anhydride, the acetylation proceeds smoothly in good yields (64% with cyclohexanone). The conversion of 4-isopropylcyclohexanone (III) to the cyanohydrin acetate (V) was then carried out in two stages, but without purification of the intermediate cyanohydrin (IV), in a yield of 70%.

The method of Burns, Jones and Ritchie[8] and others[9] for the pyrolysis of esters gave excellent results with 4-isopropylcyclohexanone cyanohydrin acetate (V). The optimum temperature for our ester was 575–600°, which resulted in a small amount of charring in the pyrolysis tube, but nevertheless gave the highest yields (74%) of 4-isopropyl-1-cyano-1-cyclo-

(1) Presented in part at the St. Louis meeting of the American Chemical Society, 1948, before the Division of Organic Chemistry.

(2) This is the second communication on the chemistry of terpenes. For the first, see THIS JOURNAL, **71**, 1387 (1949).

(3) Schimmel's Report, 1904, Oct., p. 88; Simonsen, "The Terpenes," Cambridge University Press, 2nd edition, 1947, Vol. I, p. 308.

(4) Wallach, *Ann.*, **340**, 13 (1905); **343**, 33 (1905).

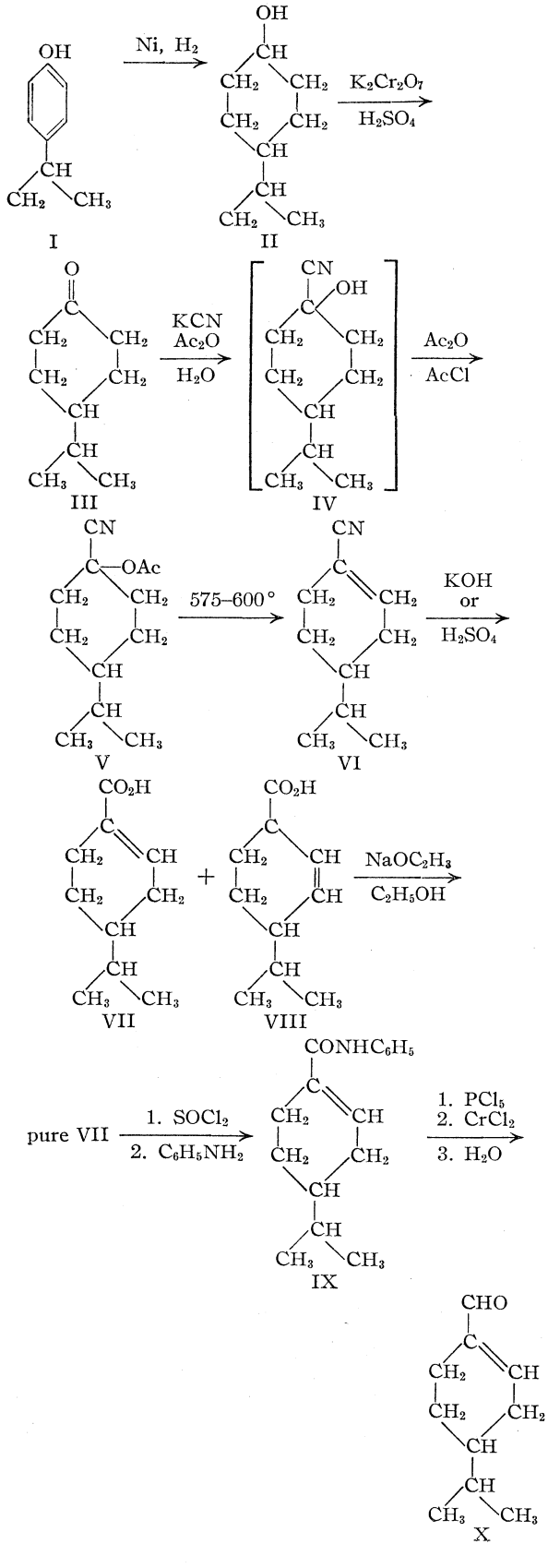
(5) (a) Cooke and Macbeth, *J. Chem. Soc.*, 1408 (1938); (b) Cooke, Macbeth and Swanson, *ibid.*, 808 (1940); (c) Burger and Macbeth, *ibid.*, 145 (1946).

(6) Evans and Gillam, *ibid.*, 565 (1943).

(7) Snyder, Stewart and Myers, THIS JOURNAL, **71**, 1055 (1949).

(8) Burns, Jones and Ritchie, *J. Chem. Soc.*, 400 (1935).

(9) (a) Schniepp and Geller, THIS JOURNAL, **67**, 54 (1945); (b) Ratchford and Fisher, *ibid.*, **69**, 1911 (1947).



hexene (*dl*-phellandronitrile, VI). The nitrile (VI) was assumed to have its unsaturation in the position α,β to the cyano group on the basis of its ultraviolet absorption spectrum (maxima at 212 mμ, log ϵ 3.95, and 271 mμ, log ϵ 2.01)[10,11] and on the basis of previous reports that rearrangement of the double bond seldom occurs in this type of pyrolysis.[12]

Hydrolysis of *dl*-phellandronitrile (VI) was accomplished under both alkaline and acidic conditions. In either case, however, mixtures resulted due to α,β–β,γ shifting of the double bond.[13] Saponification with 10% aqueous potassium hydroxide gave a mixture of solid acids, presumably VII and VIII, of m. p. 119–142°. Recrystallization from numerous solvents failed to effect separation. Hydrolysis with 75% sulfuric acid gave a similar mixture from which phellandric acid (VII) could not be isolated but which did give a 44% yield of an isomer we believe on the basis of infrared data to be the Δ^2 acid (VIII).

Various means, described in the Experimental Part, were used to obtain pure *dl*-phellandric acid (VII) from the mixture. Best results were obtained by refluxing the mixture in ethanolic sodium ethoxide to give an 80% yield of the pure Δ^1 acid (VII).

Reduction of *dl*-phellandric acid to *dl*-phellandral was accomplished readily, although in low yield (16% from the anilide), by the von Braun and Rudolph modification of the Sonn–Müller reduction.[14] The *dl*-phellandral was characterized by means of its physical properties and formation of its oxime, semicarbazone and 2,4-dinitrophenylhydrazone. Ultraviolet absorption spectra of the synthetic aldehyde and its semicarbazone corresponded with those reported for natural phellandral by Cooke and Macbeth[5a] and Evans and Gillam[6] (Fig. 1).

We were particularly interested in the properties of the oxime because of the structural similarity between phellandral and perilla-aldehyde. The *anti*-oxime of the latter has been reported to be 2000 times as sweet as sucrose.[15] We obtained only one oxime of *dl*-phellandral; it was not sweet.

Resolution of *dl*-phellandric acid (VII) was partially accomplished through its quinine salt. This salt reached constant rotation when the acid was about 56% resolved, and the resolution was completed by means of *l*-α-phenylethylamine.

(10) Braude, *Ann. Repts. Chem. Soc.*, **42**, 122 (1945).

(11) Ultraviolet absorption spectra were kindly carried out by Mrs. Calvin Brantley using a Model D Beckmann spectrophotometer. The nitrile was dissolved in 95% ethanol, concentration 0.0192 g. per liter of solution.

(12) For example, the pyrolysis at 575° of the diacetate of pentamethylene glycol yields only 1,4-pentadiene, with apparently no shifting of the unsaturation into conjugation to form piperylene (see reference 9a).

(13) Boorman and Linstead, *J. Chem. Soc.*, 261 (1935).

(14) v. Braun and Rudolph, *Ber.*, **67**, 269 (1934).

(15) Kurukawa and Tomizawa, *J. Chem. Ind. Japan*, **23**, 342 (1920); (*C. A.*, **14**, 2839 (1920)).

The *d*-acid thus obtained was essentially identical in m. p. (143–144°) and rotation ($[\alpha]D^{26} + 112.2°$) with that obtained by oxidation of *d*-phellandral.[5b]

Experimental

All melting points are corrected.

p-Isopropylphenol (I).—Ninety grams (104 ml., 0.75 mole) of cumene and 83 g. (0.85 mole) of 95% sulfuric acid were heated with stirring for three hours on a steam-cone. The warm mixture was poured into 250 ml. of water, and 40 g. of sodium bicarbonate was added in small portions, followed by 105 g. of sodium chloride. Crude sodium *p*-cumenesulfonate, which precipitated on cooling, was collected on a suction filter, washed with 40 ml. of saturated aqueous sodium chloride, and dried for two days at 80°. It weighed 109 g.

A mixture of 960 g. (17.1 moles) of potassium hydroxide and 40 ml. of water was heated to 250° in a 3-l. iron pot fitted with a stirrer. To this was added with constant stirring over a period of one-half hour 360 g. (1.62 moles) of the impure sodium *p*-cumenesulfonate. The temperature was raised to 325° for ten minutes, then the contents immediately poured onto 3 l. of cracked ice. The resulting water solution was neutralized with concentrated sulfuric acid and steam distilled. Colorless crystals of *p*-isopropylphenol formed in the distillate. After drying in a vacuum desiccator for two days these weighed 118 g. (35% based on cumene), m. p. 58–59° (lit.,[16] 61°).

4-Isopropylcyclohexanol (II).—A solution of 187 g. (1.37 moles) of *p*-isopropylphenol in 250 ml. of ethanol (purified by stirring for three hours with 2 g. of Raney nickel) was hydrogenated over 6.0 g. of Raney nickel at 190° and 125-atm. pressure. Fractional distillation gave 189 g. (96%) of 4-isopropylcyclohexanol, b. p. 123–124° (40 mm.), $n^{20}D$ 1.4660 (lit.,[17] 1.4661).

4-Isopropylcyclohexanone (III).—To a solution of 59 g. (0.20 mole) of potassium dichromate in 455 ml. of water in a 1-l., three-necked flask fitted with a dropping funnel, a reflux condenser, a thermometer and a stirrer was added 80 g. (0.56 mole) of 4-isopropylcyclohexanol. Concentrated sulfuric acid (52 ml.) was added dropwise with stirring at such a rate that the temperature was kept between 55° and 60° (about 10 ml. of acid was added before the temperature began to rise). The reaction mixture was cooled to room temperature, the oily layer separated, and the aqueous layer extracted with ether. The oily layer and the extracts were combined, washed with 5% aqueous sodium hydroxide, then water, and dried over anhydrous magnesium sulfate. Fractional distillation in a 12-in. Fenske-type column gave 64.6 g. (82%) of 4-isopropylcyclohexanone, b. p. 90–91° (13 mm.), $n^{20}D$ 1.4560 (lit.,[17] 1.4552^{25}°). The semicarbazone, prepared according to the method of Shriner and Fuson,[18a] melted at 187–188° (lit.,[19] 187–188°).

Cyclohexanone Cyanohydrin.—A solution of 65 g. (1.00 mole) of potassium cyanide in 125 ml. of water was added dropwise with stirring to a mixture of 94 ml. (102 g., 1.00 mole) of acetic anhydride and 52 ml. (49 g., 0.50 mole) of cyclohexanone in a 1-l. flask fitted with a mechanical stirrer, a dropping funnel and a reflux condenser. During the addition the mixture was cooled in an ice-bath. Stirring was continued for fourteen hours at room temperature, after which the reaction mixture was homogeneous. Saturated aqueous sodium carbonate was added until the mixture was alkaline to litmus. A red oil separated during this time; it was removed, and the water layer extracted with three 50-ml. portions of benzene. The extracts and oil were combined, washed with three 50-ml. portions of 30% aqueous sodium bisulfite, dried over magnesium sulfate, and the benzene distilled at 15-mm. pressure. The residual oil crystallized when a spot on the flask was cooled with Dry Ice. It was purified by rapid distillation at 91–95° (2 mm.) from a Claisen flask to yield 47.7 g. (76%) of colorless liquid, $n^{20}D$ 1.4643, which crystallized on chilling. An analytical sample was prepared by washing these crystals with chloroform, ether and acetone; m. p. 35°.

Anal.[20] Calcd. for $C_7H_{11}ON$: C, 67.17; H, 8.86. Found: C, 67.21; H, 8.88.

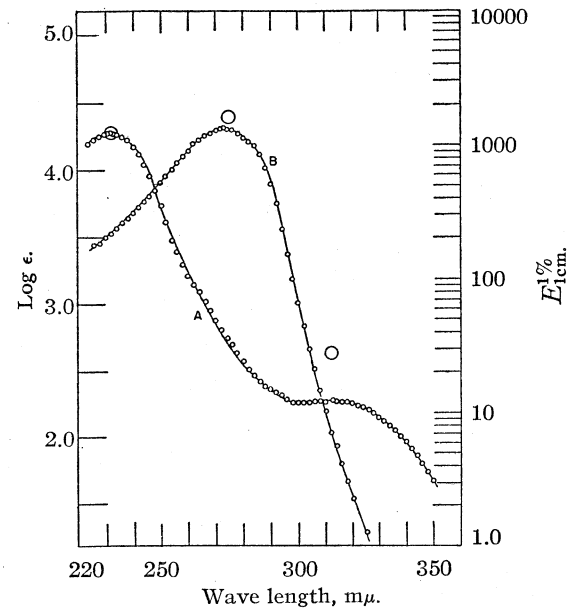


Fig. 1.—Ultraviolet absorption of *dl*-phellandral (A) (0.00418 g. per liter of ethanol solution) and its semicarbazone (B) (0.600 g. per liter of ethanol solution). The large circles represent the literature values (references 5a and 6).

Cyclohexanone Cyanohydrin Acetate.—To 68 ml. (73 g., 0.75 mole) of acetic anhydride and 0.8 ml. of acetyl chloride heated to boiling was slowly added 85.0 g. (0.68 mole) of cyclohexanone cyanohydrin. The mixture was refluxed for one hour after the end of the addition; it turned dark red during this time. Direct fractional distillation gave 91.0 g. (80%) of product, b. p. 125° (13 mm.), which crystallized on cooling; m. p. 48° (lit.,[8] 48–49°).

The same experiment, carried out with acetic anhydride containing no acetyl chloride, yielded 19% of the cyanohydrin acetate.

4-Isopropylcyclohexanone Cyanohydrin Acetate (V).—Crude 4-isopropylcyclohexanone cyanohydrin was prepared by the method for cyclohexanone cyanohydrin, with the use of 90 ml. (98 g., 0.96 mole) of acetic anhydride, 60 g. (0.43 mole) of 4-isopropylcyclohexanone and 62 g. (0.96 mole) of potassium cyanide in 192 ml. of water. After removal of the benzene at 15 mm. from the extract of the product, the oil was refluxed for one hour with 41 ml. (44.0 g., 0.43 mole) of acetic anhydride and 0.5 g. of acetyl chloride. Fractional distillation then gave 65.5 g. (70%) of product, b. p. 145–147° (14 mm.). It crystallized on cooling; m. p. 43–44°. An analytical sample was prepared by four recrystallizations from methanol–water to yield colorless mica-like plates, m. p. 50.5–52.5°.

Anal. Calcd. for $C_{12}H_{19}O_2N$: C, 68.85; H, 9.15. Found: C, 68.86; H, 9.20.

4-Isopropyl-1-cyano-1-cyclohexene (*dl*-**Phellandronitrile, VI**).—Three hundred and fifty-seven grams (1.71

(16) Paternó and Spica, *Gazz. chim. ital.*, **6**, 535 (1876).

(17) Cahn, Penfold and Simonsen, *J. Chem. Soc.*, 1366 (1931).

(18) (a) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd edition, 1948, p. 170; (b) p. 202; (c) p. 171.

(19) Vavon and Callier, *Bull. soc. chim.*, [4] **41**, 677 (1927).

(20) Microanalyses were carried out by Misses Emily Davis, Betty Alice Snyder and Theta Spoor, Mr. Maurice Dare and the Clark Microanalytical Laboratory.

moles) of the cyanohydrin acetate of 4-isopropylcyclohexanone was pyrolyzed by passing it through a vertical 18-mm. Pyrex tube filled with eight inches of glass beads. The temperature of the reaction was 575–600°; the ester was passed through the tube over a period of twelve hours at a rate of one drop every 3.5 seconds. There was some charring in the pyrolysis tube. Direct distillation of the product in a ten-inch Fenske-type column yielded 188 g. (74%) of colorless liquid, b. p. 118–120° (15 mm.); $n^{20}D$ 1.4786; sp. gr. $\frac{20}{20}$ 0.914; *MR* calcd. (using exaltation of 0.7): 46.2, found: 46.3.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.53; H, 10.14. Found: C, 80.37; H, 9.88.

Pyrolysis of a similar amount at 500° gave a 60% yield (based on unrecovered starting material) and a 31% recovery of starting material; at 565–575° the yield was 62% with no recovery of starting material.

Hydrolysis of 4-Isopropyl-1-cyano-1-cyclohexene. A. With Potassium Hydroxide.—A mixture of 188 g. (1.26 moles) of the nitrile, 141 g. (2.52 moles) of potassium hydroxide, and 3 ml. of 1-octanol (to prevent foaming) in 1271 ml. of water was refluxed for forty-eight hours. After forty hours most of the nitrile layer had disappeared. After cooling and filtration, the solution was acidified with concentrated hydrochloric acid. A light brown precipitate formed. This was dissolved in 1500 ml. of hot nitromethane. The mother liquor was extracted with 300 ml of nitromethane and the extract combined with the main hot solution. On cooling 136 g. of white platelets deposited; m. p. 119–142°. A second crop, 18.5 g., m. p. 83–118°, raised the total yield of mixed Δ^1- and Δ^2-4-isopropyltetrahydrobenzoic acids (VII and VIII) to 73%. Crystallizations from ethanol–water mixtures and from nitromethane did not raise nor narrow the m. p. range.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.57; H, 9.52.

B. With Sulfuric Acid.—To 25 g. of 75% sulfuric acid at 120° in a 200-ml. flask equipped with a stirrer, a dropping funnel and a reflux condenser was added dropwise 6.0 g. (0.04 mole) of 4-isopropyl-1-cyano-1-cyclohexene. The mixture was stirred at 110–120° for three hours, then poured into ice-water to give a brown precipitate. Two recrystallizations from ethanol–water, with the use of Darco, and one from dioxane–water (60:40) yielded 3.0 g. (44%) of colorless needles, m. p. 105°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.46; H, 9.73.

On the basis of its neutral equivalent, 172, and its infrared spectrum, kindly furnished by Mrs. J. L. Johnson, this acid is assumed to be Δ^2-4-isopropyltetrahydrobenzoic acid (VIII). The spectrum, obtained in Nujol suspension using a Perkin–Elmer Model 12B infrared spectrometer with rock salt optics, showed weak absorption bands at 702, 736, 1071, 1086, 1109, 1178, 1217, 1274, 1286, 1301, 1314 and 1371 $cm.^{-1}$ and strong bands at 1649 (unconjugated double bond) and 1680 $cm.^{-1}$ (carboxylic carbonyl group). No absorption was observed in the region of 1750–1800 $cm.^{-1}$, characteristic of γ-lactones.[21]

***dl*-Phellandric Acid (VII).**—Thirty-eight grams (1.6 gram-atoms) of sodium was dissolved in 1400 ml. of absolute ethanol in a 3-l. flask fitted with a reflux condenser. To this was added 136 g. (0.810 mole) of the mixture of acids, m. p. 119–142°, obtained by the alkaline hydrolysis above. A lumpy precipitate formed; the mixture was refluxed for three hours and allowed to stand overnight. About half the alcohol was removed by distillation, ice-water was added to the residue and the latter then carefully acidified with concentrated hydrochloric acid. Crystals formed in the mixture, which now had a total volume of 5 l. One recrystallization from 1400 ml. of nitromethane gave 109 g. (80% from the mixture, 58% from the nitrile) of colorless needles, m. p. 142–144° (lit.,[5b] 143–144°).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.03; H, 9.31.

(21) Thompson, *J. Chem. Soc.*, 328 (1948).

Attempted lactonization of the Δ^2 acid[22] by heating a mixture of 10 ml. of 60% sulfuric acid with 0.5 g. of a sample of the mixed acids nearly to boiling for five minutes gave a recovery of the mixture, m. p. 104–135°.

In an experiment to esterify the Δ^2 acid[13] 3.0 g. (0.02 mole) of the same mixture was dissolved in 36 ml. of absolute ethanol, and 18 ml. of 1 *N* ethanolic hydrogen chloride was added. After five hours at room temperature and one-half hour of refluxing, the mixture was poured into ice-water, extracted with benzene, the benzene removed at 15 mm. pressure, and the residue recrystallized twice from nitromethane. The product, m. p. 142–143°, was the desired *dl*-phellandric acid, but weighed only 0.3 g. (10% from the mixture).

One milliliter (1.5 g.) of thionyl chloride was added to 0.57 g. of the mixture of Δ^1 and Δ^2 acids, and the resulting acid chloride mixture heated at 100–105° for two hours, then hydrolyzed by stirring in water at room temperature for three hours. The crystals, recrystallized from nitromethane, melted at 134–143°, indicating some concentration of the Δ^1 acid, but the recovery was less than 0.1 g.

***dl*-Phellandric Acid Anilide.**—One hundred grams (0.59 mole) of *dl*-phellandric acid, 500 ml. of dry benzene and 65 ml. (106 g., 1.50 moles) of thionyl chloride, connected to a suitable trap, were allowed to stand for forty-five hours. The benzene and excess thionyl chloride were removed *in vacuo*. The residual acid chloride was dissolved in 1800 ml. of dry benzene in a 3-l. flask and 163 ml. (166 g., 1.78 moles) of aniline was added directly. Some heat was evolved and a white precipitate of aniline hydrochloride formed. After four hours at room temperature, the mixture was filtered to remove the precipitate, and the filtrate evaporated in stages to yield successive crops of crystalline anilide. These were washed in turn with dilute hydrochloric acid, dilute aqueous sodium hydroxide and water. Recrystallization from 4.5 l. of high-boiling petroleum ether yielded 122 g. (84%) of product in the form of fine needles, m. p. 131–132°.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.96; H, 8.70; N, 5.76. Found: C, 79.20; H, 8.48; N, 5.87.

***dl*-Phellandral.**—The method of von Braun and Rudolph[14] was followed closely. The imino chloride of *dl*-phellandric acid anilide was prepared from 50 g. (0.21 mole) of the anilide and 43 g. (0.21 mole) of phosphorus pentachloride. Chromous chloride solution was prepared in an atmosphere of carbon dioxide from 70 g. (0.41 mole) of red chromous acetate, kindly prepared by Messrs. Aaron Herrick and Marshall Hatfield,[23] and 275 ml. of 3 *N* hydrogen chloride in absolute ether. Addition of the imino chloride in 100 ml. of dry benzene to the chromous chloride solution gave a brown chromic chloride complex as described by von Braun and Rudolph. After hydrolysis of this and extraction of the aqueous layer with ether, the combined ether–benzene solutions were united with those of a second identical reduction. Evaporation at 15-mm. pressure yielded the Schiff base of *dl*-phellandral as a light brown residue. This was decomposed by means of 1 l. of 10% aqueous oxalic acid, and the *dl*-phellandral steam distilled in about 5 l. of water. The distillate, divided into convenient portions, was extracted four times with a total of 4 l. of ether. The extracts were dried over magnesium sulfate and fractionally distilled under nitrogen in a modified Claisen flask to give 10.4 g. (16%) of *dl*-phellandral, b. p. 103–105° (9 mm.); $n^{20}D$ 1.4896 (lit. for *l*-isomer,[5a] 1.4897); sp. gr. $\frac{20}{20}$ 0.944 (lit. for *d*-isomer,[3] 0.9412[20]); *MR* calcd. (using exaltation of 0.77):[24] 46.5, found: 46.6.

Anal.[25] Calcd. for $C_{10}H_{16}O$: C, 78.88; H, 10.60. Found: C, 77.62, 77.64, 77.48; H, 9.79, 9.90, 10.28.

(22) Fittig, *Ann.*, **283**, 47 (1894).

(23) Hatfield, "Inorganic Syntheses," Vol. III, McGraw-Hill Book Co., New York, N. Y., in press.

(24) v. Auwers and Eisenlohr, *J. prakt. Chem.*, **84**, 15 (1911).

(25) The analysis indicates the presence of phellandric acid, an expected result considering the ease of oxidation of phellandral (ref. 3).

The oxime, prepared according to the directions of Shriner and Fuson,[18b] melted at 76–77° when recrystallized as plates from ethanol–water.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.80; H, 10.25. Found: C, 72.03; H, 10.42.

Ultraviolet irradiation of the oxime in benzene solution for thirty-six hours resulted in complete recovery of the material melting at 76–77°.

The semicarbazone,[18a] shiny flakes when recrystallized from methanol, melted at 199.5–200.5°.

Anal. Calcd. for $C_{11}H_{19}N_3O$: C, 63.16; H, 9.09. Found: C, 63.17; H, 9.12.

The 2,4-dinitrophenylhydrazone, prepared by the method of Shriner and Fuson,[18c] formed red microcrystals from absolute ethanol, m. p. 194.5–196°.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: N, 16.87. Found: N, 16.80.

***d*-Phellandric Acid.**—To a mixture of 2920 ml. of petroleum ether (80–110°) and 488 ml. of *n*-butyl alcohol were added 45 g. (0.27 mole) of *dl*-phellandric acid and 101 g. (0.27 mole) of quinine trihydrate. The solution was heated to 60°, filtered hot, allowed to cool slowly to room temperature and finally chilled overnight in an icebox. The precipitated salt was filtered and recrystallized from the same solvent mixture. A second 45-g. portion of acid was treated in the same manner, and the two batches of salt combined and recrystallized seven times. The rotation did not change during the last two crystallizations. There was obtained 24 g. of quinine salt, m. p. 141–143°, $[\alpha]^{25}D$ −100° (0.0288 g./ml. of methanol).

Anal. Calcd. for $C_{30}H_{40}N_2O_4$: C, 73.14; H, 8.18. Found: C, 73.34; H, 8.43.

The quinine salt was dissolved in chloroform and decomposed by shaking with 12 ml. of 5% aqueous potassium hydroxide. The chloroform layer was discarded. The aqueous layer was washed twice with chloroform and then acidified. The precipitated acid was collected on a filter, washed with water and air-dried. It weighed 6.4 g., $[\alpha]^{25}D$ +63° (0.0223 g./ml. of methanol).

The partially resolved acid was dissolved in 300 ml. of a mixture of 1 volume of *n*-butyl alcohol to 20 volumes of petroleum ether (80–110°), and an excess of *l*-α-phenylethylamine was added. The mixture was heated on a steam-cone, then allowed to cool slowly as before. After eighteen recrystallizations from the same solvent mixture the rotation of the salt remained constant. There was obtained 1.27 g. of salt, m. p. 151–152°; $[\alpha]^{25}D$ +70.0° (0.0266 g./ml. of methanol solution).

Anal. Calcd. for $C_{18}H_{27}NO_2 \cdot H_2O$: C, 70.32; H, 9.51. Found: C, 70.66; H, 9.58.

This salt was decomposed in the same manner as the quinine salt to yield optically pure *d*-phellandric acid, m. p. 143–144°, $[\alpha]^{26}D$ +112.2° (0.02054 g./ml. of methanol solution) (lit.,[5b] m. p. 144–145°, $[\alpha]^{20}D$ +112.8° (0.02083 g./ml. of methanol solution)).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.62.

Summary

The structure of the terpene phellandral has been confirmed by the total synthesis of *dl*-phellandral and the resolution of *dl*-phellandric acid.

URBANA, ILLINOIS RECEIVED MAY 31, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Flavanones and Related Compounds. VI. The Polarographic Reduction of Some Substituted Chalcones, Flavones and Flavanones

BY T. A. GEISSMAN AND S. L. FRIESS[1]

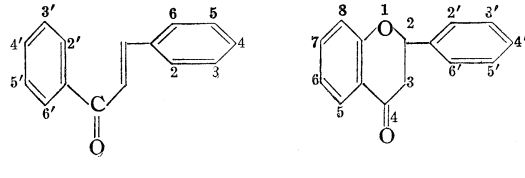
The study of the behavior at the dropping-mercury electrode of substances belonging to the C_6–C_3–C_6 (flavonoid) group of naturally occurring plant substances[2] has been continued. A more detailed examination has been made of some of the questions raised in the earlier part of this work, and a study has now been made of a group of flavones having hydroxyl and acetoxyl groups in the 5-, 7- and 4′-positions.[3] In addition, fourteen flavanones and sixteen chalcones, containing hydroxyl, methoxyl and acetoxyl groups in various positions in both aromatic rings, were examined. In each group the parent compound was included.

The objectives of this study included (1) a correlation between the kind and degree of substitution and the resulting variation in the ease of reduction at the electrode; (2) an evaluation of the most probable electrode mechanism; and (3) an attempt to account for the observed $E_{1/2}$ values on the basis of the proposed electrode reaction and the relative degrees of resonance stabilization of the reactants and products of the electrode reaction.

(1) du Pont Fellow in Chemistry, 1946–1947. Present address: University of Rochester, Rochester, N. Y.

(2) Engelkemeir, Geissman, Crowell and Friess, THIS JOURNAL, **69**, 155 (1947).

(3) Chalcones, flavones and flavanones are numbered as follows:



Experimental

The polarographic runs were made in 50% buffer–50% isopropyl alcohol mixtures at a temperature of 25 ± 0.1°, the $E_{1/2}$ values being measured against the saturated calomel electrode (S.C.E.). The *p*H values recorded for the various buffer mixtures used in the polarographic runs are the nominal ones given by the Beckman *p*H meter. They are in general about 1 *p*H unit higher than those of the aqueous buffer solutions alone.

In the case of the chalcones, the polarograph, buffers and dropping-mercury electrode were those used in the earlier study. Later, a Fisher Electropode was used, the runs with the flavones and flavanones being made with this instrument.

The capillary used for the runs on the flavones

and flavanones had the following characteristics: drop time at zero applied voltage = 3.78 sec.; m = 1.63 mg./sec.; $m^{2/3}t^{1/6}$ = 1.73. In the case of these series the buffers were all acetic acid–tetramethylammonium hydroxide mixtures. This buffer was adopted as a standard despite its poor buffering power at the higher *p*H values, since it was felt best to avoid possible complexities which the use of different (acetate, phosphate and borate) buffers might involve.[4]

Each run was carried out in duplicate, using in most cases different amounts of compound for each polarogram. The curves obtained for such duplicate runs gave reproducible half-wave potentials and wave heights proportional (by measurement, or estimation by inspection) to the sample weights.

In order to compare the Elecdropode with the instrument formerly used, a run was made on flavonol (3-hydroxyflavone), a compound not otherwise included in the present discussion. The value of the half-wave potential for this compound was found in the previous work to be −1.33 volts at *p*H 7.7; the value on the Elecdropode was −1.30 volts at *p*H 7.5. No systematic correction was applied, however, to the values found on either instrument since attention was chiefly directed to the differences observed within each group of related substances.

Since it was considered possible that certain chalcones having 2′-hydroxyl groups might be converted in solution into equilibrium mixtures containing some of the isomeric flavanone, particularly since a thirty-minute deoxygenation period preceded each run, a run was made using a mixture of 2′-hydroxychalcone and flavanone, at *p*H 7.5. The $E_{1/2}$ value for flavanone (−1.37 v.) was unaffected by the presence of the chalcone, and no wave was observed to occur at this point when 2′-hydroxychalcone was run alone under identical conditions. At no time was there any evidence that a flavanone gave rise to the corresponding chalcone, or *vice versa*, under the conditions of the polarographic runs carried out in this work.

Most of the compounds used were on hand or were prepared by known methods.[5]

Each compound was purified before use by recrystallization from an appropriate solvent. **5-Acetoxyflavone** was prepared by the acetylation of the hydroxy compound with acetic anhydride–pyridine. It formed white needles from alcohol, m. p. 121–122°. This changed on recrystallization to the value of 145° reported by Sugasawa.[6] In view of this behavior the compound was analyzed: Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.96; H, 4.52.

(4) Furman and Stone, THIS JOURNAL, **70**, 3055 (1948), in a polarographic study of some anthraquinones, found differences in the nature and position of the wave exhibited by a given compound when buffers of the same *p*H but different composition were used.

(5) Geissman and Clinton, *ibid.*, **68**, 597 (1946).

(6) Sugasawa, *J. Chem. Soc.*, 1483 (1934).

Naringenin triacetate was prepared from purified naringenin by Asahina's method.[7] The colorless needles, recrystallized from ethyl acetate–petroleum ether, melted at 82–84°.

Anal. Calcd. for $C_{21}H_{18}O_8$: C, 63.32; H, 5.55; OAc, 32.4. Found: C, 63.28; H, 5.10; OAc, 31.3.

Flavanone was prepared by refluxing 2′-hydroxychalcone in alcoholic hydrochloric acid solution.[8]

Results

In Table I are given summaries of the half-wave potentials and i_d/c values (i_d in microamperes, c in millimoles/liter) for the compounds studied. In general, i_d/c values were measured only for those curves which were clearly separated from adjoining waves. In a number of cases the amount of compound selected for a run proved to be incompletely soluble in the standard volume of buffer–isopropyl alcohol used in the polarograph cell; in such cases the concentration was not known with certainty and no i_d/c value is reported. Enough examples of i_d/c are given, however, to establish the range within which these values fall for each class of compounds studied. It is seen that most of the flavanones give single-wave, the flavones double-wave and the chalcones triple-wave polarograms. Some exceptions to this are observed, and this is regarded in most cases to be the result of the fusion of two waves into a single one. The results can most conveniently be discussed by directing attention to each class of compound separately.

Flavones.—In Fig. 1 are shown polarograms (plotted from Elecdropode readings) for 4′-hydroxyflavone, its acetate and its methyl ether. The two-step nature of the waves is evident, and is in contrast to the single wave of more highly substituted flavones[2] (*e. g.*, quercetin). This point was re-examined by repeating one of the earlier runs on kampferol (3,5,7,4′-tetrahydroxyflavone). This compound showed a single well-defined wave at −1.49 v. in a buffer of *p*H 6.1.[8a] Although some of the compounds show but one wave, it seems likely that this may be the result of the fusion of two steps which occur closely enough together to obscure the plateau between them. This is indicated by the

(7) Asahina and Inubuse, *Ber.*, **61B**, 1514 (1928).

(8) Kostanecki and Szabranksi, *ibid.*, **37**, 2635 (1904).

(8a) The single-wave polarograms of quercetin, kampferol and some related substances were interpreted in the earlier work[2] as indicating a single-electron reduction of these substances, a conclusion which was supported by wave analyses which gave "n" values of about 1. It appears from the present results that this conclusion was incorrect, and that in the case of these compounds the polarograms were actually those of two-electron processes in which two, one electron waves appeared as a single fused wave. An inspection of the diffusion current constants supports this view. In at least one case reported in that paper[2] a double wave was noted (quercetin tetramethyl ether), and it is noteworthy that when the "break" in this curve was ignored, and it was treated as a single wave, the diffusion current constant calculated from the total wave height was in line with those calculated for waves which did not show a distinct "break."

observation that in some series of runs at increasing *p*H the separation between the waves progressively decreases before the fusion into a simple wave occurs.

TABLE I[a]

		*p*H 6.1		*p*H 7.5		*p*H 8.6		*p*H 9.6	
	Flavones	$E_{1/2}$	i_d/c	$E_{1/2}$	i_d/c	$E_{1/2}$	i_d/c	$E_{1/2}$	i_d/c
1	Unsubstituted	−1.26	1.53	−1.26	1.99	−1.41	..	−1.42	..
		−1.38	..	−1.44	..	−1.75	..	−1.75[b]	..
2	4′-Hydroxy	−1.25	1.62	−1.35	1.37	−1.53	..	−1.54	..
		−1.49	2.34	−1.50	1.29	....	..	....	..
3	5-Hydroxy	−1.28	1.58	−1.33	..	−1.37[c]	..	−1.37[c]	..
		−1.41	..	−1.45	..	−1.51	..	−1.51	..
						−1.65	..	−1.65	..
				−1.36[c]					
4	7-Hydroxy	−1.26	1.23	−1.50	1.26	−1.59	..	−1.60	..
		−1.51	2.95	−1.64	..	....	..	....	..
5	4′-Acetoxy	−1.14	1.48	−1.23	1.47	−1.37	..	−1.37	..
		−1.37	2.16	−1.39	1.65	−1.73[b]	..	−1.73[b]	..
6	5-Acetoxy	−1.15	1.56	....	..	−1.35	..	....	..
		−1.31	1.60	....	..	....	..	....	..
7	7-Acetoxy	−1.14	1.24	....	..	−1.38	..	....	..
		−1.41	1.88	....	..	−1.72	..	..	..
8	4′-Methoxy	−1.20	1.09	....	..	−1.47	..	....	..
		−1.37	..						
	Flavanones								
9	Unsubstituted	−1.29	2.78	−1.37	2.62	....	..	−1.51	2.43
10	4′-Hydroxy	−1.29	..	−1.37	..	−1.51	0.62	−1.52	0.73
11	4′,5-Dihydroxy	−1.39	2.47	−1.45	2.25	−1.53	1.72	−1.54	1.91
12	4′,7-Dihydroxy	−1.45	2.20	−1.57	2.25	−1.58	0.83	−1.59	0.67
						−1.84	..	−1.84	
13	4′,5,7-Trihydroxy	−1.57	2.18	−1.62	2.24	−1.65	.82	−1.66	.57
14	3′,4′,5,7-Tetrahydroxy	−1.54	2.44	−1.61	1.98	−1.65	.73	−1.66	.70
15	3′-Methoxy-4′,5,7-trihydroxy	−1.55	2.49	−1.59	1.99	−1.65	.91	−1.65	.60
16	4′-Methoxy	−1.28	2.81	−1.34	2.41	−1.51	2.19	−1.52	..
17	4′,7-Dimethoxy	−1.40	2.28	−1.46	..	−1.64	2.25	−1.64	2.24
				−1.60	..				
18	4′,5,7-Trimethoxy	−1.36	..	−1.43	..	−1.68	..	−1.69	..
19	4′,7-Dimethoxy-5-hydroxy	−1.50	..	−1.53	..	−1.65	..	−1.67	..
20	4′-Acetoxy	−1.26	..	−1.52	..	....	..	−1.49	..
21	4′,5-Diacetoxy	−1.22	..	−1.27	..	....	..	−1.46	1.91
		−1.37		−1.43					
22	4′,5,7-Triacetoxy	−1.19	..	−1.25	..	....	..	−1.38	..
	Chalcones								
23	Unsubstituted	−0.89	1.71	−0.93	1.38	−1.08[d]	3.58	−1.10[d]	3.55
		−1.12	1.82	−1.12	1.60	1.62	2.71	−1.63	2.62
		−1.44	0.68	−1.60[e]	0.53				
24	2′-Hydroxy	−0.93	2.10	−0.98	1.87	−1.01	1.70	−1.02	1.40
		−1.12	1.77	−1.20	1.72	−1.25	1.49	−1.25	1.34
		−1.47	2.62	−1.58	1.98	−1.64	0.73	−1.63	0.80
25	2′,4-Dihydroxy	−1.04	1.43	−1.11	1.40	−1.16	1.27	−1.16	1.22
		−1.19	1.31	−1.24	1.43	−1.35	1.34	−1.35	1.35
		−1.44	2.07	−1.55	2.25	−1.64	0.76	−1.64	0.85
26	2′,3,4-Trihydroxy	....	..	−1.18[f]	2.56	....	..	....	..
				1.55	1.75				
27	2′,4,4-Trihydroxy	−1.10	0.75	−1.13	1.40	−1.24	1.02	−1.27	0.83
		−1.25	1.59	−1.28	1.42	−1.43	1.15	−1.44	1.32
		−1.55	1.67	−1.66	1.80	−1.90	0.96	−1.92	0.92
28	2′,4′,3-Trihydroxy	....	..	−1.16[d]	2.15	....	..	....	..
				1.69	1.89				
29	2′,4′,3,4-Tetrahydroxy	−1.15[d]	2.54	−1.25[d]	2.37	−1.25	..	−1.25	..
		1.57	1.94	1.69	1.82	−1.40	..	−1.40	..
						−1.85	..	−1.87	..

TABLE I (*Continued*)

	Chalcones	*p*H 6.1 $E_{1/2}$	*p*H 6.1 i_d/c	*p*H 7.5 $E_{1/2}$	*p*H 7.5 i_d/c	*p*H 8.6 $E_{1/2}$	*p*H 8.6 i_d/c	*p*H 9.6 $E_{1/2}$	*p*H 9.6 i_d/c
30	4′-Hydroxy	....	..	−1.13[d,f]	2.70	....	..	....	..
				1.79					
31	4′,4-Dihydroxy	....	..	−1.10	1.35	....	..	....	..
				−1.24	1.32				
				−1.72	0.65				
32	4′-Methoxy	....	..	−1.01	1.35	....	..	....	..
				−1.21	1.32				
				−1.68	0.65				
33	4′,4-Dimethoxy	−0.94	..	−1.04	..	−1.13	..	−1.10	..
		−1.18	..	−1.22	..	−1.26	..	−1.23	..
		−1.45	..	−1.62	..	−1.73	..	−1.73	..
34	2′-Hydroxy-4,4′,6′-trimethoxy	−1.13[d]	..	−1.19[d]	..	−1.19	..	−1.20	..
						−1.34	..	−1.34	..
		1.58	..	−1.72	..	−1.85	..	−1.85	..
35	2′,4′,6′,4-Tetramethoxy	−1.03[d]	0.85	−1.09[d]	0.88	−1.28[d]	1.71	−1.28	1.32
		−1.24	0.88	−1.24	1.17				
36	2′,3′,4′-Trihydroxy	....	..	−1.15[d,f]	3.55	....	..	....	..
				−1.77	1.15				
37	2′-Hydroxy-6′-methoxy-3,4-methylenedioxy	−0.93	..	....	..	....	..	....	..
		−1.05	..						
		−1.47	..						
38	2′-Hydroxy-4′,6′,3,4-tetramethoxy	−1.03[d]	..	....	..	....	..	....	..
		−1.13	..						

[a] Half-wave potentials are measured *vs.* the saturated calomel electrode; i_d/c values are in microamperes/millimole/liter. [b] Very small wave. [c] Triple wave with small breaks. [d] Single (fused) wave. [e] Small symmetrical wave. [f] Slight maximum in wave.

Figure 2 shows the variation in half-wave potential with *p*H for a number of the compounds examined. The abrupt shift in $E_{1/2}$ at *p*H values in the region 8–9 has been observed not only in this series but also in the case of similarly substituted chalcones and flavanones. A similar behavior has been used in the case of a series of substituted benzaldehydes by Baker, Davies and Hemming.[9] The same effect was noted in the first part of this study.[2]

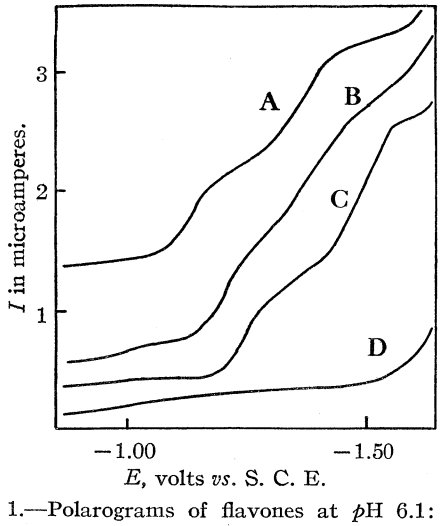


Fig. 1.—Polarograms of flavones at *p*H 6.1: A, 4′-acetoxyflavone; B, 4′-methoxyflavone; C, 4′-hydroxyflavone; D, buffer blank.

(9) Baker, Davies and Hemming, *J. Chem. Soc.*, 692 (1940).

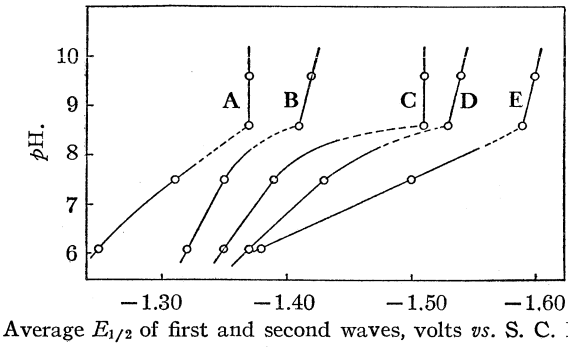


Fig. 2.—Variation of half-wave potential with *p*H: A, 4′-acetoxyflavone; B, flavone; C, 5-hydroxyflavone; D, 4′-hydroxyflavone; E, 7-hydroxyflavone.

Compared with flavone itself, the 5-, 7- and 4′-hydroxy compounds are more difficultly reducible and the corresponding acetyl derivatives more readily reducible. Since the presence of two waves makes it possible to base comparisons on

TABLE II

AVERAGE $E_{1/2}$ VALUES OF FIRST AND SECOND WAVES

Flavone	*p*H 6.1	*p*H 7.5	*p*H 8.6
4′-OH	−1.37	−1.43	−1.53
5-OH	−1.35	−1.39	−1.51
7-OH	−1.38	−1.43	−1.59
4′-OAc	−1.25	−1.31	−1.37
5-OAc	−1.23	....	−1.37
7-OAc	−1.27	....	−1.38
4′-OMe	−1.29	....	−1.47
Unsubst.	−1.32	−1.35	−1.41

either wave or on their average value, the effects of the substituents are best seen when the latter basis is adopted (Table II), although at *p*H 7.5 and 8.6 the effects are clearly apparent on either basis (Table I). 4′- and 7-hydroxyflavone show substantially the same values of $E_{1/2}$ in the range below *p*H 8.6, while 5-hydroxyflavone shows lower $E_{1/2}$ values at all *p*H's. A series of studies by Scaramelli[10,11] on hydroxybenzaldehydes and their ethers has shown a similar relationship between the effects of an ortho-(corresponding to 5- in the flavones) and a para-(corresponding to 7-) hydroxyl group, *p*- and *o*-hydroxybenzaldehydes being more difficultly reducible than benzaldehyde, but the ortho- compound being more easily reduced than the para-. Similar results are reported for the corresponding hydroxyacetophenones.[12,13]

Although the differences in $E_{1/2}$ values for the three hydroxyflavones and their derivatives are small, their reproducibility and the essential simplicity of the structures of these compounds is such that these effects are properly subject to interpretation. The decreased acidity of the 5-hydroxyl group in chromone derivatives (and in general, of hydroxyl groups *peri* to carbonyl groups in other systems) is a well-known property manifested by its greater difficulty of methylation with diazomethane and in the diminished solubility of 5-hydroxyflavone derivatives in aqueous alkali. It is to be expected, then, that throughout the *p*H range used in this work the anionic character of the 5-hydroxyl group would be less than that of the 7- or the 4′-hydroxyl group. Since, as will be shown in the sequel, there is good reason to ascribe the effects of these hydroxyl groups upon the ease of reduction of the carbonyl group to their ability to release electrons into the ring, the greater anionic character of the 7-hydroxyl group would allow it to have a greater effect upon the reducibility of the carbonyl group than the 5-hydroxyl group. The greater (negative) $E_{1/2}$ value of 7-hydroxyflavone than of 4′-hydroxyflavone at *p*H 9.6 may be ascribed to the greater acidity of the 7-hydroxyl group and its assumption of a greater degree of anionic character at this *p*H. Although at lower *p*H values, where the effects of un-ionized hydroxyl groups are probably predominant, very small differences in *pK* values would not be apparent, at higher *p*H values the increasing role of the anionic oxygen atoms should cause an increasingly wider separation of their effects. On the basis of these considerations the $E_{1/2}$ values of the hydroxylated flavones are in accord with expectations.

At a low *p*H (6.1) the hydroxyflavones and flavone itself show almost identical $E_{1/2}$ values for the first wave, the second wave only showing the greater ease of reduction of the parent compound. Since flavone contains the same heterocyclic oxygen atom as the hydroxyl-substituted derivatives, it is probable that this oxygen atom is of the greatest influence in affecting the ease of carbonyl reduction in all of these compounds, the effects of the nuclear hydroxyl groups superimposing themselves markedly upon this effect only at *p*H values which permit them to assume an appreciable amount of anionic character.

An examination of the diffusion current constants (i_d/c) for the flavones (Table I) shows that these are of about the same order of magnitude. The approximately twofold variation over all the values measured follows no consistent pattern. The values appear to be those of one-electron steps, since they correspond closely in order of magnitude with those observed by Pasternak[14] for a group of related substances. For example, Pasternak finds i_d/c values of approximately 2, with variations of about ± 0.3, in most cases, for steps involving one-electron electrode reactions of a number of carbonyl compounds. An inspection of Table I shows that for the flavones examined, i_d/c values of comparable magnitude were found. Closer agreement than is actually found need not be expected in view of the considerable structural differences in the compounds examined by Pasternak and in this work. Smith and his co-workers[15] likewise found diffusion current constants of approximately the same magnitude (*ca.* 4, for two-electron steps) for a series of hydroxychromanes and -coumaranes.[15a]

Wave analyses, by means of the equation

$$E = \text{constant} - \frac{0.059}{n} \log \frac{i}{i_d - i}$$

for a number of the compounds studied give n values of about 1 for each wave. This result, while not a demonstration that these are actually one-electron steps, since it is not known whether these are reversible processes, is at least consistent with the view that each wave represents a one-electron process. Müller[16] takes the view that while such wave analyses may not be strictly valid for irreversible processes, the n values so obtained may be regarded as approximations to the nearest integer of the number of electrons involved in the wave. In Figs. 3 and 4 are shown

(10) Scaramelli, *Atti accad. Italia, Rend.* [7] **1**, 764 (1940); *C. A.*, **37**, 1408 (1943).

(11) Scaramelli, *Boll. sci. facultà chim. ind. Bologna*, 235–238 (1940); *C. A.*, **37**, 1408 (1943).

(12) Scaramelli, *ibid.*, 768–770 (1940); *C. A.*, **37**, 1408 (1943).

(13) Scaramelli, *ibid.*, 122–123 (1941); *Chem. Zent.*, **115**, I, 417 (1944).

(14) Pasternak, *Helv. Chim. Acta*, **31**, 753 (1948). This article, which became available to us after this paper was submitted for publication, deals with compounds related to those we studied, and offers an interpretation of their behavior substantially in agreement with our original proposals.

(15) Smith, Kolthoff, Wawzonek and Ruoff, THIS JOURNAL, **63**, 1018 (1941).

(15a) Comparisons of this kind are valid only if the characteristics of the electrodes used are the same or nearly so. In the cases selected for comparison this is the case; for example, the dropping-mercury electrode used by Smith, *et al.*, had $m^{2/3}t^{1/6} = 1.63$; ours had $m^{2/3}t^{1/6} = 1.73$.

(16) Müller, *Annals N. Y. Acad. Sci.*, **40**, 91 (1940).

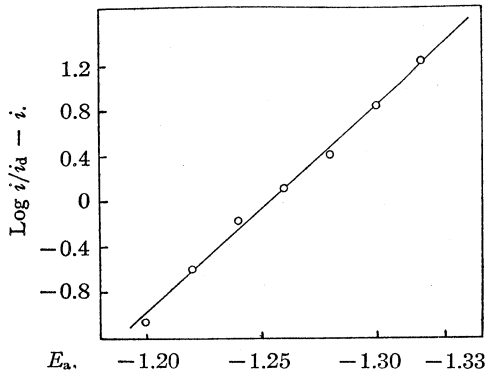


Fig. 3.—Wave analysis of first wave of 7-hydroxyflavone at *p*H 6.1.

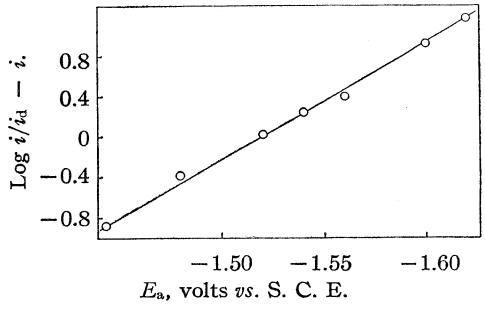


Fig. 4.—Wave analysis of second wave of 7-hydroxyflavone at *p*H 6.1.

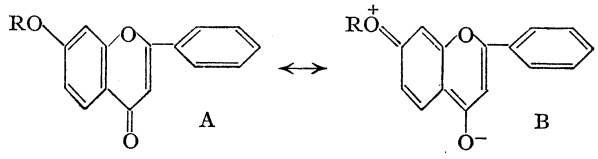
wave analyses for both waves of 7-hydroxyflavone. The values of n found from these and several other such wave analyses are given in Table III.

TABLE III

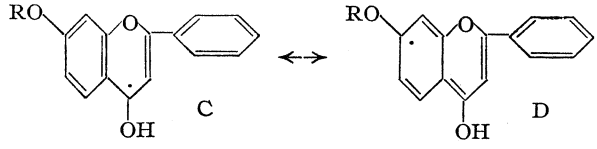
Flavone	*p*H	1/slope of *E vs.* log *i*(*id* − *i*)	*n*
7-OH (1)	6.1	−0.055	1.1
7-OH (2)	6.1	− .081	0.7
7-OH	9.6	− .112	.5
3-OH	7.5	− .064	.9
4′-OAc	8.6	− .070	.8

The polarographic reduction of organic compounds in distinct one-electron steps has been interpreted in a number of cases[14,16,17,18,19] as indicating the intermediate existence of a "semiquinone," or free radical, at the electrode. The behavior of the flavonoid compounds (of all three classes) studied in the course of the present work, can be accounted for in the light of the effects of structure upon the stabilization of the free radical produced in an initial, one-electron, electrode reaction. It is possible to arrive at a consistent treatment of the observed results if it is assumed that a greater degree of stabilization of the free radical as compared with the unreduced form (the oxidant) should result in a greater ease of reduction, as compared with another substance in which the substituents reduce the relative stabilization of the radical with respect to the oxidant.

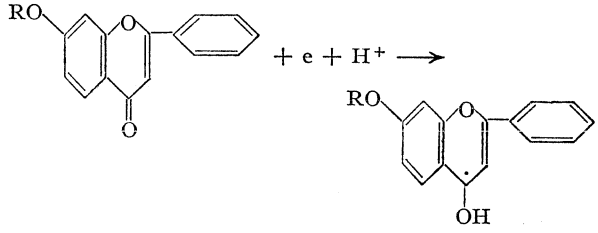
For illustration, consider the 7-substituted flavones. The forms A⟷B are among those contributing to the structure of the resonance hybrid of the unreduced form



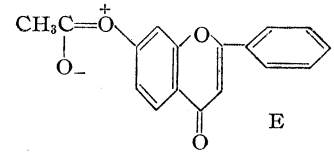
and forms C⟷D may be considered among those contributing to the structure of the one-electron-reduced product (the free radical), where forms



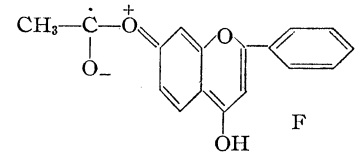
C, etc., may be considered to be the immediate product of the initial electrode reaction, according to the equation



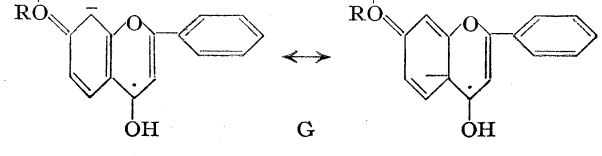
In the acetoxy compound (R = CH_3CO–), the stabilization of the oxidant will be diminished as a result of contributions from the opposing effect E



while that of the radical will be enhanced by a form F



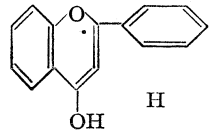
It is apparent that when R = CH_3, form B will be relatively more effective than form D, since the latter will be opposed by forms G



(17) Brdička, *Z. Elektrochem.*, **47**, 314 (1941).
(18) Tokuoka, *Coll. Czech. Chem. Comm.*, **1**, 392 (1935).
(19) Baker, Davies and Hemming, *J. Chem. Soc.*, 692 (1940).

and consequently it is to be expected that the acetoxy compound should be more easily reduced than the methyl ether.

It is seen from Table I and Fig. 5 that flavanones show single-wave polarograms, and undergo an initial electrode reaction involving one electron. A reason for two-step waves in the case of flavones can therefore be suggested. The greater stabilization of a form such as C⟷D, through participation of the chromone ring as in H



allows it to persist at the electrode and to be reduced further in a second electrode reaction. A flavanone, on the other hand, lacks the added possibilities for stabilization of the radical through the participation of such forms as H, and consequently undergoes disproportionation or dimerization in the free radical stage before a second electrode step can ensue, giving rise to a product which is not reducible at the electrode in the range of voltage used.

Flavanones.—An examination of the diffusion current constants for the flavanones studied shows that these are in most cases somewhat greater than those characteristic of a one-electron potential-determining electrode reaction. An unusual and unexplained feature of the i_d/c values for some of the flavanones is the sharp drop (from about 2 microamperes/mmole./liter to less than 1) noticed at high *p*H values. Wave analyses for a representative number of the compounds give n values of about 1, but the E *vs.* log $(i/i_d - i)$ plots showed a tendency to deviate from straight lines, vitiating even the approximate nature of this check on the number of electrons involved in the wave being analyzed.

The relative ease of reducibility of each flavanone can be related to the unsubstituted compound (9) as a standard. With increasingly more negative $E_{1/2}$ values, indicating increasing difficulty of reduction, the $E_{1/2}$ values of Table I may be used directly as a measure of the ease of reduction, and a correlation can be found between these values and particular kinds of nuclear substitution present.

It is seen by a comparison of the $E_{1/2}$ values at a *p*H of 6.1 for the flavanones 9, 10, 16 and 17 that the introduction at the 4′-position of the electron-supplying groups hydroxyl or methoxyl, or of the electron-withdrawing acetoxyl group, leads to no significant effect upon the ease of reduction relative to the unsubstituted flavanone. In view of the manner in which such substituents act to affect the ease of reduction of the flavones discussed above, this comparison demonstrates that substitution in a position not conjugated with the carbonyl group, and therefore incapable of affecting it by resonance, leads

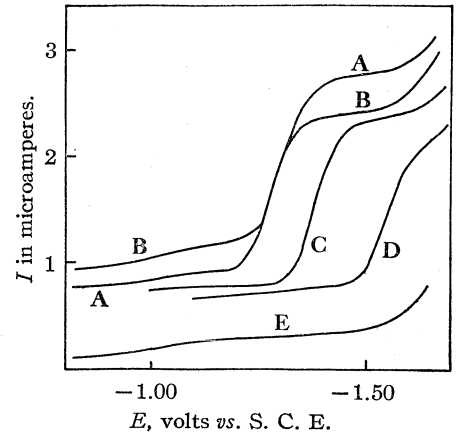


Fig. 5.—Flavanone polarograms at *p*H 6.1: A, flavanone; B, 4′-hydroxyflavanone; C, 4′,5-dihydroxyflavanone; D, 4′,5,7-trihydroxyflavanone; E, buffer blank.

to no influence on the ease of reduction of such substituted compounds. The non-effectiveness of substitution in the 2-phenyl group is further illustrated by a comparison of the $E_{1/2}$ values for compounds 14 and 15.

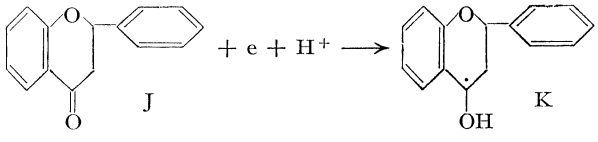
In the resonance-effective (*i. e.*, with respect to the carbonyl group) 5- and 7-positions, however, the effect of varying substitution is marked. The effect of substitution in the 5-position is shown by comparing the $E_{1/2}$ values for 9 (−1.29), 10 (−1.39), and the first wave of 21 (−1.22). Since a substituent in the 4′-position is ineffective, it is seen from this comparison that for the carbonyl-conjugated 5-position, substitution of an electron-supplying hydroxyl group increased the difficulty of reduction while an electron-withdrawing acetoxyl group decreases the difficulty of reduction as compared with flavanone (9).

The relative effectiveness of electron supply by the hydroxyl and methoxyl groups, so far as these reductions are concerned, is shown (with reference to position 7) by a comparison of the $E_{1/2}$ values for compounds 9 (−1.29), 12 (−1.45) and 17 (−1.40). Here, the order of electron supply, interpreted from the relative ease of reducibility, is OH > OMe > H, as would be expected.

The effect of the acetoxyl group with respect to electron supply is shown, for example, by a comparison of flavanone 9 with 13, 18 and 22. The acetoxyl group is evidently electron-attractive relative to hydrogen, an effect clearly shown by the behavior of flavanone 22 in this series.

It is further evident from an inspection of the $E_{1/2}$ values for the flavanones examined that a multiplicity of substituents in resonance-important positions leads to additivity of their effects upon the ease of reduction. Among the comparisons that can be cited to show this are: (1) increasing difficulty of reduction in the series 10, 11, 12, 13 (see Fig. 5), and (2) increasing ease of reduction in the series 20, 21, 22. The

magnitude of the i_d/c values indicates that the electrode reaction involves a two-electron change, although the n values from wave analyses indicate one-electron steps. An examination of the change in $E_{1/2}$ with pH shows that (Fig. 6) hydrogen ion also participates in this reaction. It is therefore likely that the electrode process involves the potential-determining reaction



The occurrence of only a single step of reduction can be ascribed to the instability of the primary electrode product K, which lacks the stabilization from the (unconjugated) 2-phenyl group found with the fully conjugated flavones and chalcones, and which immediately adds a second electron in a rapid second stage to yield a single-wave polarogram with a wave height corresponding to a two-electron reduction.

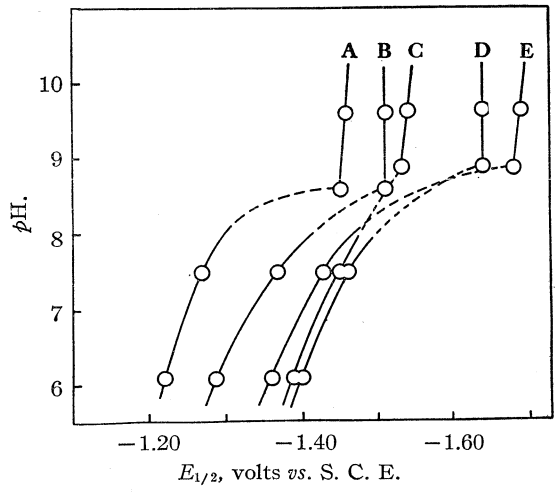


Fig. 6.—Variation of half-wave potential with pH: A, 4′,5-diacetoxyflavanone; B, flavanone; C, 4′,5-dihydroxyflavanone; D, 4′,7-dimethoxyflavanone; E, 4′,5,7-trimethoxyflavanone.

The arguments, based upon substitution effects, that favor this mechanism are virtually the same as those previously advanced in the discussion of the flavones. The substitution of electron-releasing groups such as hydroxyl or methoxyl in positions conjugated with the carbonyl group causes increased resonance stabilization in form J, relative to the unsubstituted state, but no increased (or decreased) stabilization of the reaction product K. Hence, this kind of substitution leads to increasing difficulty of the production of K by electrode reduction, as compared to the unsubstituted molecule, and is reflected in a shift of the half-wave potentials to the more negative values observed.

Chalcones.—The complex nature of the waves given by the chalcones studied is apparent from the data given in Table I. Figure 7 shows clearly the kind of curves from which these values were obtained. These polarograms are those of chalcone and of three chalcones carrying one, two and three hydroxyl groups in positions joined by conjugation with the carbonyl group.

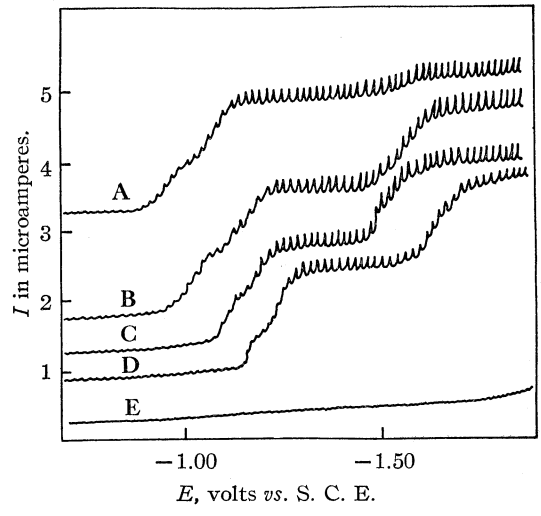


Fig. 7.—Chalcone polarograms (at pH 7.7): A, chalcone; B, 2′-hydroxychalcone; C, 2′,4-dihydroxychalcone; D, 2′,4′,4-trihydroxychalcone; E, buffer blank.

The diffusion current constants (i_d/c), while somewhat more variable than those found for the flavones and flavanones, appear to fall in the range typical of one-electron electrode reactions; the values for chalcones are in the majority of cases in the range of 1–2. Wave analyses have been carried out for a number of the polarograms, the values found for n being summarized in Table IV. In Fig. 8 are shown plots of E *vs.* log $(i/i_d - 1)$ for the three waves of chalcone (23). The agreement between the evaluation of n by this method and by estimation from diffusion current constants is shown by the data of Table IV, in which the n values range from 0.7–1.4 for the

TABLE IV

Chalcone	pH	1/slope at $E = E_{1/2}$		n
Unsubstituted	8.9	First	−0.068	1.1
	8.9	Second	− .066	1.1
	6.1	First	− .062	1.0
	6.1	Second	− .054	0.9
	6.1	Third	− .049	.8
2′-Hydroxy	6.1	First	− .051	.9
	6.1	Second	− .039	.7
	6.1	Third	− .080	1.3
	9.6	First	− .063	1.0
	9.6	Second	− .057	1.0
	9.6	Third	− .069	1.2
2′,4′,3,4-Tetrahydroxy	6.1	First (fused)	− .082	1.4
	6.1	Third	− .050	0.8
2′,4′,6′,4-Tetramethoxy	8.9	First (fused)	− .059	1.0

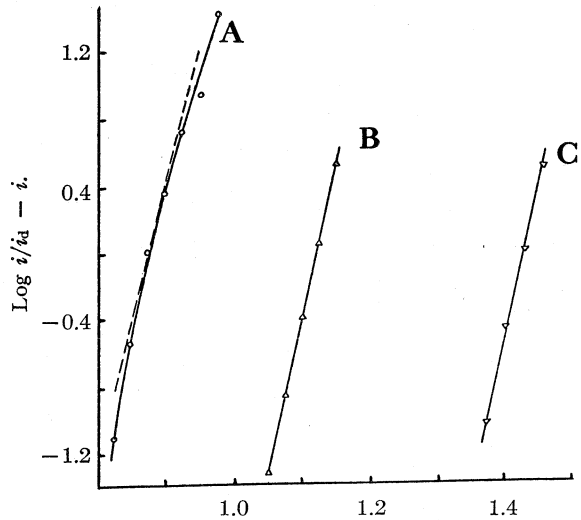
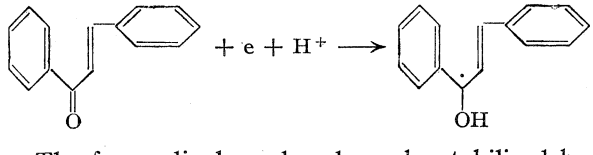


Fig. 8.—Wave analyses for the three waves of chalcone at *p*H 6.1: A, first wave; B, second wave; C, third wave.

fourteen cases listed. It appears that the conclusion is a sound one that the waves of the chalcone polarograms represent one-electron potential-determining reactions.

Of the three waves, the first two appear to depend upon the degree of hydroxylation of the chalcones. The third shows no such regular dependence upon structure. These relationships are shown more clearly in Figs. 9 and 10, in which are plotted $E_{1/2}$ values as functions of the *p*H at which they were measured (Fig. 9, averaged first and second waves; Fig. 10, third waves). The $E_{1/2}$ values become essentially *p*H-independent above *p*H values of about 8–9; and between *p*H 6–8 the slopes of the curves are reasonable approximations to 0.06 v./*p*H unit. This indicates the participation of hydrogen ions in the electrode reactions.

The dependence of the half-wave potentials upon the degree of hydroxylation resembles that observed in the cases of flavone and flavanone derivatives. The following initial electrode reaction is suggested



The free radical produced can be stabilized by resonance involving a number of contributing forms, the important ones being represented by structures having the free electron on the β-carbon atom or at three positions in each of the aromatic rings. As in the case of the flavones, the considerable stabilization afforded by the participation of a number of structures makes it possible for a second electrode reaction to occur

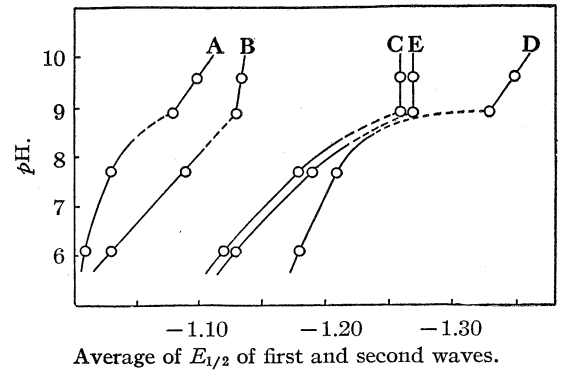


Fig. 9.—Variation of half-wave potential with *p*H: A, chalcone; B, 2′-hydroxychalcone; C, 2′,4-dihydroxychalcone; D, 2′,4′,4-trihydroxychalcone; E, 2′-hydroxy-4′,6′,4-trimethoxychalcone.

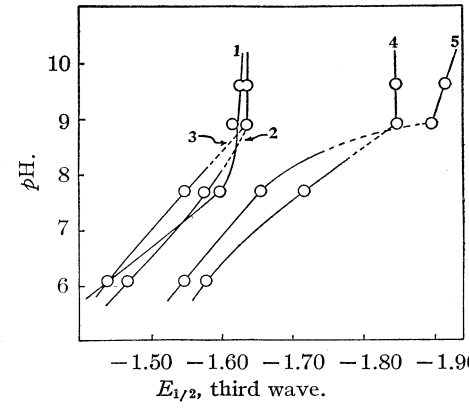


Fig. 10.—1, chalcone; 2, 2′-hydroxychalcone; 3, 2′,4-dihydroxychalcone; 4, 2′-hydroxy-4′,6′,4-trimethoxychalcone; 5, 2′,4′,4-trihydroxychalcone.

at higher potentials, leading to further reduction rather than to dimerization or disproportionation. The second wave can be the result of more than one kind of reduction of the free radical, but appears to be subject to the same kind of structural influences as affect the first wave. This is shown by the nature of the dependence of its half-wave potential upon structure and the fact that the effects of *p*H changes upon the first wave are also shown by the second wave.

The third waves show what appear at first sight to be erratic variation with those changes in substitution which cause regular variations in the first two waves. The data suggest the possibility

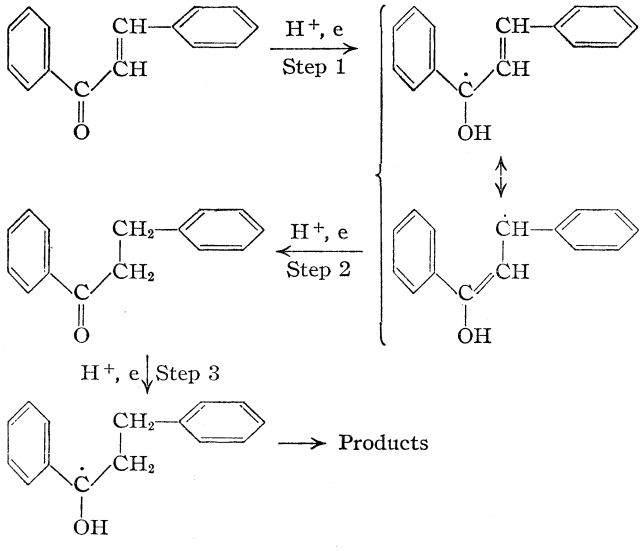
TABLE V

Compound	$E_{1/2}$(NH₄Cl)[a]	$E_{1/2}$ at *p*H 6.1[b]
2-OH Acetophenone	−1.46	....
2′-OH Chalcone	....	−1.47
2′,4-diOH Chalcone	....	−1.44
2,4-diOH Acetophenone	−1.60	....
2′,4′,4-triOH Chalcone	....	−1.55
2′,4′,3,4-tetraOH Chalcone	....	−1.57

[a] Scaramelli[12] used 0.1 *N* ammonium chloride in 50% ethanol–water. [b] From Table I.

that the third wave represents the reduction of a substance which no longer possesses an α,β-unsaturated carbonyl system, but which contains a structural element such as a carbonyl group attached to an aromatic ring. This supposition is supported by the observation that the third wave occurs at $E_{1/2}$ values in the range of those reported by Scaramelli[12] for hydroxylated acetophenone derivatives. The values in Table V show this correspondence.

From the considerations of the foregoing discussion, the following sequence of steps at the electrode can be suggested (using chalcone as a typical example).



This sequence of electrode reactions makes it possible to account for the occurrence of three waves, and also for the considerably greater ease of reduction of chalcones than of similarly substituted flavones and flavanones. If one compares the considerably greater possibility for resonance stabilization of the initial free radical, as compared with the original chalcone, with the corresponding differences between the unreduced and free-radical forms of flavones and flavanones, it is seen that the chalcone free radical is *preferentially* stabilized to the greatest degree, that of a flavone next, and that of a flavanone least. This is completely in accord with the relative ease of reduction at the electrode of chalcone > flavone > flavanone.

Summary

A study has been made of the effect of substitution of hydroxyl, alkoxyl and acetoxyl groups upon the ease of reduction of a group of flavones, flavanones and chalcones at the dropping-mercury electrode. When these groups are present in positions conjugated with the carbonyl groups in these compounds, hydroxyl and methoxyl groups decrease, and acetoxyl groups increase, the ease of reduction.

The results have been interpreted in terms of one-electron electrode reactions and the relative stabilities of the unreduced compounds and the initial free radicals produced in the first stage of the electrode process.

Flavanones give single-wave, flavones double-wave and chalcones triple-wave polarograms. It is suggested that these behaviors are due to the successive reduction at the electrode of the unreduced compound and one-electron-reduced intermediates.

LOS ANGELES, CALIFORNIA RECEIVED JULY 5, 1949

[CONTRIBUTION NO. 17 FROM THE THERMODYNAMICS LABORATORY OF THE PETROLEUM EXPERIMENT STATION, BUREAU OF MINES]

Experimental Vapor Heat Capacities and Heats of Vaporization of 2-Methylpentane, 3-Methylpentane and 2,3-Dimethylbutane[1]

BY GUY WADDINGTON, J. C. SMITH,[2] D. W. SCOTT AND H. M. HUFFMAN

This paper is a further contribution from the thermodynamic research program of the Petroleum and Natural-Gas Branch of the Bureau of Mines. The vapor heat capacities and heats of vaporization of 2,2-dimethylbutane and *n*-hexane have already been measured in this Laboratory.[3] Similar data for the three remaining hexanes are presented here. In the case of the heat-capacity measurements, the temperature range was from approximately the normal boiling point of the compound to 200°. Heats of vaporization were determined at temperatures corresponding to saturated pressures of about one-quarter, one-half and one atmosphere.

Experimental

Apparatus and Method.—Since the apparatus and experimental procedures used were essentially as described in detail in an earlier paper,[4] only a brief account of them will be given here.

A measured, constant flow of hydrocarbon vapor was produced by electrical heating in a cycling vaporizer. This was passed through a flow calorim-

(1) Not subject to copyright.

(2) Present address: Army Chemical Center, Edgewood, Maryland.

(3) Waddington and Douslin, THIS JOURNAL, **69**, 2275 (1947).

(4) Waddington, Todd and Huffman, *ibid.*, **69**, 22 (1947).

eter in which the temperature rise, produced in the vapor by a measured power input, was measured by means of platinum resistance thermometers. The apparent heat capacity of the vapor, $C_{p(\text{app.})}$ is given by $W/F\Delta T$ where W is the power supplied to the calorimeter, F is the flow per unit of time and ΔT is the observed temperature rise. Heat losses from the calorimeter are such that $C_{p(\text{app.})} = C_p + k/F$ where C_p is the true heat capacity. Hence, by measuring apparent heat capacities at several flow rates, then plotting $C_{p(\text{app.})}$ *vs.* $1/F$ and extrapolating to zero value of $1/F$, corrected values of C_p are obtained. The heat-capacity data are believed accurate to $\pm 0.2\%$. By measuring heat capacities at two or more pressures and extrapolating linearly to zero pressure the heat capacity of the ideal gas is obtained.

The proportionality between flow of vapor and electrical energy supplied to the vaporizer was determined by condensing and weighing the vapor produced, by a measured power input, during a measured time interval. This measurement, when properly corrected,[4] yields heats of vaporization believed to be accurate to about $\pm 0.1\%$.

The apparatus, as originally described,[4] has been modified slightly. The *aneroid* manostat[5] now used gives good control, and with it small or large changes of the pressure setting can be made very conveniently. The measurement of time has been made more accurate by use of fifty cycle alternating current obtained from a General Radio 816A Precision Tuning Fork Unit and a special power amplifier.

Materials.—The 2-methylpentane was Phillips Technical Grade, which, by a preliminary distillation for other purposes, had been brought to a purity of approximately 98 mole per cent. Further distillation in a 100-plate column, at an initial reflux ratio of 140:1 and a final reflux ratio of 90:1, resulted in a material having the following properties: d^{20}_4 0.6531, $n^{20}D$ 1.37145. The purity, determined from a melting curve, assuming liquid-soluble, solid-insoluble impurities, was 99.88 mole per cent.

The 3-methylpentane was also Phillips Technical Grade, which was purified by distillation at the Laramie Station of the Petroleum and Natural-Gas Branch of the Bureau of Mines. Since attempts to crystallize 3-methylpentane have not been successful, an analysis by means of the freezing behavior was impossible. By analogy with a sample of 2-methylpentane having a similar history, it is believed that the material used had a purity greater than 98 mole per cent. It had the following properties: d^{20}_4 0.6644, $n^{20}D$ 1.37647.

The 2,3-dimethylbutane was Phillips Pure Grade. It was purified further by distillation in a 100-plate column at a reflux ratio of 100:1. The purity estimated from a freezing curve was 99.87 mole %. It had the constants d^{20}_4 0.6616, $n^{20}D$ 1.37501. Whenever air had access to this compound, it was protected from peroxide formation by the addition of about 0.02 per cent. of a commercial anti-oxidant known as "tri-alkyl phenol."

Heats of Vaporization.—Table I gives a summary of the heats of vaporization of the three compounds investigated. For each compound, there is available for comparison an accurate value at 25° from the work of Osborne and Ginnings.[6] The largest difference observed, six calories at 25° for 2-methylpentane, is within the estimated $\pm 0.1\%$ uncertainty of the present work. The values reported by Lemons with Felsing[7] tend, as in the case of *n*-hexane, to be approximately 1% lower than the values here reported.

TABLE I

HEATS OF VAPORIZATION OF 2-METHYLPENTANE, 3-METHYLPENTANE AND 2,3-DIMETHYLBUTANE

t, °C.	Number of expts.	ΔH vapn. cal./mole[a]	ΔH vapn. equation
	2-Methylpentane		
25.0[6]	..	7138	7141
25.0	3	7144 ± 2[b]	7141
45.0	2	6865 ± 1	6856
60.3	3	6642 ± 2	6643
	3-Methylpentane		
25.0[6]	..	7235	7236
30.1	3	7170 ± 2	7169
50.6	3	6890 ± 3	6890
63.3	3	6711 ± 4	6707
	2,3-Dimethylbutane		
22.80	3	6988 ± 3	6987
25.00[6]	..	6960	6960
29.87	2	6900 ± 2	6899
39.97	3	6769 ± 5	6770
57.99	3	6519 ± 6	6521

[a] 1 cal. = 4.1833 int. joules; at. wt. carbon = 12.01; at. wt. hydrogen = 1.008. [b] Maximum deviations from the mean.

For interpolation to intermediate temperatures, the following equations may be used without significant loss of accuracy:

2-methylpentane: $\Delta H_{\text{vap.}} = 9173 - 0.2673T - 0.02196T^2$

3-methylpentane: $\Delta H_{\text{vap.}} = 9688 - 3.366T - 0.01629T^2$

2,3-dimethylbutane:

$$\Delta H_{\text{vap.}} = 8461 + 2.233T - 0.02438T^2$$

The last column of Table I lists values calculated with these equations.

Vapor Heat Capacities.—The molal vapor heat capacity of each compound was measured at five temperatures ranging from slightly below the normal boiling point to approximately 200°. At each temperature, measurements were made at two and, in some cases, three pressures. Table II summarizes the experimental values.

(5) Manufactured by Wallace and Tiernan Products, Inc., Belleville, N. J.

(6) Osborne and Ginnings, *J. Research Natl. Bur. Standards*, **39**, 453 (1947).

(7) J. F. Lemons with W. A. Felsing, THIS JOURNAL, **65**, 46 (1943).

TABLE II

EXPERIMENTAL VAPOR HEAT CAPACITIES, CAL./DEG./MOLE

T, °K. → / P., mm.	325.10	362.15	402.25	436.20	471.15
2-Methylpentane					
760.5		41.02	44.48	47.43	50.35
455.4	37.45	40.72			
211.9	37.10	40.51	44.21	47.24	50.23
3-Methylpentane					
T, °K. → / P., mm.	332.10	367.55	402.35	436.20	471.15
760.3		40.80	43.82	46.77	49.74
499.5	37.49	40.62			
235.8	37.16	40.42	43.55	46.60	49.61
2,3-Dimethylbutane					
T, °K. → / P., mm.	341.60	371.20	402.30	436.00	471.15
760.0	38.62	41.19	43.98	46.94	49.90
284.4	38.10	40.88	43.77	46.81	49.82

Heat Capacity in the Ideal Gas State.—From the data given in Table II, values of the heat capacity of the ideal gas were obtained at each temperature by plotting C_p *vs.* P and extrapolating to zero pressure. The validity of the linear extrapolation over the pressure range studied has been verified by determining heat capacities at three different pressures for *n*-hexane,[3] *n*-heptane[4] and benzene[8] in addition to two of the three compounds reported here. Wacker, Cheney and Scott[9] have also demonstrated this point in the case of isobutane at −30.0°.

TABLE III

HEAT CAPACITIES IN THE IDEAL GAS STATE, CAL./DEG./MOLE

T, °K.	C_p^1	C_p°	$C_p^1 - C_p^\circ$, cal./deg./mole: Expt.	2nd Virial	Berthelot
2-Methylpentane					
325.10	37.91	36.77	1.14	1.28	0.68
362.15	41.01	40.30	0.71	0.69	.49
402.25	44.48	44.08	.40	.40	.36
436.20	47.42	47.14	.28	.27	.28
471.15	50.34	50.16	.18	.18	.22
3-Methylpentane					
332.10	(37.80)	36.88	0.92	0.94	0.57
367.55	40.80	40.25	.55	.56	.42
402.35	43.81	43.43	.38	.37	.32
436.20	46.77	46.52	.25	.26	.25
471.15	49.74	49.55	.19	.19	.20
2,3-Dimethylbutane					
341.60	38.62	37.78	0.84	0.81	0.51
371.20	41.19	40.69	.50	.50	.40
402.30	43.98	43.63	.35	.32	.31
436.00	46.93	46.73	.20	.21	.25
471.15	49.90	49.77	.13	.14	.19

(8) Scott, Waddington, Smith and Huffman, *J. Chem. Phys.*, **15**, 565 (1947).

(9) Paul F. Wacker, Ruth K. Cheney and Russell B. Scott, *J. Research Natl. Bureau of Standards*, **38**, 651 (1947).

Values of C_p°, the heat capacity of the ideal gas, are summarized for the three compounds in Table III. Over the temperature range of the experiments, the following empirical equations represent the experimental results without significant loss of accuracy. The maximum deviations of the experimental points from the empirical equations are given in parentheses.

2-methylpentane: (±0.06% 341 − 471°K.)

$$C_p^\circ = 1.55 + 0.11963\ T - 3.478 \times 10^{-5}\ T^2$$

3-methylpentane: (±0.04% 332 − 471°K.)

$$C_p^\circ = 1.40 + 0.11776\ T - 3.291 \times 10^{-5}\ T^2$$

2,3-dimethylbutane: (±0.02% 325 − 471° K.)

$$C_p^\circ = -2.65 + 0.13692\ T - 5.433 \times 10^{-5}\ T^2$$

Figure 1 shows differences between the ideal gas heat capacities of the isomeric hexanes. Data used in this plot are from the present work and from earlier published work[3] from this Laboratory. Over the temperature range studied, differences between the heat capacities of the isomers do not exceed 2%.

Pitzer and Kilpatrick[10] have calculated heat capacities of the ideal gas for the isomeric hexanes by approximate statistical methods. The results so obtained have received wide distribution in the tables published under the auspices of API Project 44[11]; hence it is of interest to compare the calculated values with those obtained experimentally. Table IV makes this comparison at two temperatures. In most cases the calculated results are higher than the experimental values by amounts larger than the estimated accuracy uncertainty of the latter. However, the absence of any gross discrepancies will increase confidence in the extensive compilations of statistically calculated vapor heat capacities[11] where no experimental checks exist.

TABLE IV

CALCULATED AND OBSERVED IDEAL-GAS HEAT CAPACITIES OF THE HEXANES, CAL./MOLE/DEG.

	373.16°K. Calcd.	Obsd.	Δ	473.16°K. Calcd.	Obsd.	Δ
n-Hexane	41.70	40.96	0.74	50.24	49.84	0.40
2-Methylpentane	41.53	41.35	.18	50.32	50.37	−.05
3-Methylpentane	42.22	40.76	1.46	50.84	49.75	1.09
2,2-Dimethylbutane	41.71	41.22	0.49	50.84	50.43	0.41
2,3-Dimethylbutane	41.80	40.88	.92	50.58	49.97	.61

Second Virial Coefficients from Thermal Data.—From the heats of vaporization and from published vapor-pressure data[12] molal volumes of the vapor were calculated at several temperatures for each compound by use of the exact Clapeyron equation $\Delta H_{vap.} = T(V_g - V_l)\ dP/dT$, in which V_g and V_l indicate molal volumes of vapor and liquid, respectively. Further information concerning vapor volumes as a function of tempera-

(10) Pitzer and Kilpatrick, *Chem. Revs.*, **39**, 435 (1946).

(11) American Petroleum Institute Research Project 44 at the National Bureau of Standards, Selected Values of Properties of Hydrocarbons, Table 2v (Part I) September 30, 1944; November 30, 1946.

(12) C. B. Willingham, W. J. Taylor, J. M. Pignocco and F. D. Rossini, *J. Research Natl. Bur. Standards*, **35**, 219 (1945).

TABLE V

CALCULATED AND OBSERVED VIRIAL COEFFICIENTS

2-Methylpentane			3-Methylpentane			2,3-Dimethylbutane		
T, °K.	B, cc. Obsd.	B, cc. Calcd.	T, °K.	B, cc. Obsd.	B, cc. Calcd.	T, °K.	B, cc. Obsd.	B, cc. Calcd.
298.16	−1712	−1753	298.16[a]	−1718	−1662	295.96	−1554	−1592
298.16[a]	−1792	−1753	303.26	−1592	−1600	298.16[a]	−1569	−1557
318.16	−1487	−1485	323.71	−1418	−1408	303.03	−1496	−1500
333.43	−1332	−1330	336.45	−1285	−1308	313.13	−1400	−1388
						331.15	−1256	−1233

[a] Heat of vaporization from ref. 6.

ture was supplied by the fact that the experimentally determined values of $(\partial Cp/\partial P)_T$ are equal to $-T(\partial^2 V/\partial T^2)_P$. The two types of thermal data were correlated by means of the following empirical relations for the second virial coefficient B (defined by $PV = RT + BP$).

2-Methylpentane; $B = -390 - 40.26e^{1050/T}$ cc.
3-Methylpentane; $B = -318 - 91.9e^{800/T}$ cc.
2,3-Dimethylbutane; $B = -526 - 21.9e^{1150/T}$ cc.

The parameters were evaluated by previously reported methods.[8]

Table V gives data for 2-methylpentane, 3-methylpentane and 2,3-dimethylbutane which illustrate the correlations obtainable by use of these expressions for the second virial coefficients. In all cases differences between the observed and calculated values of B correspond to combined errors in the experimental values of $\Delta H_{vap.}$ and dP/dT of less than 0.1%. Reference to the last three columns of Table III further illustrates the correlations obtainable with the expressions for the second virial coefficients and also calls attention to the errors to which the Berthelot equation of state leads in calculating $C'_p - C^\circ_p$ in the region of the normal boiling point.

Kay[13] has made direct determinations of the densities of the isomeric hexanes from the normal boiling points to the critical temperatures. Table VI makes a comparison, at two temperatures, of Kay's data and vapor densities calculated from second virial coefficients. At the lower temperature, which is slightly above the normal boiling point, the agreement is within the ±0.0002 g./cc. which Kay[14] assigns to his work. In this region the use of the second virial coefficient might be expected to give more accurate results. The results at the higher temperature involve a considerable extrapolation of both temperature and pressure in the use of the second virial coefficients and yet the agreement is fair. The available evidence (see also ref. 8) suggests that second virial coefficients

TABLE VI

SATURATED VAPOR DENSITIES, G./CC.

	70°C.		150°C.	
	Kay	Virial	Kay	Virial
2-Methylpentane	0.0042	0.00430	0.0283	0.0283
2-Methylpentane	.0040	.00408	.0254	.0261
2,3-Dimethylbutane	.0048	.00468	.0290	.0287

(13) Kay, THIS JOURNAL, **68**, 1336 (1946).
(14) Kay, *ibid.*, **69**, 1273 (1947).

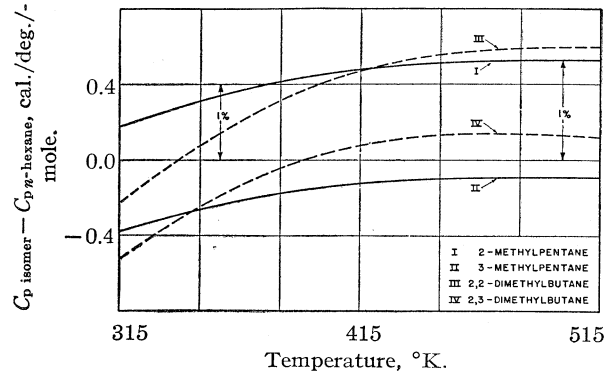


Fig. 1.—Differences between heat capacity of *n*-hexane and its isomers as a function of temperature.

derived from thermal and vapor-pressure data give an accurate and convenient method of determining volumes and related properties within the temperature and pressure range prescribed by their experimental bases.

Entropies.—The entropies of gaseous 2-methylpentane and 2,3-dimethylbutane at 298.16°K. have been computed by Pitzer and Kilpatrick.[10] The heat of vaporization and second virial coefficient data of this paper made it possible to calculate the entropies at other temperatures up to the normal boiling point and to refine the values at 298.16° K. by taking account of gas imperfection. These entropy calculations are summarized in Table VII. The values for the entropy of the liquids are from the work of Douslin and Huffman[15]; at the two higher temperatures moderate extrapolations of the heat-capacity curves for the liquids were required. The vapor-pressure equations of ref. 12 were used.

Since 3-methylpentane has never been frozen, the entropy of the liquid has not been obtained from low-temperature studies. For this compound, values for the entropy of vaporization to the ideal gas at atmospheric pressure were computed, and these calculations are included in Table VII.

Acknowledgments.—We wish to thank Mr. J. W. Tooke of the Phillips Petroleum Company for help in obtaining the hydrocarbon samples. We are also indebted to Mr. B. H. Eccleston and Mr. H. J. Coleman for the distillations and purity determinations on the three samples.

(15) Douslin and Huffman, *ibid.*, **68**, 1704 (1946).

TABLE VII

2-Methylpentane

T, °K.	298.16	318.2	333.5
S^0, liq.	69.45	72.52	74.82
Vaporization, $\Delta H_{vap.}/T$	23.95	21.58	19.92
Compression, $R \ln (P/760)$	−2.54	−1.02	0.00
Gas imperfection	0.11	0.16	0.22
S^0, gas	90.97 ±0.20	93.24 ±0.20	94.96 ±0.20

2,3-Dimethylbutane

T, °K.	298.16	313.13	331.15
S^0, liq.	66.33	68.57	71.22
Vaporization, $\Delta H_{vap.}/T$	23.34	21.62	19.69
Compression, $R \ln (P/760)$	−2.34	−1.20	0.00
Gas imperfection	0.10	0.13	0.18
S^0, gas	87.43 ±0.20	89.12 ±0.20	91.09 ±0.20

3-Methylpentane

T, °K.	298.16	323.8	336.5
Vaporization, $\Delta H_{vap.}/T$	24.27	21.28	19.95
Compression, $R \ln (P/760)$	−2.76	−0.83	0.00
Gas imperfection	0.07	0.13	0.18
ΔS°_v, liquid to ideal gas at 1 atm.	21.58 ±0.05	20.58 ±0.05	20.12 ±0.05

Summary

The vapor heat capacities of 2-methylpentane, 3-methylpentane and 2,3-dimethylbutane have been measured over the temperature range 325 to 471°K. Values of the heat capacity of the ideal gases are given by the following empirical equations.

2-Methylpentane:
$$C_p^\circ = 1.55 + 0.11963T - 3.478 \times 10^{-5}T^2$$
3-Methylpentane:
$$C_p^\circ = 1.40 + 0.11776T - 3.291 \times 10^{-5}T^2$$
2,3-Dimethylbutane:
$$C_p^\circ = -2.65 + 0.13692T - 5.433 \times 10^{-5}T^2$$

Heats of vaporization for the three compounds were measured at three temperatures ranging from about 25° to the normal boiling point. For interpolation the following equations may be used:

2-Methylpentane:
$$\Delta H_{vap.} = 9173 - 0.2673T - 0.02196T^2$$
3-Methylpentane: $\Delta H_{vap.} = 9688 - 3.366T - 0.01629T^2$
2,3-Dimethylbutane:
$$\Delta H_{vap.} = 8461 - 2.233T - 0.02438T^2$$

Entropies of 2-methylpentane and 2,3-dimethylbutane in the ideal gas state are given at the normal boiling points, at 298.16°K. and at an intermediate temperature.

Second virial coefficients derived from the thermal data are shown to be consistent with literature data on vapor densities.

BARTLESVILLE, OKLA. RECEIVED MAY 16, 1949

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF CALIFORNIA]

The Solubility of Cuprous Chloride and Silver Bromate in Aqueous Solutions of Unsaturated Alcohols[1a]

BY R. M. KEEFER, L. J. ANDREWS AND R. E. KEPNER

Extensive information concerning the reactions of allyl alcohol and certain unsaturated acids to form water-soluble complexes with cuprous ion and cuprous chloride has been accumulated.[1b,c,d,e,f]

By solubility measurements of the type used in previous investigations data have now been obtained concerning the tendency for certain allylic alcohols to form cuprous complexes. The equilibrium constants for these metalation reactions are reported here and are compared with those obtained for the unsaturated acids. Measurements of the solubility of silver bromate in aqueous solutions of certain of these alcohols and of a few other compounds of interest are also reported, the results of which may be explained satisfactorily on the assumption that a 1:1 complex between silver ion and the unsaturate is formed.[2] Thus data are available for a comparison of the relative tendencies for cuprous and silver ions to coördinate with a carbon–carbon double bond.

The Solubility Measurements.—The method of determining the solubility of cuprous chloride in aqueous solutions of unsaturated compounds has been described previously.[1d,e,f] All solutions were prepared and saturated with cuprous chloride or silver bromate at 25.0°. For the cuprous chloride series the chloride-ion concentration was varied by addition of hydrochloric acid and the ionic strength maintained at 0.100 by addition of perchloric acid prior to addition of solid cuprous chloride. In the silver bromate experiments potassium nitrate was added to the aqueous solutions of the unsaturated compounds to adjust the ionic strength to 0.10 prior to addition of solid silver bromate. Aliquots of the solutions saturated with silver bromate were analyzed for total silver ion by adding a measured excess of 0.0500 M

(1) (a) Cation Complexes of Compounds Containing Carbon–Carbon Double Bonds. V.

(1) (b) Kepner and Andrews, *J. Org. Chem.*, **13**, 208 (1948); (c) Andrews and Keefer, THIS JOURNAL, **70**, 3261 (1948); (d) Keefer and Andrews, *ibid.*, **71**, 1723 (1949); (e) Andrews and Keefer, *ibid.*, **71**, 2379 (1949); (f) Keefer, Andrews and Kepner, *ibid.*, **71**, 2381 (1949).

(2) *Cf.* Winstein and Lucas, *ibid.*, **60**, 836 (1938).

sodium chloride solution and back titrating the excess chloride ion using 0.0250 *M* silver nitrate with dichlorofluorescein as an indicator. High concentrations of alcohol interfere with the action of the indicator. In the case of 4-methyl-4-penten-2-ol, γ,γ-dimethylallyl alcohol, 3-methyl-3-buten-2-ol and 2-methyl-2-buten-1-ol the low solubility of the alcohols in water did not allow a wide variation in alcohol concentrations. With vinylacetic acid (μ = 1.0 using perchloric acid) and phenol (μ = 0.10 using potassium nitrate) the saturated solutions were analyzed for total silver ion by adding excess sodium bromide and weighing the silver bromide formed. The solubility product of silver bromate was determined in 1.00 *N* perchloric acid and in 0.100 *N* potassium nitrate. High concentrations of β-chloroallyl alcohol were needed in aqueous solution to dissolve measureable amounts of cuprous chloride. The equilibrium constants for this compound were found to vary somewhat with alcohol concentration of the medium. The results reported for this compound are thus significant only as regards the relative magnitude of the equilibrium constants as compared to those for the other alcohols studied.

Cuprous Chloride and Silver Bromate.—Cuprous chloride was prepared as described previously.[1b] Silver bromate was prepared according to the directions of Neuman.[3] The product was dried for two hours at 110°, powdered and analyzed for silver content.[4] Found: Ag, 45.90. Calcd.: Ag, 45.75.

The Unsaturated Alcohols.—The crotyl alcohol (b. p. 121.0–121.2°) was prepared from crotonaldehyde.[5] Methylvinylcarbinol (b. p. 97.3°) was prepared by hydrolysis of a butenyl chloride mixture.[6] Ethylvinylcarbinol (b. p. 113.8–114.0°) was prepared from ethylmagnesium bromide and acrolein.[7] Samples of β-methallyl alcohol (b. p. 142°), β-chloroallyl alcohol (b. p. 134.0°) and 4-methyl-4-penten-2-ol (b. p. 130.3°), furnished through the courtesy of the Shell Chemical Corporation, were dried and fractionated before use. Small samples of 3-methyl-3-buten-2-ol (b. p. 115–117°), 2-methyl-2-buten-1-ol (b. p. 138.0°), α,α-dimethylallyl alcohol (b. p. 96.0–96.5°) and γ,γ-dimethylallyl alcohol (b. p. 142–143°), kindly furnished by Professor W. G. Young and Mr. J. Rule of the University of California at Los Angeles, were dried and fractionated. J. T. Baker C. P. phenol was distilled and a fraction of b. p. 177–178° (uncor.) was collected. The preparation of the sample of vinylacetic acid has been described previously.[1e]

Results

The solubility of cuprous chloride in aqueous solutions of unsaturated alcohols is given in Table I. As in the studies of unsaturated acids[1e,f] the following equations may be shown to account for the formation of water soluble cuprous species in the experiments reported in this communication.

$$CuCl = Cu^+ + Cl^- \quad S.P. = 1.85 \times 10^{-7} \quad (1)$$

$$Cu^+ + 2Cl^- = CuCl_2^- \qquad K_2 = (CuCl_2^-)/(Cu^+)(Cl^-)^2 = 3.51 \times 10^5 \quad (2)$$

$$Cu^+ + Un = Un{\cdot}Cu^+ \qquad K_3 = (Un{\cdot}Cu^+)/(Un)(Cu^+) \quad (3)$$

$$Cu^+ + Cl^- + Un = Un{\cdot}CuCl \qquad K_4 = (Un{\cdot}CuCl)/(Un)(Cu^+)(Cl^-) \quad (4)$$

The unsaturated compound has been designated as Un and the water soluble complexes formed as Un·Cu$^+$ and Un·CuCl. The detailed procedure for evaluating K_3 and K_4 is the same as that used in previous work. The values of K_3 and K_4 are given in Table III. Table I gives the calculated

TABLE I

THE SOLUBILITY OF CUPROUS CHLORIDE IN AQUEOUS SOLUTIONS OF UNSATURATED ALCOHOLS AT 25.0° (μ = 0.10)

(Uni) mole/liter	(Cl⁻i) = 0 meas.	(Cl⁻i) = 0 calcd.	(Cl⁻i) = 0.100 *M* meas.	(Cl⁻i) = 0.100 *M* calcd.	(Cl⁻i) = 0.010 *M* meas.	(Cl⁻i) = 0.010 *M* calcd.
			(Cu⁺T) mole/liter × 10³			
Ethylvinylcarbinol						
0.0929	35.6	37.8	30.5	30.4	34.2	34.9
.0464	21.7	21.8	18.4	18.6	19.6	19.6
.0232	12.8	12.8	12.3	12.3	..	..
.0116	8.1	7.4	..	..	..	..
Methylvinylcarbinol						
.0728	30.6	30.8	25.8	26.2	..	..
.0546	24.6	24.5	21.1	21.2	..	..
.0364	18.0	17.9	16.0	16.2	16.2	15.8
.0182	10.3	10.4	..	..	..	..
α,α-Dimethylallyl alcohol						
.0910	31.1	31.7	25.3	25.5	..	..
.0682	25.2	25.2	20.5	20.6	22.5	22.7
.0455	18.5	18.5	15.8	15.9	16.5	16.2
.0228	10.9	11.0	..	..	..	..
4-Methyl-4-penten-2-ol						
.0336	12.8	12.6	11.6	12.0	10.3	10.4
.0168	7.6	7.6	9.0	9.0	6.1	5.9
.0884	4.3	4.6	..	..	..	..
γ,γ-Dimethylallyl alcohol						
.0328	10.7	10.5	10.2	10.4	7.9	7.9
.0164	..	..	8.1	8.2	5.5	5.4
3-Methyl-3-buten-2-ol						
.0504	9.1	9.3	10.0	10.1	6.8	7.1
.0378	7.7	7.6	9.0	9.1	5.5	5.4
2-Methyl-2-buten-1-ol						
.0189	4.9	5.0	8.0	8.1	3.5	3.5
β-Chloroallyl alcohol						
.500	8.2	8.0	9.5	9.5	5.8	5.6
β-Methallyl alcohol			(Cl⁻i) = 0.101 *M*		(Cl⁻i) = 0.0101 *M*	
0.0708	17.8	17.9	15.8	16.0	15.0	15.1
.0472	13.2	13.4	12.1	12.7	10.8	10.7
.0236	8.1	8.0	9.6	9.4	..	..
Crotyl alcohol			(Cl⁻i) = 0.102 *M*		(Cl⁻i) = 0.0102 *M*	
0.142	26.8	27.6	22.0	21.4	23.7	24.5
.106	..	..	17.4	17.6	18.7	19.3
.0708	..	..	13.9	13.8	..	..
.0688	16.6	16.3	..	..	..	..
.0342	10.2	10.0	..	..	..	..

(3) Neuman, THIS JOURNAL, **56**, 28 (1934).
(4) Ricci and Aleshnick, *ibid.*, **66**, 980 (1944).
(5) Young, Hartung and Crossley, *ibid.*, **58**, 100 (1936).
(6) Young and Andrews, *ibid.*, **66**, 421 (1944).
(7) (a) Delaby, *Compt. rend.*, **175**, 967 (1922); (b) Prévost, *Ann. Chim.*, [10] **113**, 147 (1928).

solubilities of cuprous chloride in solutions of the unsaturated compounds ($Cu^{+}{}_{T}$ calcd.) using the values of K_3 and K_4 given.[1e,f] The agreement between experimental ($Cu^{+}{}_{T}$ measd.) and calculated values is as good as may be expected considering the experimental errors.

The solubility of silver bromate in aqueous solutions of unsaturated compounds ($Ag^{+}{}_{T}$) is reported in Table II. These results may be explained on the assumption that equations (5) and (6) account for the formation of all water-soluble forms of silver ion.[8]

$$AgBrO_3 = Ag^+ + BrO_3^- \quad \text{S. P.} = 1.00 \times 10^{-4} \quad (5)$$

$$Ag^+ + Un = Un\cdot Ag^+ \qquad K_6 = (Un\cdot Ag^+)/(Un)(Ag^+) \quad (6)$$

TABLE II

THE SOLUBILITY OF SILVER BROMATE IN AQUEOUS SOLUTIONS OF UNSATURATED COMPOUNDS AT 25.0° (μ = 0.10)

(Uni) mole/liter	($Ag^{+}{}_{T}$) mole/liter × 10^2	K_6	(Uni) mole/liter	($Ag^{+}{}_{T}$) mole/liter × 10^2	K_6
Allyl alcohol			Methallyl alcohol		
0.585	2.98	14.0	0.470	2.42	10.8
.293	2.20	14.0	2.35	1.84	10.8
.146	1.69	13.8	.118	1.48	10.8
.0732	1.38	13.6	.059	1.27	11.2
Crotyl alcohol			Methylvinylcarbinol		
.702	1.87	3.6	.255	2.12	14.7
.527	1.73	3.9	.204	1.93	14.3
.351	1.54	4.0	.102	1.53	14.5
.176	1.30	4.0	.051	1.28	13.9
.0878	1.16	4.1	.025	1.14	12.9
Ethylvinylcarbinol			2-Methyl-2-buten-1-ol		
.472	2.68	13.8	.100	1.21	4.8
.236	2.04	14.2	.050	1.12	4.9
.0944	1.52	15.3	.020	1.05	5.5
.0472	1.28	15.2			
Vinylacetic acid[a,b]			Phenol[a]		
.467	2.90	16.2	.448	1.28	1.54
.234	2.15	16.1	.224	1.14	1.48
.117	1.67	16.1	.112	1.07	1.59
.0585	1.37	15.8	0	0.989	...
0	1.01	..			

[a] Analysis by silver bromide precipitation method. [b] μ adjusted to 1 using perchloric acid.

The concentrations of substances needed to calculate K_6 were readily obtained by use of equation (5) and equations (7) and (8) in which ($Ag^{+}{}_{T}$) represents the total molar concentration of free and complexed silver ion in solution at equilibrium, and (Un_i) is the initial molar concentration of the unsaturate in aqueous solution before the addition of silver bromate. The values of K_6 calculated are given in Table II and some of these are summarized in Table III to permit comparison with the K_3 values obtained for the formation of the corresponding cuprous complexes.

$$(Ag^{+}{}_{T}) = (BrO_3^-) = (Ag^+) + (Un\cdot Ag^+) \quad (7)$$

$$(Un) = (Un_i) - (Un\cdot Ag^+) \quad (8)$$

TABLE III

EQUILIBRIUM CONSTANTS FOR FORMATION OF THE COPPER AND SILVER COMPLEXES OF THE UNSATURATED ALCOHOLS AT 25° (μ = 0.1)

Unsaturate	Ag^+ complex $K_6 \times 10^{-3}$	Cu^+ complexes $K_3 \times 10^{-3}$	$K_4 \times 10^{-5}$
Allyl alcohol	0.014	52[a]	22[a]
Ethylvinylcarbinol	.014	39	15
Methylvinylcarbinol	.014	33	17
α,α-Dimethylallyl alcohol	....	25	12
4-Methyl-4-penten-2-ol	....	16	9.7
γ,γ-Dimethylallyl alcohol	.002	11	7.0
Crotyl alcohol	.0039	10	5.4
β-Methallyl alcohol	.011	9.2	7.6
3-Methyl-3-buten-2-ol	....	4.0	4.2
2-Methyl-2-buten-1-ol	.005	3.5	5.9
β-Chloroallyl alcohol	0	0.22	0.35

[a] Calculated from data of Ref. 1d.

Structures of the type previously proposed for silver or cuprous complexes of compounds containing carbon–carbon double bonds[1,2] seem appropriate to describe the complexes formed by the unsaturated alcohols investigated in the present study. In general the K_3 and K_4 values for cuprous complex formation of the α,β-unsaturated alcohols are somewhat higher than those observed for the α,β-unsaturated acids investigated previously. Since a carboxyl group conjugated with a carbon–carbon double bond should markedly decrease the electron density at the double bond through both resonance and inductive effects, this observation seems reasonable. As in the case of the unsaturated acids, replacement of hydrogen atoms by methyl substituents at the double bond in the unsaturated alcohols reduces the magnitude of K_3 and K_4. As previously noted this may result from steric effects of the methyl substituents. It is interesting to note that α-alkyl-substituted allyl alcohols (*cf.* crotyl alcohol and methylvinylcarbinol) also show lower K_3 and K_4 values than does allyl alcohol. Molecular models show that such alkyl substituents might inhibit the tendency for cation complexing at the double bond because of steric effects. In the case of β-chloroallyl alcohol low values of K_3 and K_4 were found as compared to those for allyl alcohol, as might be expected in view of the inductive effect of a chlorine substituent.

The values of K_3/K_4, representing the equilibrium constant for the ionization of Un·CuCl to produce Un·Cu^+ and chloride ion, vary from 2.4 × 10^{-2} for allyl alcohol to 0.6 × 10^{-2} for 2-methyl-2-buten-1-ol and β-chloroallyl alcohol. These

(8) The value for the solubility product of silver bromate is based on measurements of the solubility of silver bromate in 0.1 *N* potassium nitrate solution by titration procedures and is in good agreement with the results of Dalton, Pomeroy and Weymouth, THIS JOURNAL, **46**, 60 (1924). In the experiments with phenol using a gravimetric method of analysis for silver a solubility product of 0.978 × 10^{-4} was obtained for silver bromate in 0.1 *N* potassium nitrate solution. For the runs using vinylacetic acid the silver bromate solubility product was determined for 1 *N* perchloric acid solution by the gravimetric method as 1.029 × 10^{-4}.

values are of the same order of magnitude as were obtained for the corresponding equilibrium constants determined in the studies of the unsaturated acids.[1f] It is interesting to note that the earlier observation[1e] that the magnitude of K_3/K_4 is much less affected by changes in structure of the unsaturate than are the K_3 and K_4 values is upheld in the present investigation.

The equilibrium constants for the silver complexes of phenol, crotyl alcohol and allyl alcohol reported in Table II agree favorably with those obtained by somewhat different procedures by Winstein and Lucas[2] (2.19, 5.17 and 12, respectively) for solutions of ionic strength equal to 1. The change in ionic strength should have little effect on the equilibrium constants so that the values may be compared directly. Structures of the type previously proposed for silver ion and aromatic compounds would seem appropriate for the silver ion–phenol complex.[2,9] In general the values of K_6 follow the same trends as do the values of K_3. However, the effect of varying substituents at the double bond does not produce as marked an effect on K_6 as on K_3. It is interesting to note that the cuprous complexes are much more stable than the silver complexes as may be seen by comparing the values of K_3 and K_6 given in Table III. As in the case of the cuprous complexes, silver ion complexes vinylacetic acid to about the same extent as it does allyl alcohol. Even with saturated solutions of maleic and fumaric acid no indication of complex formation with silver ion could be obtained. This again would be in agreement with the results obtained with cuprous ion which indicated that the maleic and fumaric acid complexes were much less stable than the vinylacetic acid complex.

(9) Keefer and Andrews, THIS JOURNAL, **71**, 3644 (1949).

Summary

By measurement of the solubility of cuprous chloride or silver bromate in aqueous solutions of unsaturated alcohols, equilibrium constants for the reactions to form the complexes Un·Cu^+, Un·CuCl and Un·Ag^+ at 25° have been determined. The cuprous ion complexes are considerably more stable than the corresponding silver ion complexes. α,β-Unsaturated alcohols show a somewhat greater tendency for this type of complex formation than do α,β-unsaturated acids. When hydrogen atoms at the double bond are replaced by methyl groups, the tendency for the unsaturated alcohols to undergo cuprous complex formation is reduced.

DAVIS, CALIFORNIA RECEIVED MAY 28, 1949

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

The Exchange Reaction between Antimony(III) and Antimony(V) in Hydrochloric Acid Solutions

BY NORMAN A. BONNER

This paper deals with a preliminary study of the exchange reaction between antimony(III) and antimony(V) in hydrochloric acid solutions. The kinetics of the exchange have been studied in 6 *f* hydrochloric acid, and in addition, the rates of exchange have been measured in 3 *f* and 12 *f* hydrochloric acid. In 6 *f* acid, half-times in the neighborhood of sixty hours were observed and the rate was found to depend critically on the hydrochloric acid concentration.

Experimental

Tracers.—The 60-day Sb^{124} tracer was obtained from the Atomic Energy Commission in the form of 200 mg. of metallic antimony which had been irradiated in the Clinton Pile. The metal was boiled with a small amount of aqua regia, the resulting oxide dissolved in concentrated hydrochloric acid, and the solution boiled to remove chlorine and nitrogen oxides. Stock +3 tracer solutions were made by diluting aliquots of the above solution to about 3 *f* hydrochloric acid and passing hydrogen sulfide into the boiling solution until the antimony sulfide turned black. The sulfide was filtered off, washed, dissolved in 6 *f* hydrochloric acid, boiled to remove hydrogen sulfide and diluted to a known volume with 6 *f* hydrochloric acid.

The +5 tracer solutions were prepared in the same manner except that after the sulfide precipitate had been dissolved and the hydrogen sulfide removed, the 6 *f* hydrochloric acid solution was diluted with an equal volume of distilled water and chlorine gas bubbled through the hot solution for several hours. The solution was then boiled to remove chlorine and bring the hydrochloric acid concentration to 6 *f*. The final, known volume was obtained by dilution with 6 *f* hydrochloric acid.

As a check on the radiochemical purity of the tracer, a sample was sealed in a test-tube and the γ-radiation counted at intervals in a standard geometry with the same brass-wall Geiger–Mueller counter. The counter itself was checked against a similar 5.3-year Co^{60} standard and found to give the same corrected counting rate, within the statistical counting error, at all times.

The antimony sample decayed with a 60 ± 1-day half-life over a period of five half-lives in satisfactory agreement with the previously determined value.[1] The antimony had been received from Oak Ridge more than a month before these particular experiments were started and the standard was prepared so the activity of the 2.8-day Sb^{122} (and any short-lived impurities) had decreased to an immeasurably small value.

Reagents.—Analytical reagents were used.

The +3 and +5 antimony carriers were made up in the same manner as the corresponding tracers, but the starting material was an accurately weighed sample of antimony trioxide instead of antimony metal. The trioxide was analyzed by triiodide titration and found to be 99.9% pure.

The carrier, tracer and hydrochloric acid solutions were all analyzed gravimetrically for total chloride by the pre-

(1) Seaborg and Perlman, *Rev. Modern Phys.*, **20**, 585 (1948), list the half-life as sixty days.

cipitation of silver chloride. The precipitation was carried out in the presence of tartaric acid in the case of the carrier and tracer solutions in order to prevent the precipitation of antimony.

The hydrogen ion and chloride ion concentrations were calculated from the known total antimony and chloride concentration with the assumption that the principal forms of the +3 and +5 complexes in 6 *f* hydrochloric acid are $SbCl_4^-$ and $SbCl_6^-$, respectively. If these formulas are wrong (as is easily possible) the hydrogen ion and chloride ion concentrations will be correspondingly slightly in error.

Reaction mixtures were prepared by adding the proper amounts of carrier, hydrochloric acid and tracer solutions in the order mentioned to a 25-ml. volumetric flask. The time at which the tracer solution was added to the other reagents was taken as the time origin for the exchange reaction. At temperatures other than 25°, the carrier mixture was allowed to come to temperature equilibrium with the thermostat before the tracer was added.

The isopropyl ether used in the separation procedure was freed from peroxides by repeated shakings with ferrous ammonium sulfate solution acidified with sulfuric acid. The ether was stored over an acidified solution of ferrous ammonium sulfate. This purification step was found necessary in order to prevent the oxidation of antimony (III) to antimony(V) by the peroxides. No other purification was carried out.

Separation Procedures.—For the 6 *f* and 12 *f* runs, ether extraction was used as the separation method, the only difference between the two cases being that the aliquots from the 12 *f* run were diluted with an equal volume of water before proceeding.

An aqueous solution 2.14 *f* in magnesium chloride, 6.0 *f* in hydrochloric acid was prepared and saturated with isopropyl ether. An 11.7-ml. portion of this solution was mixed with 16.7 ml. of isopropyl ether. To carry out the separation, 5.0 ml. of the reaction mixture was added to the above two-phase system. The mixture was shaken vigorously for one minute in a centrifuge tube fitted with a ground-glass top, then centrifuged for five minutes. For the 9.8 and 25.0°-runs in 6 *f* hydrochloric acid the time at which centrifugation was started was taken as the time of separation. In the 34.6°-run, the time at which the aliquot was added to the other reagents was taken as the time of separation. In the 12.0 *f* experiment, the time of separation was considered to be the time at which the aliquot was diluted with water. Aliquots of the two phases were pipetted off, weighed to the nearest 0.02 g. and the γ-radiation counted. The total activity in each phase was calculated from the known density and with the assumption that the total volume of each phase did not change when the ether and the hydrochloric acid solutions were mixed. Semi-quantitative experiments indicated that this assumption was justified. It was further justified by the fact that the sum of the activities of the two fractions always equalled, within experimental error, the activity of a standard containing the same total amount of tracer.

Under the above conditions it was found that 98% of the antimony(V) went into the ether phase and 98% of the antimony(III) remained in the aqueous phase. No exchange (0 ± 2%) was observed during the separation.

The separation procedure used in the experiment in 3 *f* hydrochloric acid involved the precipitation of antimony (III) with 8-hydroxyquinoline. The reaction mixture (20 ml.) was added to several ml. of solution containing a total of 1 g. of citric acid. To this was added about 25 ml. of 7 *f* ammonium hydroxide and 4 ml. of a 2% solution of 8-hydroxyquinoline in 2 *f* acetic acid. The resulting mixture was heated on a steam-bath for about one and one-half hours and then filtered. The precipitate was mounted on filter paper and the β-radiation counted under cellophane. The filtrate was acidified and antimony sulfide precipitated with hydrogen sulfide. The precipitate was filtered and the β-radiation counted. Each of the two samples was analyzed for antimony.

Less than 2% exchange occurred during this separation procedure.

Counting Procedures.—Gamma radiation was counted directly from the solutions by placing a test-tube containing the sample in a standard geometry near a brass-wall Geiger–Mueller counter. The test-tubes were always filled to the same height and were calibrated so that corrections could be made for slight differences in counting rate due to differences in the dimensions of individual tubes. A correction was also applied for the difference in counting rate of the same size sample in ether and in aqueous solution. The counting rate in ether was found to be 2% higher than in the hydrochloric acid–magnesium chloride solution used.

For β-counting the sulfide or 8-hydroxyquinoline precipitates were mounted under cellophane on cards which could be placed in a standard position under an 8 mg./sq. cm. dural window in the side of a brass Geiger–Mueller counter.

No coincidence corrections were applied to either γ- or β-counting rates, since the highest counting rate used was about 2000 c./min. and the usual rate was 1000 or less. The coincidence correction on the counters used amounted to less than 2% at a counting rate of 2000 c./min.

Results

The reaction studied is $Sb^{III\prime} + Sb^{V} = Sb^{III} + Sb^{V\prime}$, where the primes indicate radioactive atoms. For this particular reaction, the logarithmic form of the first order exchange law[2] is

$$-\ln(1 - F) = \frac{R[(Sb^{III}) + (Sb^{V})]t}{(Sb^{III})(Sb^{V})}$$

where

(Sb^{III}) = total concentration (active + inactive) of Sb^{III}

(Sb^{V}) = total concentration (active + inactive) of Sb^{V}

$F = (Sb^{V})'/(Sb^{V})'_{\infty}$ = fraction exchange at time, t, when $(Sb^{V})' = 0$ at $t = 0$

($F = (Sb^{III})'/(Sb^{III})'_{\infty}$ if $(Sb^{III})' = 0$ at $t = 0$)

$(Sb^{V})'_{\infty} = (Sb^{V})'$ at time, $t = \infty$

R = actual rate at which exchange of antimony atoms occurs between Sb^{III} and Sb^{V}. R will be constant during any one experiment, since (Sb^{III}) and (Sb^{V}) are then constant.

According to this equation, a plot of log $(1 - F)$ *vs.* time should give a straight line regardless of the mechanism of the reaction. The only requirements are that the exchange reaction be homogeneous[3] and all conditions (including the concentrations of reactants and products) be kept constant. Further, if one (or both) of the reacting chemical species contains more than one antimony atom, the atoms must be chemically equivalent.

In general, a set of four measurements of F, the fraction exchange, were made at different times for each experiment. In all cases a straight line passing through the origin was obtained when log $(1 - F)$ was plotted *vs.* time. Figure 1 is a typical example of such a plot.

When 50% exchange has occurred, $F = 1/2$, $(1 - F) = 1/2$ and $t = T_{1/2}$ by definition. At this point

$$R = \frac{(Sb^{III})(Sb^{V})\ \ln 2}{[(Sb^{III}) + (Sb^{V})]T_{1/2}}$$

(2) Duffield and Calvin, THIS JOURNAL, **68**, 557 (1946), or Friedlander and Kennedy, "Introduction to Radiochemistry," John Wiley and Sons, Inc., New York, N. Y., 1949.

(3) In this situation the meaning of "homogeneous" includes the possibility that the reaction is heterogeneously catalyzed. It is necessary, however, that the reactants and products exist principally in one, homogeneous medium.

TABLE I

RESULTS OF EXCHANGE EXPERIMENTS

Expt.	Tracer	Sb(III) concn., f	Sb(V) concn., f	(Cl^-), f	(H^+), f	$T_{1/2}$, hr.	$R^a \times 10^5$	$R'^b \times 10^{14}$	$k^c \times 10^{11}$
1	III	0.0219	0.0198	5.700	5.742	97.2	7.40	1.073	7.99
2	III	.0219	.0198	5.452	5.494	178.5	4.04	1.041	7.74
3	III	.0219	.0198	5.543	4.750	261	2.76	1.100	8.18[d]
4	III	.0219	.0198	5.786	5.494	97.0	7.43	1.120	8.33[e]
5	V	.0039	.0022	3.0	3.0	~1400			[f]
6	III	.0235	.0198	12.0	12.0	0.604			
7	V	.0211	.00082	6.046	6.068	90.5	0.605	0.0414	10.41
8	III	.0219	.00792	6.016	6.045	75.5	5.34	0.388	7.89
9	III	.0217	.0196	5.950	5.992	55.5	12.88	1.068	8.04
10	III	.0219	.0396	5.836	5.898	40.2	24.3	2.55	8.85
11	III	.00082	.0198	6.048	6.069	20.8	2.62	0.1783	9.50
12	III	.00924	.0198	6.008	6.037	41.0	10.63	0.785	9.80
13	III	.0227	.0198	5.910	5.952	53.0	13.82	1.252	9.10
14	III	.0430	.0396	5.736	5.819	47.5	30.03	3.90	9.01
15	III	.0211	.0198	5.983	6.024	49.0	14.47	1.119	8.54[g]
16	V	.0211	.0214	5.881	5.923	60.5	12.17	1.172	8.19[h]
17	V	.0209	.0204	5.935	5.977	49.5	14.46	1.241	9.16
18	III	.00925	.00791	6.076	6.093	74.8	3.95	0.254	8.70
19	V	.00842	.00874	6.061	6.078	62.0	4.79	0.559	10.32
20	V	.0211	.0214	5.881	5.923	61.5	11.97	1.153	8.06
21	V	.0211	.0214	5.881	5.923	708	1.040	0.1011	0.706[i]
22	V	.0211	.0214	5.881	5.923	14.2	51.9	5.01	35.0[j]

[a] $R = (Sb^{III})(Sb^V)\ 0.693/[(Sb^{III}) + (Sb^V)]T_{1/2}$. [b] $R' = R/(H^+)^4(Cl^-)^9$. [c] $k = R'/(Sb^{III})^{0.6}(Sb^V)^{1.1}$. [d] The solution also contained 0.834 mole/l. of Na^+. [e] The solution also contained 0.3336 mole/l. of Na^+. [f] Only one point obtained on the exchange curve. [g] Low activity. β-counting used. [h] Flask packed with glass beads. [i] 9.8°. [j] 34.6°.

In any given experiment the antimony(III) and antimony(V) concentrations are known, and $T_{1/2}$ can be obtained from the plot of log $(1 - F)$ *vs.* t. It is then possible to calculate the value of R, the rate of exchange, for each experiment.

Effect of Hydrochloric Acid Concentration.—The hydrochloric acid concentration varied from one experiment to the next as the antimony concentrations were changed, so it was necessary to determine the effect of this variation. In addition, the dependence of the rate of exchange on the hydrochloric acid concentration is of interest in itself.

By a process of trial and error, with the first approximations based on experiments 1–4 (see Table I in which the data for all experiments are summarized) it was found that the best values of the dependences on hydrogen ion and chloride ion concentrations were 4.0 ± 0.5 and 9.0 ± 0.5, respectively. In other words, in a series of experiments in which the antimony concentrations are kept constant and the hydrogen ion and chloride ion concentrations are varied, the expression $R/[(H^+)^4(Cl^-)^9]$ is essentially constant. R is the measured rate of the reaction. Any other values of the exponents give a less constant result.

The total variation in the hydrogen ion concentration was from 4.7 f to 6.1 f, and the chloride ion concentration varied from 5.4 f to 6.1 f. In experiments 3 and 4 Na^+ was added, as sodium chloride solution, to allow independent variation of (H^+) and (Cl^-).

The actual numbers 4 and 9 have no fundamental significance under these circumstances since the activity coefficients of hydrogen ion, chloride ion and the antimony ions undoubtedly suffer large changes with small changes in the hydrochloric acid concentration.

The function $R' = R/[(H^+)^4(Cl^-)^9]$ is thus an empirical expression which corrects the measured rates for changes in the concentrations of hydrogen ion and chloride ion. Furthermore, it corrects the rate for variations in the activity coefficients of hydrogen ion, chloride ion and the antimony ions resulting from changes in the hydrochloric acid concentration.

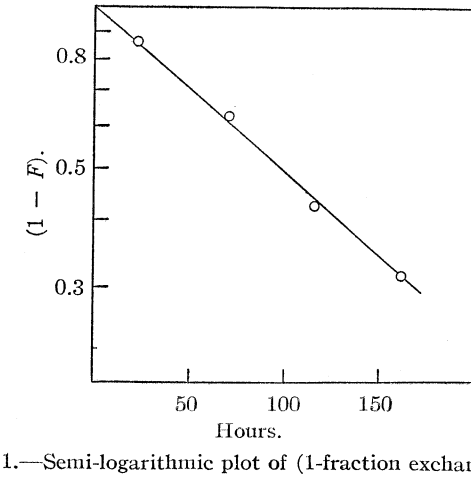


Fig. 1.—Semi-logarithmic plot of (1-fraction exchange) *vs.* time for run 1: $T_{1/2}$ = 97.2 hr.

In addition to the series of experiments in 6 *f* hydrochloric acid, one experiment was carried out in 3 *f* and one in 12 *f* hydrochloric acid. Both experiments were done at 25.0°.

In the 3 *f* experiment (No. 5), only one point was measured on the exchange curve. At 191.5 hours, exchange was 9.3% complete with antimony(III) and antimony(V) concentrations of 0.0039 *f* and 0.0022 *f*, respectively. The half-time is thus approximately 1400 hours. The 8-hydroxyquinoline precipitation method was used for the separation.

In 12.0 *f* hydrochloric acid with antimony(III) and antimony(V) concentrations of 0.0235 *f* and 0.0198 *f*, respectively, the half-time was 36.2 min. (Expt. no. 6). A plot of the values of log $(1 - F)$ *vs.* t for the four points obtained gave a straight line passing through the origin.

Effect of Antimony Concentrations.—Figure 2 is a plot of log $R' = R/(Cl^-)^9(H^+)^4]$ *vs.* log (Sb^V) with the antimony(III) concentration held at 0.0219 *f* (Experiments 7–10). In two cases the concentrations were slightly different from 0.0219 and the rates were adjusted according to the correction discussed in the next paragraph. The slope of the line, and therefore the dependence of the rate on the antimony(V) concentration, is 1.1 ± 0.1.

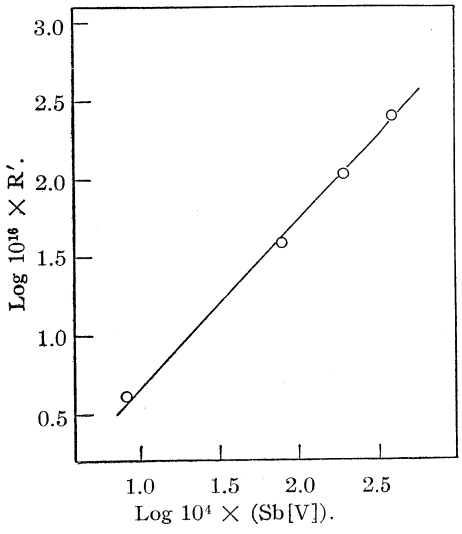


Fig. 2.—Dependence of rate of exchange on antimony(V) concentration: antimony(III) concentration = 0.0219 *f*; slope = 1.1 ± 0.1.

Figure 3 is a similar plot of log R' *vs.* log (Sb^{III}), the antimony(V) concentration being 0.0198 *f*. Also included is a point corresponding to an antimony(V) concentration of 0.0396 *f* which has been corrected to 0.0198 *f* (Experiments 11–14). The slope of the line is 0.60 ± 0.05.

An inspection of Table I shows that the rates are the same within experimental error regardless of whether the tracer is added in the form of antimony(III) or antimony(V).

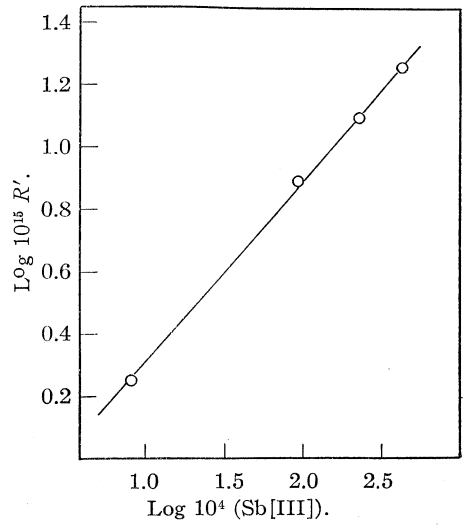


Fig. 3.—Dependence of rate of exchange on antimony (III) concentration: antimony(V) concentration = 0.0198 *f*; slope = 0.6 ± 0.05.

It should be emphasized at this point that the values 0.6 and 1.1 for the antimony(III) and antimony(V) concentration dependences are much less arbitrary than are the values for the hydrogen ion and chloride ion concentration dependences. The corrected rate, R', includes empirical corrections for changes in the activity coefficients of the antimony ions caused by changes in the hydrochloric acid concentration.

As a result, the values 0.6 and 1.1 are probably very nearly the correct ones. It seems likely that the true values are 0.5 and 1.0.

One effect has not been allowed for, however. No corrections have been made for variations in the activity coefficients of the antimony ions resulting from changes in their own concentrations. At an ionic strength of about 6, one might expect these particular changes to be small.[4] Since no accurate method is known for making corrections of this type, it has been assumed for the present that the effect is small.

Effects of β-Radiation.—In order to eliminate the possibility that β-radiation was affecting the rate of exchange a run was made in which the amount of active antimony was approximately $^1/_{80}$ of the maximum amount used. In this experiment the separation was carried out by ether extraction as usual, but the antimony in the samples was precipitated as sulfide and β-counted. The value of the rate constant for this run (no. 15) was, within experimental error, the same as the average value. Therefore, any effect of radiation is negligible.

Effect of Surface Area of the Reaction Vessel.—A run was made in a 100-ml. volumetric

(4) Nachtrieb and Fryxell, THIS JOURNAL, **70**, 3552 (1948), in studies of the distribution of iron(III) between ether and hydrochloric acid solutions have found effects which can be explained by assuming that a change in the (small) iron concentration causes an appreciable change in the activity coefficient in spite of the fact that the hydrochloric acid concentration is kept constan .

flask packed with soft glass beads instead of in the usual 25-ml. flask. The flask was rotated in the thermostat in such a way that the solution was continuously flowing over the beads. The rate constant for this run (no. 16) was the same as the average, within experimental error.

The Rate Law.—From the foregoing discussion, it appears that the empirical rate law for the antimony(III)–antimony(V) exchange reaction at 25.0° is

$$R = (8.8 \pm 0.9) \times 10^{-11} (Sb^{III})^{0.6}(Sb^{V})^{1.1}(H^{+})^{4}(Cl^{-})^{9}$$

where all concentrations are uncorrected formal concentrations, and the units of R are moles $\times$ liters^{-1} $\times$ hr.$^{-1}$.

The chloride ion concentrations were calculated by analyzing for total chloride and subtracting the amount of chloride complexed with antimony, assuming the formulas $SbCl_4^-$ and $SbCl_6^-$ for the +3 and +5 states, respectively. The hydrogen ion concentrations are then the sum of the chloride ion and the total antimony concentrations. (Except in the case where Na^+ was present, when in addition an analysis of the added sodium chloride solution was necessary.)

This rate law is valid in the ranges of concentration (H^+) = 4.7 f to 6.1 f, (Cl^-) = 5.4 f to 6.1 f, antimony(III) = 0.0008 f to 0.040 f antimony(V) = 0.0008 f to 0.040 f, and (Na^+) = 0.0 f to 0.8 f.

Most of the variation in the value of the rate constant is probably due to slight uncertainties in the hydrochloric acid concentration. A difference of 1% in the hydrochloric acid concentration would lead to a difference of almost 15% in the rate.

The Activation Energy.—Three experiments were carried out at temperatures of 9.8, 25.0 and 34.6°, respectively (Expts. 20–22). The solutions were all made up at the same time, using the same pipets in order that differences in the concentrations of the various ions be minimized.

The experimental activation energy calculated from this set of data is 27 ± 2 kcal./mole.

Discussion of Results

At the present time there appears to be a considerable lack of knowledge concerning the nature of the ions existing in solutions of antimony in hydrochloric acid. There is a large amount of experimental information on the behavior of antimony solutions,[5] but it is mostly not applicable to a determination of the true nature of the ions in 6 f hydrochloric acid.

Lingane[6] presents some polarographic evidence that the formula of the antimony(V) ion in 6 f hydrochloric acid is $SbCl_6^-$. In addition, the acid $HSbCl_6$ and its salts have been prepared.[7] The evidence is admittedly far from conclusive, but since there appears to be no particular reason to doubt this formula, it is the generally accepted one.

The case of the antimony(III) ion (or ions) is even more uncertain. Either of the formulas $SbCl_4^-$ or $SbCl_6^{\equiv}$ is generally assumed,[8] but formulas such as $SbOCl_2^-$ are not necessarily excluded.[9] In the case of solutions in hydrobromic acid there is even a small amount of evidence for the ion $Sb_3Br_{11}^{\equiv}$.[10]

Probably the most interesting result of the exchange experiments is that the rate of exchange does not depend on the first power of the antimony(III) concentration. If the activated complex for the exchange is an ion such as $Sb_2Cl_{12}^{=4}$ ($SbCl_6^{\equiv}$ + $SbCl_6^-$) in which the two antimony atoms are equivalent, one would expect the rate to be first order with respect to the concentrations of antimony(III) and of antimony(V). Since the rate actually depends on the ~1/2 power of the antimony(III) concentration, it is possible that an ion such as $Sb_2Cl_n^{-(n-6)}$ might be the principal antimony(III) ion in solution and be in equilibrium with $SbCl_6^{\equiv}$.

There is some evidence for the existence of the antimony(III)–antimony(V) complex $Sb_2Cl_{12}^{-4}$. The salts of the type Rb_2SbCl_6 are diamagnetic,[11] indicating that the antimony atoms are alternately in the (+3) and (+5) oxidation state, and not in the (+4) state. In addition Whitney and Davidson[12] have obtained spectrophotometric evidence for a +3–+5 complex ion in 11.3 f hydrochloric acid. The concentration of the complex, however, is proportional to the first power of each of the antimony oxidation states.

Furthermore, the experiment in 12.0 f hydrochloric acid (No. 6) would be expected to indicate extremely rapid exchange if the complex observed by Whitney and Davidson were the activated complex. The half-time at 25° was actually 36.2 minutes.

It thus appears that the complex observed by Whitney and Davidson is not the activated complex of the exchange reaction.

Whitney, *et al.*,[13] have found the same effect in the case of the tin(II)–tin(IV) system in hydrochloric acid. A colored complex is formed, but the exchange reaction is relatively slow. Their tentative explanation is that either the slow step in the reaction is the exchange of tin atoms between two different complexes of tin in the same oxidation state (the complex which is

(5) For example, Thorneycroft, Vol. VI, part V of Friend's "Textbook of Inorganic Chemistry," Charles Griffin and Co., Ltd., London, 1936.

(6) Lingane, THIS JOURNAL, **69**, 530 (1947).

(7) Weiland and Feige, *Ber.*, **36**, 244 (1903); and Weiland and Schmid, *Z. anorg. Chem.*, **44**, 37 (1905).

(8) See, for example, Latimer, "The Oxidation States of the Elements and their Potentials in Aqueous Solutions," Prentice Hall, Inc., New York, N. Y., 1938, p. 111.

(9) A few qualitative transference experiments done by the author of this paper show definitely that the antimony ions are negatively charged in 6 f hydrochloric acid.

(10) Vournasos, *Z. anorg. allgem. Chem.*, **192**, 369 (1930).

(11) Elliott, *J. Chem. Phys.*, **2**, 298 (1934).

(12) Whitney and Davidson, THIS JOURNAL, **69**, 2076 (1947).

(13) Whitney, Browne, McConnell and Davidson, *Brookhaven Conference Report*, **BNL-C-8**, p. 196, December 1–3, 1948.

responsible for the optical interaction and the exchange reaction is then assumed to be present at very low concentration), or the colored complex is not the activated complex for the exchange.

As a result of the lack of accurate knowledge concerning the nature of the ions in solution, it seems rather futile to attempt to decide definitely on the mechanism of the exchange reaction at present.

Further experiments designed to obtain more information about the nature of the antimony ions are planned.

Summary

1. A method has been developed for the separation of antimony(V) from antimony(III) by means of an ether extraction from hydrochloric acid solution.

2. A study of the rate of the exchange reaction between antimony(III) and antimony(V) shows that the rate law at 25.0°, with hydrogen ion concentrations from 4.7 f to 6.1 f, chloride ion concentration from 5.4 f to 6.1 f, antimony(III) concentrations from 0.0008 f to 0.040 f, antimony (V) concentrations from 0.0008 f to 0.0040 f and Na^+ concentrations from 0.0 f to 0.8 f is $R = (8.8 \pm 0.9) \times 10^{-11} (Sb(III))^{0.6} (Sb(V))^{1.1} (H^+)^4 (Cl^-)^9$ mole $\times$ liter$^{-1} \times$ hr.$^{-1}$.

3. In the same ranges of concentrations the experimental activation energy is 27 ± 2 kcal./mole (measurement made at 9.8, 25.0 and 34.6°).

4. In 12.0 f hydrochloric acid at 25.0° the half-time for exchange is 36.2 minutes with an antimony(III) concentration of 0.0235 f and an antimony(V) concentration of 0.0198 f.

ST. LOUIS, MO. RECEIVED MAY 31, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE COLLEGE OF WASHINGTON]

Polarography of Calcium, Strontium and Barium in Liquid Ammonia

BY C. J. NYMAN

The polarographic characteristics of several ions in liquid ammonia have been previously reported.[1] The present paper deals with the reduction of calcium, strontium and barium salts in this solvent.

Experimental

The electrolysis cells and apparatus for preparing the anhydrous liquid ammonia solutions have been described previously.[1] The cell with the internal reference electrode was used in all cases.

The dropping mercury electrode had the following characteristics in a saturated solution (0.021 M) of tetraethylammonium iodide in liquid ammonia at −36°. At a pressure of 20 cm., the drop time t was 5.1 sec. (open circuit) and the mass of mercury m flowing through the capillary was 1.184 mg./sec.

A Fisher Elecdropode, calibrated in the usual manner, was used in this investigation. All applied potentials were checked by means of a student type potentiometer.

The ammonia, barium nitrate and strontium nitrate were C. P. materials of commerce. Calcium iodide was prepared in the following way: 3 g. of calcium hydroxide was made into a slurry with 100 cc. of water, and then ammonium iodide was added until all the calcium hydroxide dissolved. The solution was filtered, and an additional 15 g. of ammonium iodide was added. The solution was evaporated almost to dryness on a hot-plate, and the resulting paste was transferred to porcelain boats. These were placed in a Pyrex combustion tube and heated by means of a tube furnace. A stream of dry hydrogen was used to sweep the water vapor and excess ammonium iodide from the region of the boats. The temperature was raised slowly to about 150° and held for two hours, when it was increased to 400° for two hours. The material was allowed to cool with the stream of hydrogen still passing through the tube. On analysis, the calcium iodide contained less than 0.5% impurity. The purification of the tetraalkylammonium salts has been described previously.[1]

(1) For previous papers, see H. A. Laitinen and C. J. Nyman, THIS JOURNAL, **70**, 2241, 3002 (1948).

Data and Discussion

Figure 1 shows typical polarograms obtained on electrolysis of calcium iodide solutions when using tetraethylammonium iodide as indifferent electrolyte. A maximum was observed even with low concentrations of calcium ion, and it was only partially suppressed by traces of methyl red. Higher concentrations of methyl red did not completely eliminate the maximum. A similar behavior was exhibited by the strontium ion (see Fig. 2), but the barium ion did not show a maximum when using tetraethylammonium iodide as the indifferent electrolyte (see curve II, Fig. 3). With tetrapropylammonium iodide, barium exhibits a maximum which is not suppressed by either methyl red or methyl cellulose (see curve I, Fig. 3).

TABLE I

DIFFUSION CURRENTS OF CALCIUM, STRONTIUM AND BARIUM IN LIQUID AMMONIA AT −36°

Ion	C	D	$m^{2/3}t^{1/6}$	i_d, microamp. Calcd.	Obs.	% Δ
Ca	0.38	1.91×10^{-5}	1.019	2.05	2.0	−2.5
Ca	.82		1.019	4.4	4.5	+2
Sr	.37	1.94×10^{-5}	1.180	2.32	2.39	+3
Sr	.52		1.180	3.28	3.27	...
Sr	.78		1.185	4.94	5.21	+6
Ba	.43	1.77×10^{-5}	1.249	2.72	2.65	−3
Ba	.63		1.249	4.00	3.90	−3

The diffusion currents for various concentrations of the alkaline earth metal ions, as measured in liquid ammonia at −36°, are recorded in Table I. Tetraethylammonium iodide served

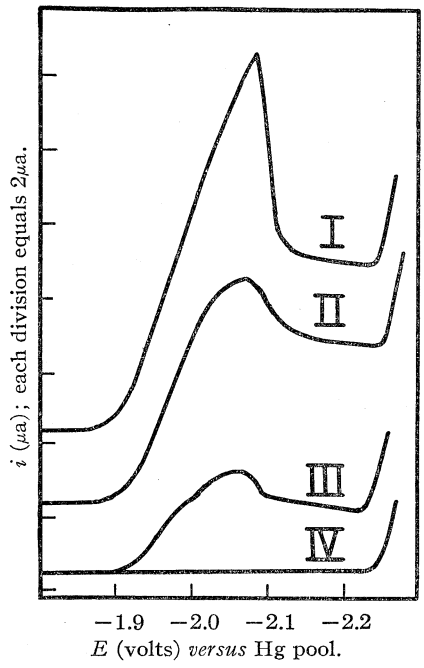


Fig. 1.—Polarograms of calcium iodide in saturated tetraethylammonium iodide: curve I, 8.2×10^{-4} *M;* curve II, 8.2×10^{-4} *M* plus a trace of methyl red; curve III, 3.8×10^{-4} *M* plus a trace of methyl red; curve IV, saturated solution of tetraethylammonium iodide.

as the supporting electrolyte. Theoretical values were calculated by means of the Ilkovic equation[2,3]

$$i_d = 605nCD^{1/2}m^{2/3}t^{1/6}$$

which relates the diffusion current i_d (microamperes) of an ion to n, the number of faradays of electricity required per mole of electrode reaction, to its concentration C (millimoles per liter), to its ionic diffusion coefficient D (sq. cm./sec.), and to the capillary characteristics m (mg./sec.) and t (sec.). The ionic diffusion coefficient D can be evaluated by means of the expression[4,5]

$$D = RT\lambda^0/zF^2$$

where R is 8.317 volt-coulombs per degree, T is the absolute temperature, λ^0 is the equivalent conductance of the ion at infinite dilution (ohm^{-1}-sq. cm.-equiv.$^{-1}$), z is the charge of ion, and F is 96,500 coulombs. Most of these terms are experimental quantities which can be easily evaluated. Gurjanowa and Pleskov[6] reported the equivalent ionic conductance at −40° of calcium, strontium and barium at infinite dilution as 180, 183 and 167 ohm^{-1}-sq. cm.-equiv.$^{-1}$, respectively.

(2) D. Ilkovic, *Coll. Czech. Chem. Commun.*, **6**, 498 (1934).

(3) D. MacGillavry and E. K. Rideal, *Rec. trav. chim.*, **56**, 1013 (1937).

(4) W. Nernst, *Z. physik. Chem.*, **2**, 613 (1888).

(5) I. M. Kolthoff and J. J. Lingane, THIS JOURNAL, **61**, 825 (1939).

(6) E. N. Gurjanowa and V. A. Pleskov, *Acta Physicochim. U. R. S. S.*, **5**, 509 (1936).

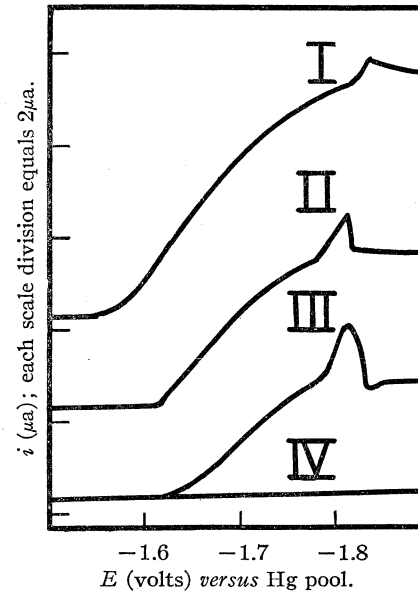


Fig. 2.—Polarograms of strontium nitrate in saturated tetraethylammonium iodide: curve I, 7.8×10^{-4} *M* plus a trace of methyl red; curve II, 5.2×10^{-4} *M* plus a trace of methyl red; curve III, 3.7×10^{-4} *M;* curve IV, saturated solution of tetraethylammonium iodide.

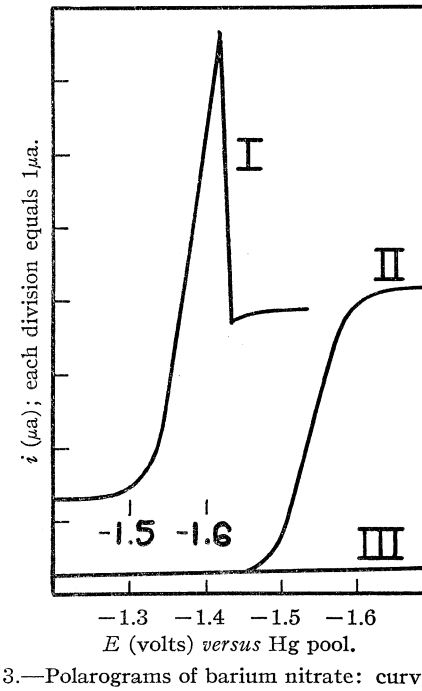


Fig. 3.—Polarograms of barium nitrate: curve I, 4.3×10^{-4} *M* in saturated tetrapropylammonium iodide; curve II, 6.3×10^{-4} *M* in saturated tetraethylammonium iodide; curve III, saturated solution of tetraethylammonium iodide.

As can be seen, the agreement between the observed and calculated values of i_d is good, and it is considerably better than that observed in the case of the alkali metal ions[1] where the ob-

served values were higher by 10%. This is attributed to the fact that the migration current has been markedly reduced by the higher relative concentration of indifferent electrolyte. The solubility of tetraethylammonium iodide, which was used in this investigation, is about four times as great as that of tetrabutylammonium iodide, which was used in the investigation of the alkali metal ions.

TABLE II

$E_{1/2}$ IN LIQUID AMMONIA AT $-36°$ *versus* MERCURY POOL

Ion	*C.* mmole/l.	$E_{1/2}$, volts	Slope of $E_{d.e.}$ *vs.* log $\left(\frac{i_d - i}{i}\right)$
Ca	0.38	−1.96	0.058
Ca	.82	−1.96	.044
Sr	.37	−1.69	.061
Sr	.52	−1.68	.078
Sr	.78	−1.67	.117
Ba	.58	−1.54	.033
Ba	.63	−1.54	.040

Since the shape of a polarographic reduction wave, when the metal is soluble in mercury, is given by the expression[7]

$$E_{d.e.} = E_{1/2} + \frac{2.303RT}{nF} \log \frac{(i_d - i)}{i}$$

(7) J. Heyrovsky and D. Ilkovic, *Coll. Czech. Chem. Commun.*, **7**, 198 (1935).

the slope of a plot of $E_{d.e.}$ *versus* log $(i_d - i)/i$ can be used as a test for reversibility. $E_{d.e.}$ is the potential of the dropping mercury electrode; $E_{1/2}$ is the half-wave potential; i_d is the diffusion current; and i is the current flowing at a potential $E_{d.e.}$. A reversible two-electron reduction would give a slope of 0.024.

In Table II are recorded values for the half-wave potentials of calcium, strontium and barium in liquid ammonia at $-36°$ and also the slope of $E_{d.e.}$ *vs.* log $(i_d - i)/i$. The approach of the reduction to reversibility is not so close in the case of the alkaline earth ions as it is in the case of the alkali metal ions.[1] There is a parallel behavior between these ions and the alkali metal ions in that the largest ion is the most readily reduced to the amalgam. Insufficient data are available to calculate theoretical values of the half-wave potentials.

Summary

The diffusion currents of calcium, strontium and barium ions were measured and found to agree with those calculated by the Ilkovic equation.

The half-wave potentials were determined, and the reduction was found to be less reversible than in the case of the alkali metal ions.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY AND THE PURDUE RESEARCH FOUNDATION]

Polarographic Behavior of Organic Compounds. I. The Maleate and Fumarate Species

BY PHILIP J. ELVING* AND CHARLES TEITELBAUM

Although extensive polarographic investigations of maleic and fumaric acids have been carried out, there was felt to be a need for a thorough study of the acids with a more careful control of the factors affecting polarographic reduction.

Insufficient attention was paid in much of the previous work[1] to such factors as buffering, electrolyte concentration, capillary characteristics, temperature control and concentration. The most thorough previous work is that of Vopicka,[1c] although the concentrations he used were somewhat high, capillary characteristics were not given, buffering at the ends of the *p*H range studied was not satisfactory, no measurements were made between *p*H 5.3 and 9.0, and no temperature control was attempted. He developed an equation to express the effect of *p*H on half-wave potential. Herasymenko[1e] interpreted Vopicka's results on the basis of a new equation, which gave slightly better agreement with the experimental results. The only previous work on the calculation of the "*n*" values (apparent electron change per molecule reduced) is that of Furman and Bricker[1k] for maleic acid where values of 1.17 and 1.22 were obtained. No clear relationship between diffusion current and *p*H has been established; Vopicka[1c] indicates a straight line relation between half-wave potential, $E_{0.5}$, and *p*H. No previous report has been found of the appearance of double waves in buffered solution. No previously reported polarographic investigation of the esters has been located.

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(1) (a) Herasymenko, *Z. Elektrochem.*, **34**, 74 (1928); (b) Schwaer, *Chem. Listy*, **26**, 485 (1932); (c) Vopicka, *Coll. Czechoslav. Chem. Commun.*, **8**, 349 (1936); (d) Semerano and Bettinelli, *Gazz. chim. ital.*, **66**, 744 (1936); (e) Herasymenko, *Coll. Czechoslav. Chem. Commun.*, **9**, 104 (1937); (f) Miolati, *Mem. accad. Italia, Classe. sci. fis. mat. nat.*, **8**, 215 (1937); (g) Semerano and Bettinelli, *ibid.*, **8**, 255 (1937); (h) Miolati and Semerano, *Ricerca sci.*, **8**, II, 243 (1937); (i) Semarano and Rao, *Mikrochemie*, **23**, 9 (1937); (j) Semerano, *ibid.*, **24**, 10 (1938); (k) Furman and Bricker, THIS JOURNAL, **64**, 666 (1942); (l) Clark and Knopf, ACS, Abstracts of Papers, Meeting in Print, p. 3L, Sept., 1945; (m) Warshowsky, Elving and Mandel, *Anal. Chem.*, **19**, 161 (1947).

Experimental

Buffer solutions of varying *p*H (Table I) were prepared from reagent grade chemicals by weighing out one mole of the first named buffer constituent, diluting to approximately 800 ml., adding enough of the second component to reach the approximate *p*H desired, diluting to 1 liter and determining the exact *p*H.

Maleic acid (Pfanstiehl C. P., m. p. 133–136°) was used as received. Fumaric acid (Eastman Kodak Co. practical grade) was recrystallized three times from 1 *N* hydrochloric acid and decolorized with Norit; the white solid melted at 282–284° in a sealed tube. Solutions, 0.1 *M*, of the acids were prepared; 4 g. of sodium fluoride was added to each liter to inhibit mold growth. The diethyl maleate and diethyl fumarate were Eastman Kodak Co. White Label grade; diethyl maleate, $n^{20}D$ 1.4400 (literature value[2] 1.4407) and diethyl fumarate, $n^{20}D$ 1.4405 (literature value[3] 1.4410). The purified[4] 1,4-dioxane had $n^{20}D$ 1.4221 in exact agreement with the literature value.[3] Since aqueous solutions of the esters would hydrolyze, 0.5 *M* stock solutions were prepared in 1,4-dioxane; only 1 ml. of stock solution was used in making 100 ml. of test solution. The absence of additional polarographic waves due to impurities supports the adequacy of the purity of the materials used.

TABLE I

BUFFER SOLUTIONS, 1 *M* IN MEASURED CONSTITUENT

No.	*p*H	Measured constituent	Unmeasured constituent
1	2.03	KCl	HCl
2	3.98	NaOAc	HOAc
3	4.89	NaOAc	HOAc
4	5.90	NaOAc	HOAc
5	6.98	HOAc	NH_4OH
6	7.90	NH_4Cl	NH_4OH
7	8.68	K_2HPO_4	.....
8	8.86	NH_4Cl	NN_4OH
9	9.87	NH_4Cl	NH_4OH

TABLE II

EFFECT OF CONCENTRATIONS OF BUFFER, ADDED ELECTROLYTE AND MALEIC ACID ON HALF-WAVE POTENTIAL OF MALEIC ACID IN SODIUM ACETATE–ACETIC ACID BUFFER SOLUTIONS

No.	Maleic acid *M* × 10^4	KCl, *M*	NaOAc, *M*	Final *p*H	Half-wave potentials: Whole wave, volts	First wave, volts	Second wave, volts
1	5		0.1	4.50	....	−1.15	−1.63
2	5		.3	5.86	−1.13	−1.11	−1.30
3	5		.7	5.85	−1.13	−1.11	−1.25
4	5		.9	5.88	−1.12	....	....
5	5	*ca.* 0.6	.3		−1.12	−1.09	−1.27
6	5	*ca.* 1.2	.3		−1.11	−1.09	−1.25
7	2		.1	5.85		−1.12	−1.34
8	5		.1	4.50		−1.15	−1.63
9	2		.9	5.89	−1.12		
10	5		.9	5.88	−1.12		

A Sargent Polarograph Model XXI was used. Potential measurements were checked with a potentiometer. A Beckman Model G *p*H meter was used for all *p*H measurements. An H-type polarographic cell was used with a water-jacket around the sample leg and a saturated calomel electrode in the other half of the cell. Water at 25 ± 0.2° was circulated through the water-jacket.

The operations involved in the measurements were the usual ones used in polarographic studies. All solutions were degassed by a stream of oxygen-free nitrogen. The *p*H was determined after the solution had been degassed and the curves determined so that any effect of the degassing on the *p*H would not be ignored.

Calculation of the resistance through the cell with the concentrations of buffers used indicated that any correction for the potential drop would be within the experimental error. Confirmation for this view was received in the polarographing of solutions of cadmium chloride in 0.1 *M* potassium chloride where satisfactory agreement with the literature values was obtained. Since the buffers used had a higher conductivity than 0.1 *M* potassium chloride, no correction was considered necessary. The accuracy of the potential measurements were periodically checked by measurement of cadmium chloride solutions.

Experiments and Data

The "*m*" value for the capillary into distilled water was 2.17 mg. per second.

The effect of buffer concentration on the polarographic waves for maleic acid was determined at *p*H 5.9, where very clear waves were obtained. In solutions of low buffer concentration two waves were obtained; as the concentration of buffer was increased, the two waves gradually merged (Table II, Nos. 1 to 4). Where a reasonable distinction could be made, the $E_{0.5}$ values of both waves and of the whole, composite wave were measured. Although the significance of $E_{0.5}$ for a whole wave is perhaps doubtful in those cases where the waves consist of two separate and distinct parts, such values are included for comparison with the cases where the waves were not resolvable and were reported as one wave. To test whether the effect was due to the change in buffer capacity or to the change in ionic strength, varying concentrations of potassium chloride were added to a fixed concentration of buffer (Table II, nos. 5 and 6). Finally, to test the constancy of $E_{0.5}$ at varying concentrations of reducible species and to demonstrate further the optimum concentration of buffer, the concentration of maleic acid was varied in two buffer concentrations (Table II, nos. 7 to 10).

The effect of *p*H on $E_{0.5}$ of maleic acid was studied over the *p*H range of 2 to 9 using buffer solutions which were 0.1 *M* or 0.9 *M* in the major buffer constituent. The values obtained in 0.1 *M* solution showed an irregular relation between $E_{0.5}$ and *p*H; the values for 0.9 *M* solution are given in Table III. Similar studies on fumaric acid and the diethyl esters in solutions of varying concentration of buffer constituent and reducible

(2) Knops, *Ann.*, **248**, 193 (1888).

(3) Lange, "Handbook of Chemistry," 6th ed., Handbook Publishers, Inc., Sandusky, Ohio, 1946.

(4) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 369.

TABLE III

POLAROGRAPHIC BEHAVIOR OF 0.5 mM. MALEIC ACID IN SOLUTIONS 0.9 *M* IN BUFFER

Buffer	Final *p*H	No. of waves[a]	Half-wave potential, volts	Drop time, sec.	Diffusion current, microamp.
1	2.43	2	−0.73	3.1	4.23
2	4.00	2	−0.89	3.1	2.90
3	4.89	1 or 2	−0.96	3.0	3.76
4	5.88	1	−1.12	...	4.01
5	6.93	1	−1.27	2.7	3.99
6	7.80	1	−1.34	2.6	2.46
7	8.72	1	−1.43	2.4	2.88
8	8.60	1	−1.37	2.5	2.79
9	9.63	1	−1.42	2.5	0.96

[a] At higher *p*H values, a second wave may have escaped observation due to an irregular diffusion current. $E_{0.5}$ refers to the value for the first wave where two waves were obtained; to the whole wave where only one wave was apparent.

species indicated that low concentrations of buffer constituent such as 0.1 *M* are inadequate but that 0.9 *M* is adequate. The results for fumaric acid and the two esters in the latter type solution are given in Tables IV, V and VI. The effect of the dioxane from the stock solutions of the esters was shown to be negligible by taking equal quantities of diethyl maleate with and without dioxane; the curves obtained were identical within the experimental accuracy. A second wave was obtained for both esters in buffer 9 (Table VII). The relation between $E_{0.5}$ and *p*H for all compounds studied is shown in Fig. 1.

TABLE IV

POLAROGRAPHIC BEHAVIOR OF 0.5 mM. FUMARIC ACID IN SOLUTIONS 0.9 *M* IN BUFFER

Buffer	Final *p*H	Half-wave potential, volts	Drop time, sec.	Diffusion current, microamp.
1	2.56	−0.79	3.2	3.99
2	4.00	−0.94	3.1	4.00
3	4.89	−1.06	2.9	3.49
4	5.83	−1.21	2.9	0.91
5	6.87	−1.48	2.1	3.88
6	7.81	−1.55	2.1	4.33
7	8.78	−1.71	2.0	3.98
8	8.41	−1.58	2.4	3.74
9	9.50	−1.58	2.6	3.56

TABLE V

POLAROGRAPHIC BEHAVIOR OF 0.5 mM. DIETHYL MALEATE IN SOLUTIONS 0.9 *M* IN BUFFER

Buffer	Final *p*H	Half-wave potential, volts	Drop time, sec.	Diffusion current, microamp.
1	2.20	−0.87	3.9	3.36
2	3.98	−0.95	3.8	2.40
3	4.88	−0.99	3.6	2.89
4	5.86	−1.04	3.3	2.74
5	6.96	−1.03	4.0	2.82
6	7.90	−1.03	3.9	3.13
7	8.68	−1.05	4.1	2.25
8	8.65	−1.03	4.1	3.02
9	9.70	−1.05	3.5	1.83

TABLE VI

POLAROGRAPHIC BEHAVIOR OF 0.5 mM. DIETHYL FUMARATE IN SOLUTIONS 0.9 *M* IN BUFFER

Buffer	Final *p*H	Half-wave potential, volts	Drop time, sec.	Diffusion current, microamp.
1	2.16	−0.75	3.8	1.87
2	3.97	− .84	3.4	2.43
3	4.86	− .86	3.6	2.55
4	5.90	− .93	3.6	2.57
5	6.94	− .97	...	3.09
6	7.62	−1.01	4.0	1.77
7	8.66	−1.07	3.5	0.89
8	8.62	−1.62	3.6	1.68
9	9.63	−1.15	3.1	2.48

Calculations for the "*n*" values were made by plotting $\log i/(i_D - i)$ *vs.* E[5] (Table VIII).

TABLE VII

SECOND POLAROGRAPHIC WAVE OF 0.5 mM. DIETHYL ESTERS OF MALEIC AND FUMARIC ACIDS IN BUFFER OF *p*H 9.87 AND 0.9 *M* BUFFER

Reducible species	Final *p*H	Half-wave potential, volts	Diffusion current, microamp.
Diethyl maleate	9.70	−1.46	0.92
Diethyl fumarate	9.63	−1.37	1.32

TABLE VIII

ELECTRON CHANGES (*n* VALUES) FOR 0.5 mM. CONCENTRATION OF REDUCIBLE SPECIES AND 0.9 *M* CONCENTRATION OF BUFFER

Reducible species	Buffer no.	Final *p*H	"*n*" value
Maleic acid	4	5.88	1.03
Fumaric acid	4	5.83	1.02
Diethyl maleate	1	2.20	0.44
	2	3.98	.68
	4	5.86	.81
	6	7.90	.87
	9	9.70	1.17[a]
Diethyl fumarate	4	5.90	1.37
	6	7.62	1.04

[a] Slope of line from first part of curve only used for calculation.

Discussion

Effect of Buffer Concentration.—Low concentrations of buffer were definitely indicated as not adequate. Ordinarily, it is expected that a molar ratio of buffer to reducible species of 100:1 is adequate for the desired constancy of *p*H throughout the solution. Considering that the usual concentration of reducible species used was 0.5 mM, a buffer concentration of 0.05 *M* should be adequate. However, the inadequacy of buffer solutions of low electrolyte concentration becomes more understandable if we consider the role of the buffer in the reduction. The reduction of the acids may be written as

$$C_4H_4O_4 + 2H^+ + 2e \longrightarrow C_4H_6O_4$$

Since the reaction tends to use up hydrogen ions and make the solution more basic, only the acidic

(5) Kolthoff and Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1946, p. 145.

component of the buffer is effective in maintaining a constant *p*H. In the case of the sodium acetate–acetic acid buffer of *p*H 5.9, only the basic component, sodium acetate, was measured. The approximate concentration of the acidic form, acetic acid, can be calculated from the known *p*H and the concentration of the acetate.[6] Such a calculation indicates that the ratio of sodium acetate to acetic acid is approximately 18:1. Hence, the 0.1 *M* concentration of buffer gives a ratio of acidic form of buffer to reducible species of only 56:1; the 0.3 *M*, 160:1; the 0.7 *M*, 390:1; and the 0.9 *M*, 500:1. These facts explain the $E_{0.5}$ data for fumaric acid at *p*H 5.9 at different buffer concentrations: −1.242 (0.1 *M*), −1.224 (0.3 *M*), −1.213 (0.7 *M*), and −1.210 (0.9 *M*). This would indicate that there is inadequate buffering at the lower values and that, in this case, the minimum sufficient concentration of sodium acetate is between 0.3 and 0.7 *M*. In terms of the ratio of the acid component of the buffer to reducible species, a ratio of between 160:1 and 390:1 is required. The $E_{0.5}$ would be expected to be constant at varying concentrations of reducible species only if there were adequate buffering. The data for maleic acid in 0.1 *M* concentrations of measured buffer constituent give a very irregular relation when $E_{0.5}$ is plotted against *p*H while the relation for the 0.9 *M* buffer is quite regular; the former, apparently, is due to the irregularly inadequate buffering. It may be noted that Vopicka[1c] used a sodium acetate–acetic acid buffer at *p*H 9, in which the concentration of acidic form must have been negligible.

The foregoing comments on buffering capacity have applied only to buffer 4 which had the highest *p*H of any of the acetic acid buffers (2, 3 and 4) and thus the smallest concentration of acetic acid. If a 0.9 *M* concentration in measured constituent of this buffer was sufficient, then a similar concentration of the other buffers should most certainly be sufficient since the concentration of the acid component of the other buffers would be still higher. For buffer 5, the concentration of acetic acid is 0.9 *M*, which should be sufficient. For buffers 6 to 9, the acidic form, ammonium chloride or potassium hydrogen phosphate, is also fixed at 0.9 *M*. In buffer 1, the buffering capacity is admittedly dubious but since the results obtained were consistent with the others, it may be concluded that either the buffering was adequate or that good buffering was not necessary in this *p*H range.

An anomaly which seems difficult to interpret is the effect of buffer concentration on the polarographic waves of maleic acid. Two waves are obtained at *p*H 5.90 when low concentrations of buffer are used; these waves gradually merge as the concentration of buffer is increased. The addition of a presumably inert electrolyte, such as potassium chloride, has, to some degree, the same effect as the increase of buffer concentration. Two waves appear only at low *p*H. As previously noted, incomplete buffering should lead to more basic conditions. The appearance of two waves only at a low concentration of buffer of *p*H 5.9 might indicate that a high *p*H favors the appearance of two waves; however, two waves appear only in buffers of low *p*H. To explain the effect of the addition of a presumably inert electrolyte, one can only postulate that the phenomenon observed is at least partially caused by an ionic strength effect and that the appearance of two waves is not an indication of a varying ratio of different dissociated forms. The polarographic reduction of fumaric acid yielded only one wave in all buffers.

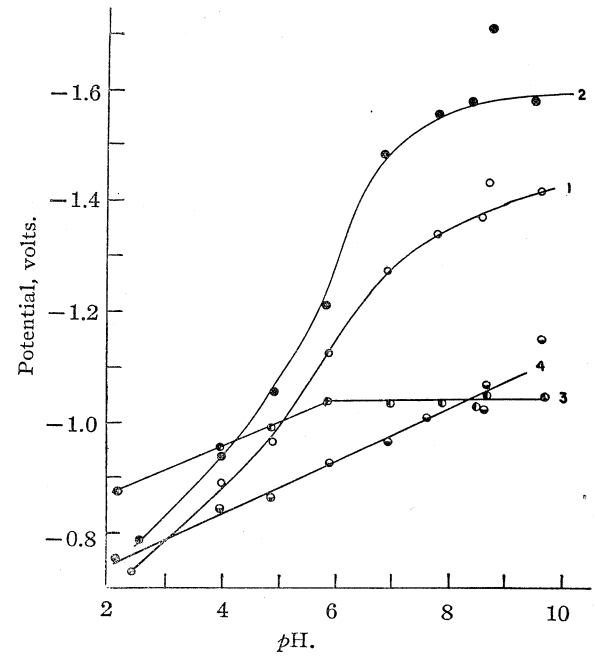


Fig. 1.—Variation of half-wave potential with *p*H: 1, maleic acid; 2, fumaric acid; 3, diethyl maleate; 4, diethyl fumarate.

Polarography of the Esters.—Freshly prepared stock solutions of diethyl fumarate gave curves with a distinct maximum while solutions which had been allowed to stand for some time did not. Since the addition of very small amounts of fumaric acid also suppressed the maximum, its disappearance was attributed to the slow partial hydrolysis of the ester in the stock solution by traces of water.

The appearance of two waves in the reduction of the diethyl esters can only be attributed to a two-step reduction since only one form of the reducible species exists. This might, by analogy, indicate that the two waves for maleic acid might be due to a two-step reduction and not to the reduction of two different forms. However, in the

(6) Clark, "The Determination of Hydrogen Ions," 3rd ed., Williams and Wilkins Co., Baltimore, Md., 1928, p. 220.

case of the esters two waves occur only at high pH values while for the maleic acid it happens only at low pH, indicating a fundamental difference in the two phenomena. It certainly indicates that a proof by analogy would be dubious.

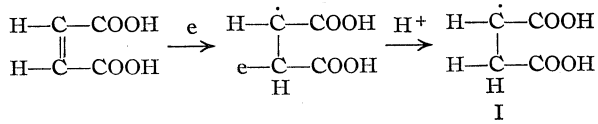
Interpretation of $E_{0.5}$–pH Curves for Maleic and Fumaric Acids.—The curves for maleic and fumaric acids, relating $E_{0.5}$ to pH, are of similar flattened S-shapes (Fig. 1). The fumaric acid curve is more negative at all points. The greater thermodynamic stability of fumaric acid would lead us to expect it to have the more negative $E_{0.5}$ values since the more stable of two compounds yielding the same product on reduction would be expected to be the less easily reduced. The facts, that at most pH values a single wave is obtained for the reduction and that a smooth curve is obtained when $E_{0.5}$ is plotted against pH, lead to the assumption that we may treat the curve as representing the composite behavior of the three possible forms of the acid: undissociated, half-dissociated and fully dissociated. The observed $E_{0.5}$ is a function of the ease of reduction of all of the forms present and their relative concentrations; the effect of pH on half-wave potential will be considered in this light.

The fact that maleic acid becomes still less stable at high pH values may be due to the electrostatic repulsion of the two negatively charged carboxylate groups in close proximity to one another. In the first ionization stage, maleic ($K_{a_1} = 1.5 \times 10^{-2}$) is a stronger acid than fumaric ($K_{a_1} = 1 \times 10^{-3}$); on the other hand, in the second ionization stage, maleic ($K_{a_2} = 2.6 \times 10^{-7}$) is a much weaker acid than fumaric ($K_{a_2} = 3 \times 10^{-5}$). This may be explained as being due to the difficulty of removal of the second positively charged proton in such close proximity to the negative charge of the carboxylate group. Roberts and Kimball[7] account for the anomalous *cis*-addition of bromine to maleic acid in basic solution on the basis of rupture of the three-membered ring of the primary addition product and rotation to the fumaroid configuration in which configuration the electrostatic repulsion is considerably less because of the wider separation of charge. This evidence also indicates that the close proximity of the two carboxylate groups causes a decreased stability of the doubly-charged maleate ion. These lines of evidence agree with the observations of this study, that the difference in stability between fumaric and maleic acids, as reflected by their $E_{0.5}$ values, is greatest at high pH values.

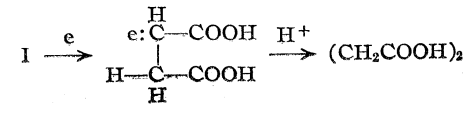
This explanation says nothing about the $E_{0.5}$ of each acid individually; the curve for each acid is difficult to interpret because there is involved in the effect of pH upon $E_{0.5}$ not only the activity of hydrogen ion but also the presence of three different forms of the reducible species and three different forms of the presumed product of reduction, succinic acid. However, one would predict that the change in the difference in $E_{0.5}$ should be greatest at the same pH as where the greatest change in the concentration of the doubly-charged maleate ion occurs. If the first ionization of maleic acid, which is very largely complete at the pH values considered, is neglected, it is found that $p\mathrm{H} = pK_{a_2} + \log [\mathrm{A}^=]/[\mathrm{HA}^-]$, so that the ratio, $[\mathrm{A}^=]/[\mathrm{HA}^-]$, changes one hundred-fold when the pH changes from $(pK_{a_2} + 1)$ to $(pK_{a_2} - 1)$. This, then, is the pH region (5.3 to 7.3) where one would expect to find the greatest change in concentration of doubly-charged maleate ion and, correspondingly, the greatest difference in $E_{0.5}$ values. That this prediction is at least roughly realized is shown in Fig. 1. The presence of the points for buffer 7 above the rest of the curve suggests the possibility of some sort of complex formation between the phosphate and the acid.

The calculated electron changes (Table VIII) involved in the reduction of both acids gave values of close to one. The wide variance of the diffusion current in varying pH led to the conclusion that calculations of the n value by the Ilkovic equation would be meaningless.

The previously mentioned interpretation of the $E_{0.5}$–pH curve stated that the difference in $E_{0.5}$ is explicable by the difference in thermodynamic stability. If this explanation is valid, then it seems likely that the potential-determining step in both cases leads to the same product, for the differences in energy of the two acids can have significance only if they are referred to a common standard. An electron change of one in the potential-determining step indicates that succinic acid cannot be the product of the potential-determining step since formation of succinic acid involves a two-electron change. The production of nascent hydrogen does not seem likely as the step since this should give a $E_{0.5}$–pH relationship unaffected by the nature of the acid and the two acids should give identical $E_{0.5}$ values. What seems more likely as the potential-determining, probably reversible step is the formation of a radical ion which would, perhaps simultaneously, acquire a proton



I would be expected to have free rotation about the central bond and thus be the same for maleic and fumaric acids. The pH dependence of the reduction seems to indicate a proton being added before the second step. The further reduction of I would then not be potential-determining and would proceed as follows



(7) Roberts and Kimball, THIS JOURNAL, **59**, 947 (1937).

Interpretation of $E_{0.5}$–pH Curves for Diethyl Maleate and Diethyl Fumarate.—The diethyl esters were chosen for study in the belief that the factors influencing the polarographic reduction would be simplified. Since the ethyl groups are not as labile as protons and the hydrolysis of the esters is relatively slow, one need only consider one form of the reducible species and one form of the reduced product. The expectation that the curves of $E_{0.5}$ *vs.* pH would be considerably simpler to interpret, was not realized. Generally, the change in $E_{0.5}$ with varying pH is smaller for the esters than for the acids, but the variations in this change are actually less easily understandable for the esters than for the acids.

The curve of $E_{0.5}$ *vs.* pH for diethyl maleate consists of two straight lines (Fig. 1), intersecting at pH 5.8 and crossing the single straight line for diethyl fumarate at pH 8.4. As in the case of the acids, the greater stability of the fumarate should cause it to have the more negative $E_{0.5}$ value; this expectation is realized at high pH values.

The distinct break in the $E_{0.5}$–pH curve for diethyl maleate indicates two distinct mechanisms for the polarographic reduction, a pH-dependent mechanism at low pH and a pH-independent mechanism at high pH. It seems clear that the mechanism for the reduction of diethyl maleate at high pH differs from the mechanism for diethyl fumarate. At low pH values, the similarity of mechanisms for both esters seen in the parallel lines of the $E_{0.5}$–pH curve, whose slope lies between that expected for a reaction involving one proton and one involving two protons.

The "n" values calculated for diethyl maleate (Table VIII) seem to indicate an irreversible reaction at low pH values and a possible electron change of one for the potential-determining step at high pH values. The "n" values calculated for diethyl fumarate imply a mechanism of reduction similar to the acids, that is, a potential-determining reduction to a radical ion simultaneously with or immediately followed by a proton addition. Another electron and another proton would then be added to complete the reduction. This is supported by the appearance of a double wave at high pH values, indicating a two-step reduction.

There are two observed anomalies for which possible causes should be discussed, the higher $E_{0.5}$ of the less stable diethyl maleate at low pH and the change in mechanism of its reduction. Price[8] has explained anomalous effects in the reactivity of the two esters in copolymerization on stereochemical grounds. Based on relative stabilities diethyl maleate should copolymerize more readily than diethyl fumarate. However, the reactivity of the latter toward copolymerization is almost 12.5 times that of the former. On the other hand, the reactivity of maleic anhydride is almost 10 times that of diethyl fumarate. Price postulates that at some step in the copolymerization one of the intermediates is stabilized by resonance which requires a copolar configuration. Construction of molecular models indicates that there is steric strain involved in the assumption of a coplanar configuration by diethyl maleate but no such strain for diethyl fumarate or maleic anhydride. If one assumes that a planar intermediate is involved in the potential-determining step of the pH-dependent mechanism but not in the pH-independent mechanism, the two anomalies mentioned become understandable. For the similar pH-dependent mechanisms of the two esters, the steric strain in the intermediate makes the diethyl maleate more difficultly reducible. This does not necessarily mean that the product of the addition of the first electron is not the same but may merely imply that a higher energy barrier must be crossed in the change from diethyl maleate to the first product than in the case of diethyl fumarate. As the pH is raised, the reduction becomes more difficult. Finally, the reduction becomes so difficult by the pH-dependent mechanism as the hydrogen ion activity is decreased that another mechanism is favored. This does not happen for diethyl fumarate because there is no steric strain to make the pH-dependent mechanism a difficult one and also because the increased thermodynamic stability of the fumarate would make the pH-independent mechanism more difficult for it as opposed to diethyl maleate.

Acknowledgment.—This work was made possible by the award of a Frederick Gardner Cottrell Grant by the Research Corporation to whom the authors wish to express their gratitude.

Summary

The polarographic curves for maleic acid, fumaric acid, diethyl maleate and diethyl fumarate have been determined over a pH range of 2 to 9. A concentration of major buffer constituent exceeding 0.5 M was found necessary for adequate buffering action. Mechanisms of reduction consistent with the half-wave potential–pH curves and other related data have been proposed.

Maleic acid gave two waves at low pH in solutions of low concentration of buffer; increase in concentration of buffer constituents caused gradual merging of the waves into one. The same effect could be caused by adding potassium chloride to a fixed concentration of buffer, indicating the cause of the merging of the two waves to be probably a change in ionic strength and excluding as the cause of the two waves the successive reduction of different dissociated forms of the acid.

WEST LAFAYETTE, INDIANA RECEIVED[9] JULY 5, 1949

(8) Price, "Mechanisms of Reactions at Carbon–Carbon Double Bonds," Interscience Publishers, Inc., New York, N. Y., 1946, pp. 98–100.

(9) Original manuscript received January 14, 1949.

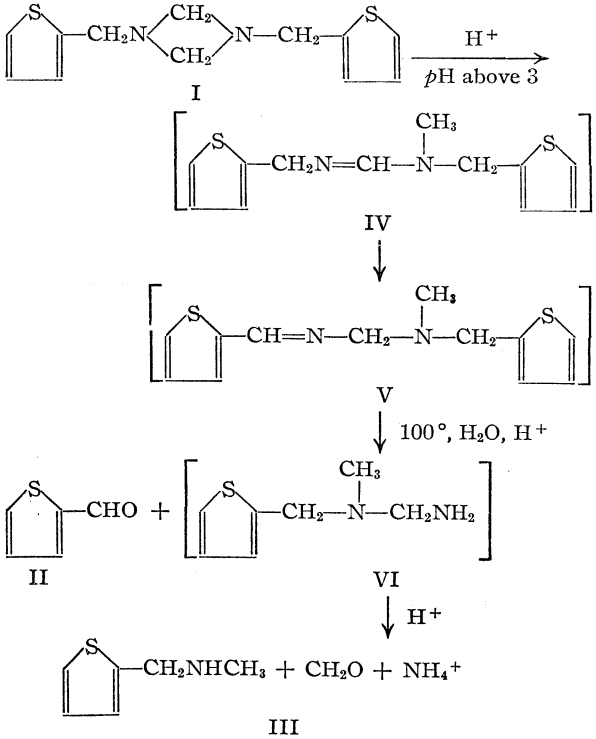
[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES (A DIVISION OF SOCONY-VACUUM OIL CO., INC.) RESEARCH AND DEVELOPMENT DEPARTMENT]

Aminomethylation of Thiophene. IV. Preparation of 2-Thiophenaldehydes from the N-(2-Thenyl)-formaldimines

BY HOWARD D. HARTOUGH AND JOSEPH J. DICKERT, JR.

Prior articles in this series[1,2,3] have dealt with reaction factors in the aminomethylation of thiophene, with preparation of the N-(2-thenyl)-formaldimines and with their reactions.

It has now been found that N,N′-di-(2-thenyl)-1,3-diazacyclobutane, I, can be hydrolyzed in dilute acid solution at a *p*H of 3 to 6.8 to give a 48% yield of 2-thiophenealdehyde, II, and a 47% yield of N-methyl-2-thenylamine, III. Ninety-five per cent. of the sulfur in I appears in the two products. At a lower *p*H than 3, formaldehyde is evolved and resinification occurs; at a *p*H above 7, no hydrolysis occurs. The hydrolysis of I is best expressed by the equation



Based upon the above postulated mechanism of hydrolysis, the yields of II and III become 96 and 94%, respectively.

In postulating the above mechanism the authors have assumed from data previously published[2,3] that the structure of I contains the diazacyclobutane ring and that structures IV and V are irreversible structures formed by rupture of the four-membered ring. I has previously been shown to exist in a dynamic equilibrium with N-(2-thenyl)-formaldimine, VII. The actual form depends upon the *p*H of the solution. At *p*H of 1 to 2, the existence of the monomer, VII, has been demonstrated.[3] Above *p*H of 3, I appears to exist and it has been isolated directly from a solution of *p*H 6 by extraction with ether.

Further positive evidence that I is the active intermediate in the hydrolysis to II and III is indicated by the fact that N,N′,N″-tris-(5-methyl-2-thenyl)-tetrahydro-1,3,5-triazine, VIII, does not yield 5-methyl-2-thiophenealdehyde under hydrolytic conditions. The dimeric form of N-(5-methyl-2-thenyl)-formaldimine corresponding to I could not be isolated in a prior work.[2]

A number of possible reaction courses are conceivable in this hydrolysis and should be considered. Analogy with the mechanism proposed by Sommelet[4] for production of benzaldehyde would suggest that VII was the active intermediate and a prototropic shift occurred in that compound to form N-methyl-2-thenaldimine, IX, which would subsequently be hydrolyzed to II. However, this mechanism does not account for the formation of III. IX has been prepared and characterized to substantiate that it could not be isolated in these hydrolysis experiments. Its inherent instability, however, would militate against its isolation under the drastic hydrolysis conditions applied.

Since this article was originally submitted for publication, Angyal and Rassack[5] have briefly reported a study of the reaction of benzylamine hydrochloride and formaldehyde to form benzaldehyde, N-methylbenzylamine and ammonia. A thiophene, formaldehyde and ammonium chloride mixture will form a 2-thenylamine[1] and, therefore, a reaction similar to that proposed by Angyal and Rassack should be considered. Their mechanism would postulate the reaction of formaldehyde with the 2-thenylamine to form the formaldimine and subsequent reaction of equimolar amounts of the amine and the formaldimine to yield the 2-thiophenealdehyde, ammonia and an N-methyl-2-thenylamine. It will be noted that this mechanism gives the same products and in the same ratios as that involving the dimer, I, of the formaldimine as a reactant. Angyal and Rassack[5] discuss oxidation of benzylamine by formaldimine, $CH_2{=}NH$ (from hexamethylenetetramine), to yield benzaldehyde, methylamine and ammonia. Graymore and Davies[6] describe

(1) Hartough, Lukasiewicz and Murray, THIS JOURNAL, **70**, 1146 (1948).

(2) Hartough, Meisel, Koft and Schick, *ibid.*, **70**, 4013 (1948).

(3) Hartough and Meisel, *ibid.*, **70**, 4018 (1948).

(4) Sommelet, *C. R. Acad. Sci., Paris*, **157**, 852 (1913).

(5) Angyal and Rassack, *Nature*, **161**, 723 (1948).

(6) Graymore and Davies, *J. Chem. Soc.*, **293** (1945).

the similar oxidation of benzylformaldimine, and assume aminomethyl alcohol (from hexamethylenetetramine) to be the oxidizing agent. If such reactions occur in the thiophene series they produce one mole of 2-thiophenealdehyde from each mole of amine or formaldimine—twice the amount resulting from the mechanisms above. In addition to this oxidizing action, formaldehyde may cause a stepwise reduction of formaldimines to secondary or tertiary amines.[5,7]

Related to the hydrolysis of I is the treatment of 2-thenylamine and N-(2-thenyl)-formaldimine with hexamethylenetetramine, X, and hydrochloric acid. Angyal and Rassack[5] discussed treatment of benzylamine with X to form benzaldehyde, and Graymore and Davies[6] described the similar reaction of benzylformaldimine with X, with suitable concentrations of hydrochloric acid, to give the aldehyde. By analogy, similar reactions might be expected with thiophene isologs. When carefully acidified 2-thenylamine (sufficient acid to form the hydrochloride was employed) was added to X, the aldehyde, II, was formed. The reaction was not allowed to go to completion and the results definitely indicated that I was an intermediate since it was isolated by extraction with ether from the hydrolysis mixture at a *p*H of 4. Therefore, it appears that the mechanism of Angyal and Rassack[4] is not applicable to the present case.

2-Thiophenealdehyde, II, can also be obtained in 20–25% yield by warming I with formaldehyde and ammonium chloride. The remainder of I presumably reacts with formaldehyde and ammonium chloride to give a product containing a greater percentage of nitrogen than I. The product probably contains about 50% of bis-2,5-(methyleneiminomethyl)-thiophene, since it can be oxidized to a mixture of 2,5-thiophenedicarboxylic acid and 2-thiophenecarboxylic acid.

The formation of II and III does not require the prior separation of I. If the reaction mixture of thiophene, formaldehyde and ammonium chloride having a *p*H of 1.5 is adjusted to a *p*H of 3 to 6.8 and the mixture steam distilled, II can be obtained in 35–45% yield and III in 10–25% yield. If the *p*H is left at 1.5, only a trace of II is obtained. The *p*H dependence is probably associated with the fact[2] that I exists as the monomeric hydrochloride in solutions of *p*H 1 to 2 and as the dimer in more alkaline solutions. The yields of III were lower at higher *p*H values and the residual high boiling amines increased substantially. One would anticipate that at the lower *p*H value of about 6, the compound VI would hydrolyze more slowly to III.

The products obtained by hydrolysis of a reaction mixture from 2-methylthiophene, formaldehyde and ammonium chloride are not strictly analogous to those from thiophene. While 5-methyl-2-thiophenealdehyde, XI, was recovered it was not possible to isolate any N-methyl-5-methyl-2-thenylamine or, for that matter, any amine but the unhydrolyzed N-(5-methyl-2-thenyl)-formaldimine. The formaldimine produced from the reaction of 2-methylthiophene, formaldehyde and ammonium chloride[2] is a trimer of N-(5-methyl-2-thenyl)-formaldimine, VIII. Attempts to hydrolyze an isolated sample of VIII gave no aldehyde, XI. Polymerization of VIII occurred. The experimental observations might well be explained by the Sommelet mechanism, assuming that the formaldimine reacts as the monomer in acid solution. There is no experimental evidence of the existence of a dimer when 2-methylthiophene is employed.[2] Graymore and Davies[6] decided that, in the case of benzylformaldimine, trimerization to tribenzyltrimethylenetriamine precluded the prototropic shift and subsequent reaction and, to obtain the aldehyde, conditions avoiding polymerization were required.

When a reaction mixture obtained from 3-methylthiophene is hydrolyzed, products corresponding to those from thiophene are obtained at a *p*H of about 3 but at a *p*H of 6 no N-methyl-3-methyl-2-thenylamine was isolated. Instead, the amine N,N-dimethyl-3-methyl-2-thenylamine was isolated in low yield. Similarly, 2-chlorothiophene and *t*-butylthiophene produced N,N-dimethylamines but no N-methyl-2-thenylamines were isolated. Experimental work was not sufficiently extensive in these cases nor in the case of 2-methylthiophene to define the reaction courses. Formation of the N,N-dimethyl derivatives may take place stepwise through the reducing action of formaldehyde on the formaldimine.[5,7]

Experimental

The purity of thiophene, 2- and 3-methyl-, and 2-chlorothiophene, as determined by infrared analysis, was greater than 99 mole per cent. The *t*-butylthiophene used was later found to contain almost equimolar portions of 2-*t*-butyl- and 3-*t*-butylthiophene.[8] All melting points are corrected; boiling points are uncorrected.

General Procedure.—To the aqueous reaction mixture containing the N-(2-thenyl)-formaldimines as described in prior references[2,3] was added enough 10% sodium hydroxide solution to raise the *p*H of the solution to about 6 as determined by Hydrion paper. Normally a heavy oil separated from the reaction mixture. The well-stirred mixture was steam distilled (still temperature 105–110°) until no trace of the characteristic odor of thiophenealdehydes was noted in the distillate. The distillate, slightly basic, was neutralized with a little hydrochloric acid and extracted three times with ether. The extract was dried over anhydrous calcium sulfate, the ether evaporated and the product distilled *in vacuo*.

In the case of 5-chloro-2-thiophenealdehyde and the *t*-butyl-2-thiophenealdehyde the products were not sufficiently volatile with steam to be collected readily in that

(7) Werner, *J. Chem. Soc.*, **111**, 844 (1917).

(8) This material was previously thought to be pure 2-*t*-butylthiophene but was reinvestigated after Appleby, Sartor, Lee and Kapranos reported formation of isomers in alkylation of thiophene at the 112th Meeting of the American Chemical Society, New York City, September, 1947. This information was later published: THIS JOURNAL, **70**, 1552 (1948).

TABLE I

2-THIOPHENEALDEHYDES

Substituent	Yield, %	B. p. °C.	Mm.	$n^{20}D$	Acid M. p., °C.	Semicarbazone M. p., °C.	Formula	Calcd.	Found
.....	45	72.5	7.0	1.5920	.....	223–224	$C_6H_7N_3OS$	N, 24.85	N, 25.24
5-Methyl	37	52.5	0.7	1.5742	137–138[a]	207–208	$C_7H_9N_3OS$	S, 17.5	S, 17.4
3-Methyl[c]	42	65	2.2	1.5860	147–148[a]	211–212	$C_7H_9N_3OS$	N, 22.93	N, 22.54
5-Chloro	48	63–64	0.7	1.5942	151.5–152.5[a]	218–219	$C_6H_6ClN_3OS$	N, 20.59	N, 20.51
t-Butyl	44	155–162	1.0	1.5356[b]	128–128.5[a]	212–214	$C_{10}H_{15}N_3OS$	S, 14.23	S, 14.16

[a] Mixed melting point with an authentic sample[10] of acid showed no depression. [b] Refractive index at 30°. [c] No trace of 4-methyl-2-thiophenecarboxylic acid could be detected on oxidation. This is consistent with the data presented in ref. 3. It appears then that the aminoalkylation reaction takes place exclusively at the 2-position.

TABLE II

N-METHYL-2-THENYLAMINES

-2-Thenylamines	B. p. °C.	Mm.	$n^{20}D$	Derivatives: Compound	M. p., °C.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Carbon Calcd.	Carbon Found	Sulfur Calcd.	Sulfur Found
N-Methyl-[a]	41–42	1.2	1.5369	Phenylthiourea	127–128	$C_{13}H_{14}N_2S_2$	10.68	10.49	...	...	24.42	24.26
				Hydrochloride	195.5–196 dec.	$C_6H_{10}ClNS$	8.56	8.74	...	...	19.56	19.51
				Picrate[f]	181.5–182 dec.	$C_{12}H_{12}N_4O_7S$	15.73	16.00	40.45	39.70	9.00	9.06
N-Methyl-3-methyl-[b]				Phenylthiourea	148–149	$C_{14}H_{16}N_2S_2$	10.15	9.38[c]	...	...	...	...
N,N-Dimethyl-3-methyl-	61	2.5	1.5386	Methiodide[g]	179.5–180.5	$C_9H_{16}INS$	4.71	4.76	36.36	35.86	10.8	10.8
N,N-Dimethyl-5-chloro-[d]	42–44	0.5	1.5335	Methiodide[h]	193.5–194.5	$C_8H_{13}ClINS$	4.40	4.38	30.18	30.15	...	...
N,N-Dimethyl-*t*-butyl-[d,e]				Methiodide	193–194 dec.	$C_{12}H_{22}INS$	4.13	4.50	...	...	...	...

[a] Yield from hydrolysis of pure IV was 48%. Yields from hydrolysis of reaction mixtures generally ranged from 10–25%. [b] Isolated from the reaction mixture as the amine hydrochloride, m. p. 196–199° dec., by extracting the concentrated steam hydrolysate with chloroform. [c] Sample lost before check analyses could be obtained. [d] Obtained in low yields—generally below 10%. [e] Product not distilled. Identified as the methiodide. [f] Calcd.: H, 3.37. Found: H, 3.37. [g] Calcd.: H, 5.39. Found: H, 5.42. [h] Calcd.: H, 4.09. Found: H, 3.80.

manner. The hydrolysate, after boiling for two hours, was cooled and extracted with ether. After drying, the aldehydes were obtained by distillation *in vacuo*.

Isolation of the amine fraction was carried out in the following manner. Any oily or semi-resinous water-insoluble material was separated by decantation and discarded. The aqueous layer was neutralized with 40% sodium hydroxide, the amines were extracted with ether and dried, the ether was evaporated, and the amines were distilled *in vacuo* from a Claisen flask. Higher boiling complex amine mixtures were also noted from continued distillation but no simple products could be isolated.

Distillation of the insoluble oil obtained by the decantation step above, which normally was discarded, yielded, in the case of thiophene, only a small amount of aldehyde and higher boiling complex oxygen-containing products containing no active alcohol, aldehyde or acid components. These materials resinified in concd. hydrochloric acid indicating them to be methylene thenyl ethers. One relatively pure product from thiophene, b. p. 110° at 0.5 mm., $n^{20}D$ 1.5780, analyzed as follows: C, 55.65; H, 5.65; S, 26.78. These analyses indicate an empirical formula of $C_{11}H_{13}O_2S_2$. The product was oxidized with alkaline permanganate to 2,5-thiophenedicarboxylic acid, m. p. 358.5–359.5° (sealed tube on melting point block). No simple structure that oxidizes to this acid can be reconciled with the empirical formula $C_{11}H_{13}O_2S_2$.

Any significant departure from the above general procedure can be found in footnotes to the tables.

Hydrolysis of N,N'-Di-(2-thenyl)-1,3-diazacyclobutane, I.—To 21 g. (0.164 mole) of I obtained by a method previously described,[2] was added 12 g. of concd. hydrochloric acid in 200 ml. of water. This mixture was heated at the reflux temperature for one hour and then steam distilled. 2-Thiophenealdehyde, 9.0 g. (48%), was obtained by extraction of the distillate with ether. Caustic neutralization of the hydrolysate mixture, followed by ether extraction, yielded 10.0 g. (47%) of N-methyl-2-thenylamine, b. p. 184–185° (uncor.).

Reaction of I with Formaldehyde and Ammonium Chloride.—To 25 g. of N-(2-thenyl)-formaldimine dimer, I, were added 13 g. of ammonium chloride and 42 g. of 36% formaldehyde. The temperature fell to 18° and then slowly rose to 40°. I dissolved in the aqueous solution during the temperature rise. When the heat of reaction was no longer noticeable the reaction mixture was warmed to 70–80° for two hours. After cooling, 5.5 g. (20%) of 2-thiophenealdehyde was extracted from the mixture with ethyl ether and identified as the semicarbazone, m. p. 223–224°.

The amine portion of the reaction product, obtained in the usual manner by caustic neutralization,[2] contained 13.63% nitrogen. A 5-g. sample slurried with 10 g. of sodium hydroxide in 125 ml. of water was oxidized slowly by adding 10 g. of potassium permanganate in 150 ml. of water at 40° to the slurry. After obtaining the crystalline acids (3.2 g.) in the conventional manner, there were obtained 2.2 g. of 2,5-thiophenedicarboxylic acid, m. p. 358.5–359.5° and 1.0 g. of 2-thiophenecarboxylic acid, m. p. 128–129°. These acids are conveniently separated by digesting in benzene, the 2,5-thiophenedicarboxylic acid being very insoluble.

N-Methyl-2-thenaldimine was prepared by a modification of the method used for the preparation of N-methylpyrrolaldimine.[9] To 36 g. (0.3 mole) of 25% ethylamine was added with stirring 34 g. (0.3 mole) of 2-thiophenealdehyde during the course of one hour. The temperature rose to 35° after the addition was completed following which the mixture was heated at a temperature of 60° for two hours.

The mixture was then washed three times with 50-ml. portions of water. About 120 ml. of 17% hydrochloric acid was added and the mixture extracted with ether. Evaporation of the ether layer yielded 21 g. of unreacted 2-thiophenealdehyde. The residue was neutralized with caustic and the imine extracted with ether. The ether solution was dried and the ether was removed by evaporation; the residue of N-methyl-2-thenaldimine (9 g.) boiled at 48–49° (1.5 mm.); $n^{20}D$ 1.5864.

(9) Emmert, Diehl and Gollwitzer, *Ber.*, **62**, 1733 (1929).

(10) Hartough and Conley, THIS JOURNAL, **69**, 3096 (1947).

Anal. Calcd. for C_6H_7NS: N, 11.2; S, 25.6. Found: N, 11.4; S, 26.0.

This compound must be analyzed immediately since it is hydrolyzed rapidly by the moisture in the air. One sample which was allowed to stand for two days had only 9.73% nitrogen. This same sample was allowed to stand for several weeks and at that time had only 5.07% nitrogen.

An attempt to prepare a picrate of this compound gave only the picrate of methylamine, m. p. and mixed m. p. 209–211° uncor.

Anal. Calcd. for $C_7H_8N_4O_7$: C, 32.31; H, 2.96. Found: C, 32.01; H, 3.07.

Reaction of 2-Thenylamine Hydrochloride and Hexamethylenetetramine.—One mole (140 g.) of hexamethylenetetramine in 500 ml. of water was heated to boiling in a flask equipped for distillation. To this boiling mixture, one mole, 113 g., of 2-thenylamine[3] in 100 g. of 36% hydrochloric acid and 200 ml. of water was added dropwise over a period of approximately ninety minutes. 2-Thiophenealdehyde, 15 g., was obtained from the distillate after this period of time. The reaction was stopped at this point, not because the aldehyde formation had stopped, but in order that the insoluble yellow oily layer could be investigated. The *p*H of the reaction mixture was approximately 6 at this point as determined by Hydrion paper. After cooling to 20°, 150 ml. of concd. hydrochloric acid was added. The *p*H changed from 6 to approximately 4 during this addition but the yellow oil did not dissolve. Extraction with ether yielded 90 g. of a bright yellow oil which when distilled gave 10 g. of 2-thiophenealdehyde. The remaining material, b. p. 116–124.5 (0.8 mm.), was identified as I, N,N'-di-(2-thenyl)-1,3-diazacyclobutane.[2]

Acknowledgment.—The authors are grateful to Dr. D. E. Badertscher for his advice and interest in this problem and to Dr. Seymour L. Meisel for the preparation of N-methyl-2-thenaldimine and determination of its properties in connection with another phase of this problem.

Summary

A convenient synthesis of several 2-thiophenealdehydes is described in which the aminomethylation intermediates, the N-(2-thenyl)-formaldimines, undergo a prototropic shift and are hydrolyzed to the corresponding aldehydes. The reaction is complicated by side reactions and N-methyl- and N,N-dimethyl-2-thenylamines are also isolated.

PAULSBORO, N. J. RECEIVED SEPTEMBER 10, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Small-Ring Compounds. III. Synthesis of Cyclobutanone, Cyclobutanol, Cyclobutene and Cyclobutane[1]

BY JOHN D. ROBERTS AND CHARLES W. SAUER[2,3]

The formation of methylenecyclobutane from the reaction of pentaerythrityl bromide with zinc represents one of the simplest methods for the synthesis of a cyclobutane derivative in good yield from readily available starting materials. This reaction, which was discovered by Gustavson[4] and studied by a large number of other investigators,[5] gives methylenecyclobutane along with lesser amounts of 2-methyl-1-butene and spiropentane. Derfer, Greenlee and Boord[6] have extended the scope of the reaction considerably by showing that 1,1,1-tri-(bromomethyl)-alkanes react with zinc to give alkenyl- and alkylidenecyclobutanes.

Methylenecyclobutane has been converted to cyclobutanone in 30–36% yield by ozonization[7] and in small yield by oxidation with potassium permanganate in aqueous acetone[8] or *via* reduction of the corresponding nitrosite.[9] Other methods for the preparation of cyclobutanone, with the exception of the reaction of ketene with diazomethane,[10] involve at least five steps from available starting materials and give over-all yields of less than 10%.[11]

In the present work, methods for the preparation of cyclobutanone from methylenecyclobutane were investigated. Ozonization was not attempted because of the relative difficulty of adapting this procedure to large-scale laboratory operation. Satisfactory yields of cyclobutanone were obtained from methylenecyclobutane by oxidation to 1-(hydroxymethyl)-1-cyclobutanol and cleavage of the glycol with lead tetraacetate. Gustavson[4] has previously obtained 1-(hydroxymethyl)-1-cyclobutanol in 40% yield by oxidation of methylenecyclobutane with dilute aqueous potassium permanganate. In the present investigation, 80–83% yields were achieved by performic acid oxida-

(1) Earlier papers in this series, THIS JOURNAL, **67**, 1281 (1945); **68**, 843 (1946).

(2) An abstract of a thesis submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

(3) Present address: Arthur D. Little, Inc., Cambridge, Mass.

(4) Gustavson, *J. prakt. Chem.*, [2] **54**, 97, 104 (1896); Gustavson and Bulatoff, *ibid.*, [2] **56**, 93 (1897).

(5) See Marrian, *Chem. Rev.*, **43**, 149 (1948), for a number of leading references.

(6) Derfer, Greenlee and Boord, THIS JOURNAL, **67**, 1863 (1945); **71**, 175 (1949).

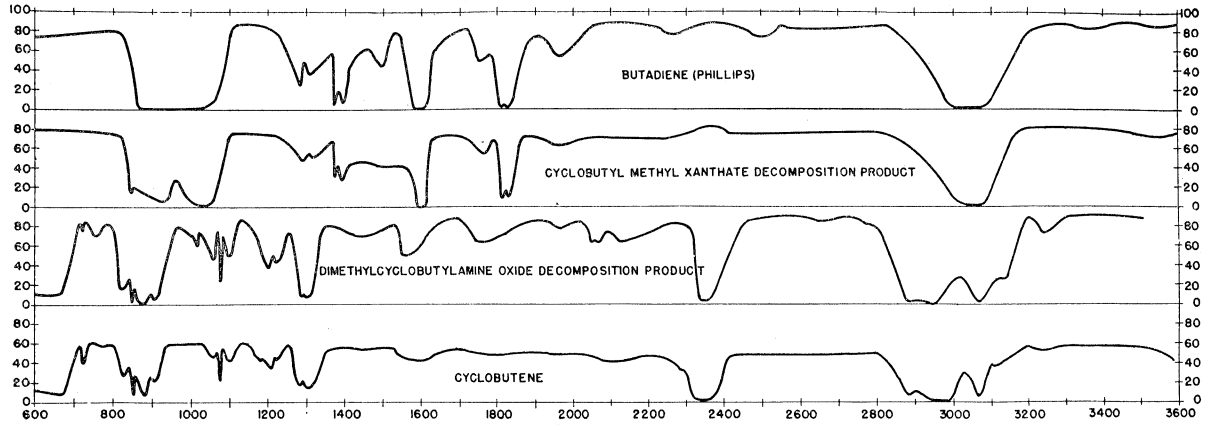
(7) Bauer and Beach, *ibid.*, **64**, 1142 (1942), cite unpublished work by Whitmore and Williams; *cf.* Williams, Ph.D. Thesis, Pennsylvania State College, 1941, and Krimmel, Ph.D. Thesis, Pennsylvania State College, 1945.

(8) Filipow, *J. Russ. Phys.-Chem. Soc.*, **46**, 1141 (1914); *J. prakt. Chem.*, [2] **93**, 162 (1916).

(9) Demjanow, *Ber.*, **41**, 915 (1908); Demjanow and Dojarenko, *J. Russ. Phys.-Chem. Soc.*, **49**, 193 (1917); *Ber.*, **55**, 2727 (1922).

(10) (a) Lipp and Köster, *Ber.*, **64**, 2823 (1931); (b) Lipp, Buchkremer and Seeles, *Ann.*, **499**, 1 (1932); (c) Benson and Kistiakowsky, THIS JOURNAL, **64**, 80 (1942).

(11) (a) Kishner, *J. Russ. Phys.-Chem. Soc.*, **37**, 106 (1905); (b) **39**, 922 (1907); (c) Demjanow and Dojarenko, *Ber.*, **40**, 4393 (1907); (d) **41**, 43 (1908); (e) **55**, 2737 (1922); (f) Demjanow, *J. Russ. Phys.-Chem. Soc.*, **61**, 1861 (1929); (g) Demjanow and Shuikina, *J. Gen. Chem. (USSR)*, **5**, 1213 (1935); (h) Demjanow and Telnow, *Bull. acad. sci. URSS, Classe sci. math. nat. sci. chim.*, 529 (1937); (i) Curtius and Grandel, *J. prakt. Chem.*, [2] **94**, 359 (1916); (j) Wagner, Ph.D. Thesis, Pennsylvania State College, 1941.



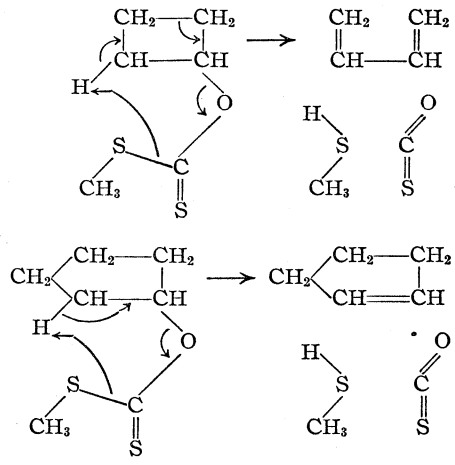
Wave numbers, cm.$^{-1}$.

Fig. 1.—Infrared spectra.

tion using a modification of the procedure employed by Roebuck and Adkins[12] for the preparation of *trans*-cyclohexandiol-1,2. A 39% yield was obtained in a single experiment using hydrogen peroxide in *t*-butyl alcohol.[13] Oxidation of the glycol with lead tetraacetate in methylene chloride solution gave yields of cyclobutanone up to 90%. Periodate oxidation of the glycol was not successful. The over-all yield of cyclobutanone from pentaerythritol was 40%.

Cyclobutane was obtained from cyclobutanone in 82% yield by the Huang-Minlon[14] modification of the Wolff–Kishner reduction.[15] Reduction of cyclobutanone to cyclobutanol was achieved in 90–100% yields using lithium aluminum hydride.[16]

The direct dehydration of cyclobutanol to cyclobutene does not appear to be feasible. Dojarenko[17] has reported that cyclobutanol is converted largely to propylene and butadiene over alumina at 360–390°. In the present work the indirect Tschugaeff method was investigated since this procedure has been shown to give olefins from alcohols in many cases with little skeletal rearrangement.[18] Cyclobutanol was converted to O-cyclobutyl S-methyl xanthate by successive treatments in diethyl ether with sodium hydride,[19] carbon disulfide and methyl iodide. The xanthate ester was pyrolyzed by dropwise addition to boiling diphenyl. The sodium hydroxide-insoluble gaseous product was shown to be quite pure 1,3-butadiene by comparison of its infrared spectrum (Fig. 1) with the infrared spectra of authentic samples of cyclobutene (prepared by the method of Willstätter and von Schmaedel[20]) and 1,3-butadiene. Application of the Tschugaeff method to cyclopentanol, investigated as a model case, resulted in a 70% yield of the normal dehydration product, cyclopentene, which was isolated as the dibromide. The abnormal behavior of the cyclobutyl xanthate ester as compared with the corresponding cyclopentyl ester on pyrolysis may be due to a different mode of reaction available only to the former ester. In this formulation the 2,3-bond of the cyclobutane ring is considered to be cleaved as an integral part of the pyrolysis reaction.



For the preparation of cyclobutene, cyclobutanone was converted to cyclobutyldimethylamine by reductive amination with excess methylamine followed by methylation of the resulting cyclobutylmethylamine with formaldehyde and formic acid. The procedure for the reductive amination was similar to that used by Hancock and Cope[21] for the preparation of isopropylaminoethanol while the methylation procedure was that of

(12) "Organic Syntheses," Vol. 28, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 35.

(13) Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936).

(14) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(15) For discussion of earlier methods for the preparation of cyclobutane see Cason and Way, *J. Org. Chem.*, **14**, 31 (1949).

(16) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

(17) Dojarenko, *J. Russ. Phys.-Chem. Soc.*, **58**, 1, 16, 27 (1926).

(18) Hückel, Tappe and Leguthe, *Ann.*, **543**, 191 (1939); Stevens and Richmond, THIS JOURNAL, **63**, 3132 (1941).

(19) Sodium hydride appears to be considerably superior to other reagents for forming the alkoxide in this preparation.

(20) Willstätter and von Schmaedel, *Ber.*, **38**, 1992 (1905).

(21) "Organic Syntheses," Vol. 26, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 38.

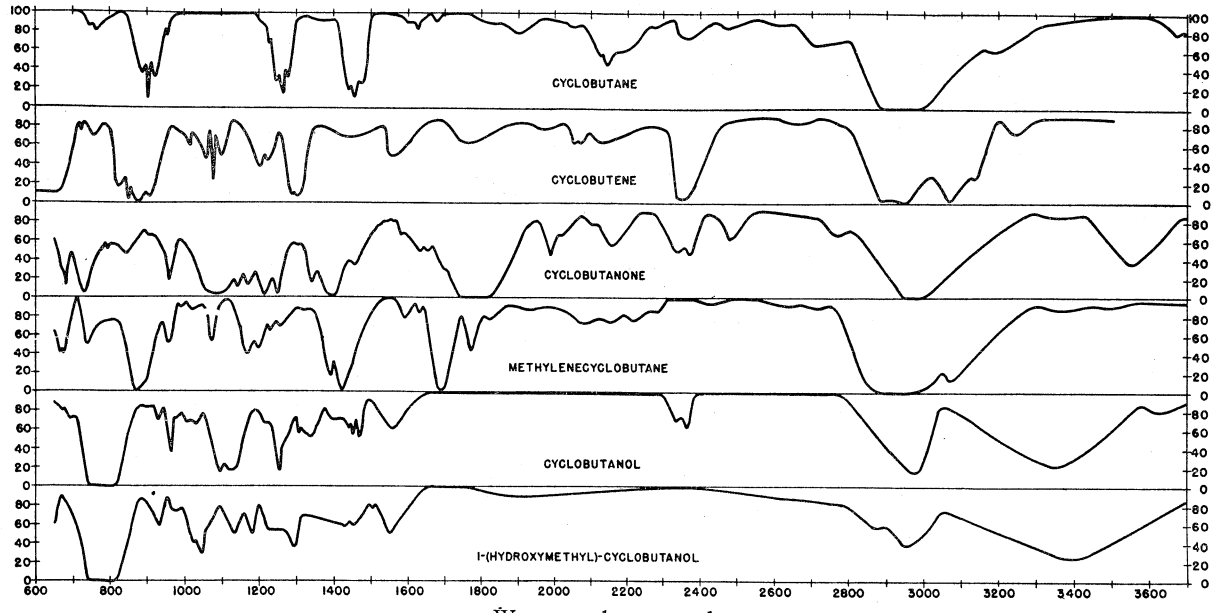


Fig. 2.—Infrared spectra.

Clarke, Gillespie and Weishaus.[22] Part of the cyclobutyldimethylamine was converted to cyclobutene through the quaternary iodide by the method of Willstätter.[20] Contrary to earlier reports[20,23] the cyclobutene obtained in this ways contained no appreciable amount of 1,3-butadiene (*cf.* infrared curves of Fig. 1). Cyclobutene, free of 1,3-butadiene, was also obtained from the pyrolysis of cyclobutyldimethylamine oxide by the method of Cope, Towle and Foster.[24] The amine oxide was prepared by oxidation of dimethylcyclobutylamine with 10% hydrogen peroxide. Cyclobutene was obtained by this method in 50–60% yields with recoveries of 28–30% of the starting material as cyclobutyldimethylamine. The yield of cyclobutene from the quaternary iodide is somewhat better (70%) and about 30% of cyclobutyldimethylamine is recovered.

Acknowledgment.—We are indebted to Dr. R. C. Lord, Jr., Mr. R. S. McDonald and Mr. E. Slowinski for the infrared determinations.

Experimental

Methylenecyclobutane.—The reaction of pentaerythrityl bromide with zinc is more easily controlled using the following procedure than the one described by Shand, Schomaker and Fischer.[25]

A solution of 10 g. of zinc bromide and 30 ml. of ethanol in 700 ml. of water was placed in a 3-l. three-necked creased flask equipped with a stainless-steel stirrer driven by a 1/4-h. p. 10,000 r. p. m. motor. One neck of the flask was equipped with a thermometer which extended into the solution and a 30-cm. air-cooled reflux condenser with a Claisen head at the top connected to a water-cooled spiral condenser. The receiver at the bottom of the spiral condenser was fitted with a Dry Ice-cooled condenser. Stirring was begun and 476 g. (7.3 gram atom) of zinc dust added. Purified pentaerythrityl bromide[26] (678 g., 1.75 moles) was placed in a 1-l. Erlenmeyer flask attached to the third neck of the creased flask by a rubber tube.[27] The contents of the reaction flask were heated to 90° and a portion of the bromide was added. The reaction began immediately and the remainder of the bromide was added portionwise as rapidly as permitted by the foaming of the mixture. The temperature was maintained at 90 ± 1° during the addition of the bromide and afterwards at 95° for one-half hour. The hydrocarbon which steam-distilled was washed with ice water and dried over calcium chloride. The yield of crude product was 102 g. (86%). Fractionation of the material from several runs through a 2 × 60 cm. glass-helix packed column gave a 70% yield (based on pentaerythrityl bromide) of methylenecyclobutane, b. p. 41.5–42°. No spiropentane could be isolated from the reaction products. The infrared spectrum of the methylenecyclobutane is given in Fig. 2.

Pentaerythrityl benzenesulfonate failed to react with zinc dust in boiling 50% absolute ethanol in the presence of sodium iodide or sodium bromide.

1-(Hydroxymethyl)-1-cyclobutanol.—A. To an ice-cooled solution of 12 g. (0.176 mole) of crude methylenecyclobutane, 88 ml. (0.194 mole) of 7.5% hydrogen peroxide in *t*-butyl alcohol was added 1 ml. of a 0.5% solution of osmium tetroxide in *t*-butyl alcohol. The mixture was kept in a refrigerator for two days. At the end of this period, the solution gave a negative test for peroxide. The *t*-butyl alcohol was removed by distillation and the residue distilled under reduced pressure. The yield of the glycol, b. p. 78–85° (2 mm.), was 7.0 g. (39%).

Anal. Calcd. for $C_5H_8O_2$: C, 58.80; H, 9.86. Found: C, 59.10; H, 9.79.

B. To a stirred mixture of 600 ml. (13.4 moles) of 87% formic acid and 120 ml. (1.1 moles) of 35% hydrogen peroxide was added slowly 68 g. (1.0 mole) of purified methylenecyclobutane. The temperature of the reaction mixture was maintained at 20–30° with an ice-bath. The mixture was then allowed to stand at room temperature

(22) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(23) Heisig, *ibid.*, **63**, 1698 (1941).

(24) Cope, Towle and Foster, *ibid.*, **71**, 3929 (1949).

(25) Shand, Schomaker and Fischer, *ibid.*, **66**, 636 (1944).

(26) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 476.

(27) Fieser, "Experiments in Organic Chemistry," second edition, D. C. Heath and Co., New York, N. Y., 1941, p. 311.

overnight. The formic acid and water were removed by distillation on a steam-bath at water-pump pressure. The residue was treated with an ice-cold solution of 80 g. (2.0 moles) of sodium hydroxide in 150 ml. of water. The alkaline solution was warmed to 45°, allowed to cool and then extracted with methylene chloride in a continuous extractor for twenty-four hours. The methylene chloride was removed and the residue distilled. The yield of the glycol, b. p. 93° (5 mm.), was 83.2 g. (83%); $n^{25}D$ 1.4715. The infrared spectrum of the liquid product is shown in Fig. 2.

Cyclobutanone.—In a 1-liter creased flask equipped with a stainless-steel stirrer was placed 85.0 g. (0.833 mole) of 1-(hydroxymethyl)-1-cyclobutanol and 500 ml. of methylene chloride. One neck of the flask was closed with a stopper while the other was fitted with a vertical vapor extractor topped by a reflux condenser. The extractor tube held a large Soxhlet thimble containing 420 g. (0.948 mole) of crude lead tetraacetate. The stirrer was started and the mixture heated to reflux. The lead tetraacetate was extracted by the methylene chloride and carried into the solution of the glycol. When the extraction was complete, the mixture was refluxed and stirred for an hour and then allowed to stand overnight. Water (250 ml.) was added and the mixture steam-distilled until about 1 liter of steam-distillate was collected. The distillate was cooled in ice and neutralized with 40% sodium hydroxide solution and then continuously extracted with methylene chloride. Distillation through a 1.6 × 25 cm. glass-helix packed column 52.8 g. (90.5%) of cyclobutanone, b. p. 98–100°, $n^{25}D$ 1.4189. The infrared spectrum of the pure material (liquid) is given in Fig. 2. The product was identified by its 2,4-dinitrophenylhydrazone, m. p. 146–146.5° (lit., 132–133°,[10a] 146.3–146.7°,[6] 147–147.2°[28]) and semicarbazone, m. p. 206–207° dec. (lit., 201°[11b], 202°[29,11d], 202.6–203°,[6] 211–212°,[10a,11e,i] 212–212.5°,[28] 216°,[30] 221°).[11a]

Anal. (semicarbazone). Calcd. for $C_5H_9ON_3$: C, 47.23; H, 7.13. Found: C, 47.08; H, 7.25.

Cyclobutane.—A 200-ml. flask containing a mixture of 7.0 g. (0.1 mole) of cyclobutanone, 10 ml. of 85% hydrazine hydrate, 50 ml. of Carbitol and a solution of 14 g. (0.3 mole) of potassium hydroxide in 50 ml. of Carbitol was attached to a 12 × 250 mm. Vigreux column the top of which was connected to a Dry Ice-cooled trap. The flask was heated in an oil-bath and the evolved cyclobutane collected in the trap. The heating was continued until no water distilled from the reaction mixture with the bath at 200°. The cyclobutane was distilled through a short Vigreux column with an ice-cooled reflux condenser, b. p. 12.5°; yield 4.6 g. (82%). The infrared spectrum of the gaseous material is shown in Fig. 2. A similar procedure gave an 86% yield of cyclopentane from cyclopentanone.

Cyclobutanol.—Cyclobutanone (30 g., 0.43 mole) was added dropwise to a stirred suspension of 5 g. (0.125 mole) of lithium aluminum hydride in 200 ml. of dry ether. After the addition was complete the mixture was refluxed for one hour. Sufficient 10% sulfuric acid was added slowly with stirring to dissolve the solids and the cyclobutanol was extracted with ether. Distillation through a 16 × 250 mm. glass-helix packed column, gave, other than diethyl ether: 8.6 g., b. p. 121–125°, and 19.1 g., b. p. 125°, of cyclobutanol. The combined yield was 90%. The pure material showed $n^{25}D$ 1.4347. The infrared spectrum of the liquid is shown in Fig. 2.

Cyclobutyl phenylurethan was prepared from cyclobutanol and phenyl isocyanate; m. p. 130.6–131.2° (lit.,[31] 110–111°) after recrystallization from hexane.

Anal. Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85. Found: C, 69.35; H, 6.78.

A similar lithium aluminum hydride reduction of cyclopentanone gave an 85% yield of cyclopentanol.

(28) Buchman, Schlatter and Reims, THIS JOURNAL, **64**, 2701 (1942).

(29) Demjanow, *Ber.*, **40**, 4393, 4961 (1907).

(30) Zelinsky and Gutt, *ibid.*, **40**, 4744 (1907).

(31) Demjanow and Dojarenko, *ibid.*, **40**, 2594 (1907).

O-Cyclobutyl S-Methyl Xanthate.—The procedure for this preparation was similar to that employed by Whitmore and Simpson.[32]

To a stirred suspension of 3.5 g. (0.146 mole) of sodium hydride in 100 ml. of dry ether was added dropwise 8 g. (0.11 mole) of cyclobutanol. The mixture was refluxed for three hours and then treated successively with 9.7 g. (0.135 mole) of carbon disulfide and 19.2 g. (0.135 mole) of methyl iodide. After each addition, the mixture was refluxed for three hours. Water was added to dissolve the solids, the ether layer was separated and dried over magnesium sulfate. The ether, excess carbon disulfide and methyl iodide were removed and the cyclobutyl methyl xanthate distilled under reduced pressure. The yield was 14.3 g. (84%), b. p. 67° (1.5 mm.).

Anal. Calcd. for $C_6H_{10}OS_2$: C, 44.41; H, 6.21. Found: C, 44.37; H, 6.43.

O-Cyclopentyl S-methyl xanthate, b. p. 88° (2.5 mm.), was prepared by a similar procedure in 90% yield.

Anal. Calcd. for $C_7H_{12}OS_2$: C, 47.69; H, 6.86. Found: C, 47.66; H, 6.93.

Pyrolysis of O-Cyclobutyl S-Methyl Xanthate.—The xanthate ester (1.84 g., 0.011 mole) was added to boiling diphenyl and the evolved gases collected over concentrated sodium hydroxide solution to dissolve the carbon oxysulfide and methyl mercaptan formed in the pyrolysis. The residual gas amounted to 250 ml. Comparison of the infrared spectrum (Fig. 1) of the gas with that of a sample of 1,3-butadiene (Phillips Petroleum Company, "Special Purity") showed the product to be apparently pure 1,3-butadiene. Pyrolysis of 13.5 g. (0.077 mole) of O-cyclopentyl S-methyl xanthate by the same procedure gave cyclopentene which was isolated as the dibromide, b. p. 75° (17 mm.). The yield of the dibromide was 12.2 g. (70%).

Cyclobutyldimethylamine—Cyclobutanone (21 g., 0.30 mole) was dissolved in 102 ml. of a 5.9 *M* solution of methylamine in absolute alcohol. The mixture was allowed to stand overnight and then shaken with hydrogen at 10–35 lb. per sq. in. over previously reduced platinum oxide catalyst. The theoretical quantity of hydrogen was absorbed in two hours. The excess methylamine was removed by distillation and the residue cooled, then acidified with 45 ml. of concentrated hydrochloric acid. The hydrogenation catalyst was separated by filtration and the alcohol and water removed from the filtrate by distillation under reduced pressure. The sirupy residue was heated with 75 ml. of 87% formic acid and 75 ml. of 35% formaldehyde solution on a steam-bath until a vigorous evolution of carbon dioxide began. The flask was removed from the bath until the gas evolution subsided, after which heating was continued overnight. The next day, 15 ml. more of 35% formaldehyde solution was added and the mixture was heated under reflux for four hours. The excess formaldehyde and formic acid were removed under reduced pressure and the residue was dissolved in 75 ml. of water. A solution of 40 g. of sodium hydroxide in 60 ml. of water was added dropwise with stirring and the liberated amine extracted with xylene. The xylene extracts were combined, dried over sodium hydroxide and distilled from sodium. The yield of cyclobutyldimethylamine, b. p. 97–100°, was 22.4 g. (75.5%).

In an attempt to isolate **cyclobutylmethylamine** from a reductive amination using 35 g. (0.5 mole) of cyclobutanone and methyl Cellosolve instead of ethyl alcohol as solvent, 29.7 g. of product, b. p. 84.5–88°, was isolated which was apparently a stable hydrate of the amine.

Anal. Calcd. for $C_5H_{11}N \cdot H_2O$: C, 58.21; H, 12.70; neut. eq., 103.1. Found: C, 57.62; H, 12.74; neut. eq., 105.8.

Methylation of the hydrated amine with formic acid and formaldehyde gave dimethylcyclobutylamine, b. p. 98–100°, in good yield.

Cyclobutyldimethylamine picrate was prepared from the amine and picric acid in benzene and recrystallized from isopropyl alcohol; m. p. 193.5–195° (dec.).

(32) Whitmore and Simpson, THIS JOURNAL, **55**, 3809 (1933).

Anal. Calcd. for $C_{12}H_{16}N_4O_7$: C, 44.14; H, 5.13. Found: C, 43.90; H, 4.91.

The **picrylsulfonate** was obtained from amine and picrylsulfonic acid in isopropyl alcohol. After recrystallization from ethanol containing a little water, the melting point was 194.5–195° (dec.).

Anal. Calcd. for $C_{12}H_{16}N_4O_9S$: C, 36.73; H, 4.11. Found: C, 36.97; H, 4.22.

Cyclobutene from Cyclobutyltrimethylammonium Hydroxide.—Willstätter and von Schmaedel[20] prepared cyclobutene from cyclobutyltrimethylammonium hydroxide but did not give experimental details.

To 10 g. (0.1 mole) of cyclobutyldimethylamine dissolved in 100 ml. of ether was added 16.5 g. (0.11 mole) of methyl iodide. Heat was evolved and the quaternary iodide began to crystallize at once. The mixture was allowed to stand in a refrigerator overnight. The yield of the quaternary iodide was quantitative.

A solution of 25 g. (0.1 mole) of the quaternary salt in 100 ml. of water was shaken with 0.30 mole of freshly prepared silver oxide for two hours. The mixture was filtered and concentrated under reduced pressure. The sirupy quaternary hydroxide was added dropwise to a flask heated to 140° with an oil-bath. The pressure within the flask was maintained at 50 mm. The evolved gases were bubbled through a 1 *N* solution of hydrochloric acid and then condensed in a Dry Ice-cooled trap. The contents of the trap were allowed to evaporate into a gas holder. The yield of cyclobutene calculated from the gas volume was 0.073 mole (73%). The infrared spectrum of the product is shown in Figs. 1 and 2.

The contents of the hydrochloric acid bubbler were made basic and extracted with xylene. The xylene extracts were dried over sodium hydroxide and distilled from sodium. The recovery of cyclobutyldimethylamine, b. p. 98–102° was 2.8 g. (23%).

Cyclobutene from Cyclobutyldimethylamine Oxide.—To an ice-cooled stirred mixture of 20 ml. of 35% hydrogen peroxide and 50 ml. of water was added 10 g. (0.1 mole) of cyclobutyldimethylamine at such a rate as to keep the temperature of the reaction mixture below 10°. The solution was allowed to warm to room temperature and left overnight. Platinum foil was added to decompose the excess peroxide and the solution was concentrated under reduced pressure.

The sirupy amine oxide was decomposed at 160° as described above for cyclobutyltrimethylammonium hydroxide. The yields of cyclobutene were 50–60%. From 28–32% of cyclobutyldimethylamine, b. p. 98–102°, was recovered from the hydrochloric acid bubbler. The infrared spectrum of the cyclobutene prepared from the amine oxide pyrolysis is shown in Fig. 1.

Cyclobutyldimethylamine oxide picrylsulfonate was prepared from the amine oxide and picrylsulfonic acid in isopropyl alcohol; m. p. 168.8–169.5°, after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{12}H_{16}O_{10}N_4S$: C, 35.29; H, 3.95. Found: C, 35.24; H, 4.06.

Summary

Cyclobutanone has been prepared in good yield by hydroxylation of methylenecyclobutane with performic acid and cleavage of the resulting glycol with lead tetraacetate.

Cyclobutanone has been converted to cyclobutane by the Wolff–Kishner reaction, cyclobutanol by reduction with lithium aluminum hydride, and cyclobutyldimethylamine by reductive amination with methylamine followed by methylation with formaldehyde and formic acid.

O-Cyclobutyl S-methyl xanthate on pyrolysis gives 1,3-butadiene. Under similar conditions, O-cyclopentyl S-methyl xanthate gives cyclopentene.

Cyclobutene, free of 1,3-butadiene, was prepared by the pyrolysis of cyclobutyltrimethylammonium hydroxide and cyclobutyldimethylamine oxide.

CAMBRIDGE 39, MASS. RECEIVED APRIL 12, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

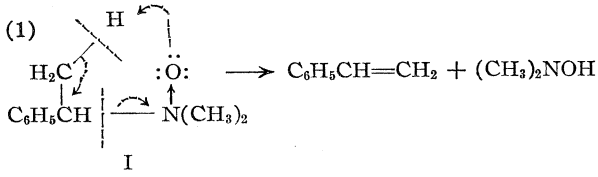
Thermal Decomposition of Amine Oxides to Olefins and Dialkylhydroxylamines[1,2]

BY ARTHUR C. COPE, THEODORE T. FOSTER AND PHILIP H. TOWLE

A number of allyldialkylamine oxides and benzyldimethylamine oxide recently have been shown to rearrange to trialkylhydroxylamine derivatives on heating at temperatures of 80 to 165°, with migration of the allyl and benzyl groups from nitrogen to oxygen.[3] In extending this work, it has

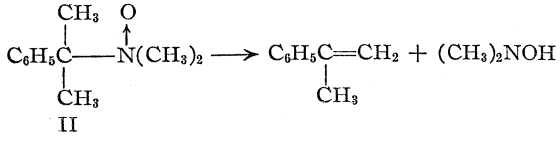
$$R_2N{\rightarrow}O \longrightarrow R_2NOC_3H_5$$
$$\quad\quad\quad

yield of I obtained by oxidation was 98%. After removal of the water from the solution of I by distillation under reduced pressure, the non-volatile amine oxide on heating at 85–115° and 5 mm. pressure was converted into volatile products which collected as a distillate. The distillate was separated by extraction with hydrochloric acid into N,N-dimethylhydroxylamine (isolated in 94% yield as the hydrochloride) and styrene (isolated in 70% yield and characterized as the dibromide). There was no evidence of partial isomerization of I into the rearrangement product, O-(α-phenylethyl)-N,N-dimethylhydroxylamine. This elimination reaction resembles the thermal decomposition of trimethylalkylammonium hydroxides into olefins, trimethylamine and water (Hofmann exhaustive methylation), which proceeds by attack of hydroxyl ion on hydrogens beta to the nitrogen linkage.[5] The conversion of I to styrene can be formulated in a similar way. The process is represented as intramolecular, but an equivalent intermolecular route is equally in accord with the facts known at present.

(1) 

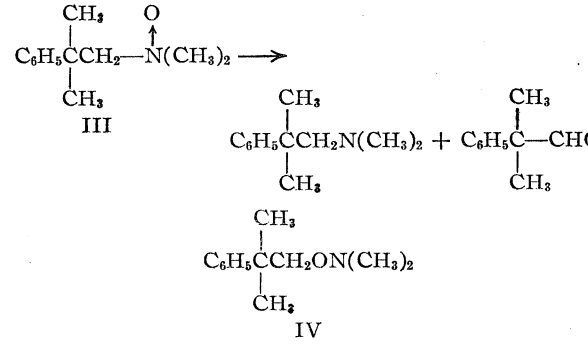
I

In order to obtain evidence concerning the validity of this interpretation, homologs of I containing no α- and no β-hydrogen atoms were investigated. N,N-Dimethyl-(α,α-dimethylbenzyl)-amine was prepared from benzyl cyanide by methylation, hydrolysis of the α,α-dimethylbenzyl cyanide to α,α,α-dimethylphenylacetamide, and degradation of the amide to α,α-dimethylbenzylamine by the Hofmann reaction, followed by methylation with formaldehyde and formic acid. Oxidation of the tertiary amine with 35% hydrogen peroxide gave N,N-dimethyl-(α,α-dimethylbenzyl)-amine oxide (II), from which the crystalline picrate was obtained in 96% yield (based on the tertiary amine). II decomposed readily on heating at 75–85° into α-methylstyrene (isolated in 78% yield and characterized as the nitrolpiperidine derivative) and N,N-dimethylhydroxylamine (isolated in 63% yield as the hydrochloride). Occurrence of the elimination with II indicates that α-hydrogen atoms are unnecessary for the reaction. There was no evidence of partial rearrangement of II into O-(α,α-dimethylbenzyl)-N,N-dimethylhydroxylamine.



II

A related amine with no β-hydrogens, N,N-dimethyl-(β-phenylisobutyl)-amine, was prepared by the Friedel–Crafts alkylation of benzene with β-methylallyldimethylamine.[6] N,N-Dimethyl-(β-phenylisobutyl)-amine oxide (III) was prepared by oxidation of the tertiary amine with 35% hydrogen peroxide. III was isolated as a crystalline hydrate, and proved to be much more stable than I or II. It did not decompose on heating until a temperature of 148° was reached, at which temperature exothermic decomposition occurred. From the decomposition products were isolated 39% of the original tertiary amine, N,N-dimethyl-(β-phenylisobutyl)-amine, and 7.7% of α,α-dimethylphenylacetaldehyde, identified as the semicarbazone and by oxidation to α,α-dimethylphenylacetic acid. A smaller amount (4.4%) of a weakly basic compound was isolated, which was not obtained completely pure, but from an approximate analysis, solubility characteristics and physical properties was probably the rearrangement product, O-(β-phenylisobutyl)-N,N-dimethylhydroxylamine (IV). The formation of IV by



IV

rearrangement could occur in a manner analogous to the rearrangement of benzyldimethylamine oxide,[3] even though the α-carbon of the β-phenylisobutyl group is less electron attracting than the α-carbon of a benzyl group, because the elimination reaction is blocked by the absence of β-hydrogens. Decomposition of samples of III at atmospheric pressure produced relatively small amounts of gas, which contained carbon dioxide and oxygen. Other products must have been formed to account for the remainder of III, but they were not isolated. The relative stability of III (compared to I and II) and the fact that III did not decompose to yield an olefin (possible only with rearrangement such as occurs in the dehydration of neopentyl alcohol) furnishes evidence that the elimination proceeds by attack of the amine oxide oxygen on a β-hydrogen atom, as shown in equation (1). A similar decomposition of N-methyl and N-ethyltetrahydroquinoline oxides has been reported by Dodonov[7] to yield tetrahydroquinoline and formaldehyde and acetaldehyde, respectively.

The behavior of benzyldiethylamine oxide (V) on heating proved to be interesting in that both

(5) Hanhart and Ingold, *J. Chem. Soc.*, 997 (1927).

(6) Weston, Ruddy and Suter, THIS JOURNAL, **65**, 674 (1943).

(7) Dodonov, *J. Gen. Chem.* (*U. S. S. R.*), **14**, 960 (1944); [*C. A.* **39**, 4612 (1945)].

elimination and rearrangement occurred as competitive reactions. Five products were isolated from the decomposition of V. N-Benzyl-N-ethylhydroxylamine (VI), the olefin elimination product, was isolated in 34% yield, and in a separate decomposition at atmospheric pressure the ethylene formed was collected and characterized as ethylene dibromide (14% yield). The rearrangement product, O-benzyl-N,N-diethylhydroxylamine (VII), was isolated in 31% yield (equation 3). Finally, 21% of N,N-diethylhydroxylamine

(2) $C_6H_5CH_2\overset{\uparrow O}{N}(C_2H_5)_2 \longrightarrow CH_2{=}CH_2 + C_6H_5CH_2NOH$ (with C_2H_5)

V VI

(3) $V \longrightarrow (C_2H_5)_2NOCH_2C_6H_5$

VII

(VIII) and 16% of O,N-dibenzyl-N-ethylhydroxylamine(IX) were isolated. These products are believed to arise through a bimolecular alkylation reaction (equation 4), in which the amine oxide (V) alkylates the olefin elimination product, N-benzyl-N-ethylhydroxylamine (VI). Alkylation of phenols with replacement of the active hydrogen by a benzyl group has been reported with benzyldimethylphenylammonium chloride as the alkylating agent,[8] and aryl allyl ethers have been prepared with allyldimethylphenylammonium hydroxide as the alkylating agent.[9] The similarity of the bond between the benzyl group and nitrogen in benzyldialkylamine oxides and quaternary ammonium salts and bases containing a benzyl group is apparent, and the ease with which the bond is broken in a nucleophilic displacement reaction presumably accounts for the occurrence of the alkylation reaction (equation 4).

(4) $C_6H_5CH_2\overset{\uparrow O}{N}(C_2H_5)_2 + C_6H_5CH_2NOH \longrightarrow$ (with C_2H_5)

V VI

$(C_6H_5)_2NOH + C_6H_5CH_2NOCH_2C_6H_5$ (with C_2H_5)

VIII IX

The structures of the products formed by the decomposition and rearrangement of V were determined as follows. N-Benzyl-N-ethylhydroxylamine (VI) was reduced with stannous chloride and hydrochloric acid to benzylethylamine, which was characterized as the hydrochloride and picrate. O-Benzyl-N,N-diethylhydroxylamine (VII) was hydrogenated in the presence of palladium and yielded diethylamine (isolated as the picrate) and benzyl alcohol, which was identified by conversion to benzyl chloride and subsequently to benzylisothiouronium picrate. O,N-Dibenzyl-N-ethylhydroxylamine (IX) was hydrolyzed in the presence of hydrochloric acid and yielded N-benzyl-N-ethylhydroxylamine (isolated as the picrate) and benzyl chloride, which was converted to benzylisothiouronium picrate. N,N-Diethylhydroxylamine (VIII) was characterized by its physical properties, analysis, analysis of the picrate and conversion to the known hydrochloride and neutral oxalate.

Work is in progress to determine the usefulness of the decomposition of alkyldimethylamine oxides to olefins and dimethylhydroxylamine as a method for the synthesis of olefins compared to the Hofmann exhaustive methylation reaction, and to determine whether the elimination is intramolecular as represented in equation (1), or intermolecular.

Experimental[10]

N,N-Dimethyl-(α-phenylethyl)-amine.—α-Phenylethylamine[11] was methylated by treatment with formaldehyde and formic acid[12] in 69% yield to N,N-dimethyl-(α-phenylethyl)-amine; b. p. 71° (11 mm.), $n^{25}D$ 1.5000, d^{25}_4 0.8989; M_D calcd., 48.72; found, 48.83; m. p. of the picrate 140–140.5°.

N,N-Dimethyl-(α-phenylethyl)-amine Oxide (I).—N,N-Dimethyl-(α-phenylethyl)-amine (11.0 g.) was stirred with 18.3 g. (150% excess) of 35% aqueous hydrogen peroxide for eleven hours at room temperature. The excess hydrogen peroxide was decomposed by stirring the mixture with 8 sq. cm. of clean platinum foil until the evolution of oxygen ceased. Most of the water was removed by distillation at 35 mm. pressure and a bath temperature of 45–55°; the distillate and material which condensed in a trap cooled with a mixture of Dry Ice and trichloroethylene in the vacuum line were saved. The residual sirup was diluted with 25 ml. of absolute ethanol, reconcentrated under reduced pressure while nitrogen was admitted through a capillary ebulliator inlet, and the process was repeated twice to remove as much water as possible. The amine oxide remained as a viscous sirup, which from its odor contained a small amount of styrene.

N,N-Dimethyl-(α-phenylethyl)-amine oxide picrate was prepared in 98% yield by treating an aliquot of the aqueous solution of the amine oxide with an equivalent amount of picric acid in aqueous solution, and was recrystallized to constant m. p. from 95% ethanol, m. p. 155.5–156.5°.

Anal. Calcd. for $C_{16}H_{18}N_4O_8$: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.76; H, 4.77; N, 14.19.

Decomposition of N,N-Dimethyl-(α-phenylethyl)-amine Oxide (I).—A 100-ml. round-bottomed flask fitted with a capillary nitrogen inlet and containing the amine oxide was connected by a large-diameter tube to a condenser set for distillation, which led to two receivers in series cooled in a mixture of Dry Ice and trichloroethylene. The system was evacuated to 5 mm. and the flask was immersed in an oil-bath at 85°. The bath temperature was raised slowly to 115° during thirty-five minutes, at which time almost all of the material had distilled. The bath temperature was raised to 150° to complete the distillation; 0.35 g. of a tarry residue remained. The distillate was combined with the distillate obtained in concentration of the amine oxide solution, pentane was added as a solvent, and the mixture was washed with dilute hydrochloric acid. The acid solu-

(8) Baw, *Quart. J. Ind. Chem. Soc.*, **3**, 101 (1926) [*C. A.*, **20**, 3695 (1926)].

(9) Tarbell and Vaughn, THIS JOURNAL, **65**, 231 (1943).

(10) Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy, Mrs. Louise W. Spencer and Mr. F. A. Bauman for analyses

(11) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 503.

(12) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

tion was extracted with pentane, and the pentane solutions were washed with water until neutral.

The combined aqueous layers containing hydrochloric acid were concentrated under reduced pressure to a crystalline residue, which was dried by adding absolute alcohol and reconcentrating under reduced pressure, and placed in a vacuum desiccator over phosphorus pentoxide. The yield of N,N-dimethylhydroxylamine hydrochloride was 6.73 g. (94%), m. p. 101–104° (sealed capillary). A sample which was recrystallized several times from a mixture of absolute ethanol and ether was obtained as hygroscopic white needles, m. p. 106.5–109° (sealed capillary).[13]

Anal. Calcd. for C_2H_8NOCl: C, 24.62; H, 8.27; N, 14.36; Cl, 36.35. Found: C, 24.96; H, 8.24; N, 14.12; Cl, 35.99.

The pentane solution containing the neutral product was dried over magnesium sulfate and concentrated at atmospheric pressure, after addition of a crystal of picric acid as a polymerization inhibitor. Distillation of the residue yielded 5.34 g. (70%) of styrene; b. p. 82–83° (102 mm.), $n^{25}D$ 1.5424–1.5428. The styrene was identified by conversion to the dibromide, which after recrystallization from 80% ethanol had m. p. and mixed m. p. with a known sample 72.5–73°.

α,α-Dimethylbenzyl Cyanide.—The general procedure of Haller and Bauer[14] was used, except that both methyl groups were introduced in a single alkylation. Benzyl cyanide (1 mole) in 250 ml. of dry ether was added during thirty minutes to a suspension of 2 moles of freshly prepared sodamide in 1 l. of dry ether, with stirring in a 3-l. three-necked flask equipped with a reflux condenser, dropping funnel and slip-sealed Hershberg stirrer. The mixture was heated under reflux and stirred for one hour, after which 2.2 moles of methyl iodide in 350 ml. of dry ether was added during forty minutes, while the mixture was cooled in an ice-bath. An additional 750 ml. of dry ether was added and the mixture was heated under reflux and stirred for one hour. The mixture was allowed to stand overnight, heated under reflux for one additional hour, and cooled. Ethanol was added to destroy small amounts of sodamide above the surface of the liquid, followed by water to dissolve the precipitated sodium iodide. The product was washed with dilute sodium bisulfite and sodium carbonate solutions and water, dried over sodium sulfate, and distilled through a 20 × 1.6 cm. column packed with glass helices; yield 113.5 g. (78%), b. p. 81–82° (2.2 mm.), $n^{25}D$ 1.5043–1.5055.

α,α,α-Dimethylphenylacetamide was prepared in 74% yield by warming α,α-dimethylbenzyl cyanide with 85% sulfuric acid for three hours,[14] m. p. 150–153°. A sample recrystallized to constant m. p. from absolute ethanol had m. p. 160–161.5° (ref. 14 reports m. p. 160°).

α,α-Dimethylbenzylamine.—Use of a reported procedure for the Hofmann degradation of α,α,α-dimethylphenylacetamide[15] led to recovery of part of the amide, and the following procedure[16] gave a better yield. A solution of 117 g. of sodium hydroxide in 975 ml. of water was placed in a 2-l. three-necked flask and cooled to 0° in an ice–salt bath. Bromine (46.9 g.) was added in portions with stirring, followed by 79.6 g. of α,α,α-dimethylphenylacetamide (m. p. 157.5–159.5°) in small portions during ten minutes, while the solution was at 0°. The suspension was stirred at 0° for seven hours, packed in ice, and allowed to come to room temperature overnight. The mixture was stirred and warmed on a steam-bath for thirty minutes. The product was extracted with ether, the ether solution was dried over sodium sulfate, and the amine hydrochloride was precipitated by introducing dry hydrogen chloride; yield 79.8 g. (95%), m. p. 240–241° (ref. 15 reports m. p. 240°). The amine was liberated with 6 *N* sodium hydroxide, extracted with ether, dried over sodium sulfate and distilled through a 20 × 1.6 cm. helix-packed column; yield 55 g. (83.5%), b. p. 72–73° (8 mm.); $n^{25}D$ 1.5175–1.5185.

N,N-Dimethyl-(α,α-dimethylbenzyl)-amine.—N,N-Dimethyl-(α,α-dimethylbenzyl)-amine was prepared from 55 g. of α,α-dimethylbenzylamine, 108 g. of 87% formic acid and 92 ml. of 37% formaldehyde solution by a general procedure previously described.[12] The amine was liberated from its hydrochloride, extracted with ether, and distilled through a 20 × 1.6 cm. helix-packed column; yield 62 g. (94%), b. p. 84–87° (11 mm.), $n^{25}D$ 1.5071, d^{25}_4 0.9176; M_D calcd., 53.35; found, 52.96.

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.94; H, 10.51; N, 8.84.

A picrate prepared from a sample of this amine and an equivalent amount of picric acid in 95% ethanol was recrystallized from a mixture of chloroform and ether, m. p. 210–212° (dec.).[17]

Anal. Calcd. for $C_{17}H_{20}N_4O_7$: C, 52.04; H, 5.14; N, 14.28. Found: C, 51.86; H, 5.37; N, 14.36.

N,N-Dimethyl-(α,α-dimethylbenzyl)-amine Oxide (II).—N,N-Dimethyl-(α,α-dimethylbenzyl)-amine (20 g.) was oxidized with 35% aqueous hydrogen peroxide (36 g.) during twenty-two hours. After decomposition of the excess hydrogen peroxide in the presence of 8 sq. cm. of platinum foil, an aliquot of the aqueous solution was extracted with ether to remove any remaining amine and treated with an equivalent quantity of picric acid in 95% ethanol. The picrate of II precipitated in 96% yield, m. p. 142–143°. It decomposed partially on attempted recrystallization from absolute ethanol, but was analytically pure as originally precipitated.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.23; H, 5.12; N, 13.53.

N,N-Dimethyl-(α,α-dimethylbenzyl)-amine oxide remained as a viscous sirup after concentration in the manner described for preparation of I. II was decomposed in the same manner as I by heating in a nitrogen atmosphere at 3 mm. pressure and a bath temperature of 75–85° for one and one-half hours. The distillation of the volatile products was completed by raising the temperature to 200° briefly; the residue amounted to 1.2 g. The distillate was separated into a neutral and basic fraction in the manner described for isolating the decomposition products of I. The basic fraction yielded 7.5 g. (63%) of N,N-dimethylhydroxylamine hydrochloride. Fractionation of the dried pentane extracts yielded 11.3 g. (78%) of α-methylstyrene, b. p. 59–60° (15 mm.). A sample of the α-methylstyrene was characterized by treatment with isoamyl nitrite and hydrochloric acid, which yielded the nitrosochloride, which in turn was treated with an excess of piperidine in benzene. The nitrolpiperidine derivative of α-methylstyrene so obtained was recrystallized from hexane; m. p. and mixed m. p. with a known sample[18] 121–122°.

β-Methylallyldimethylamine and N,N-Dimethyl-(β-phenylisobutyl)-amine.—β-Methylallyl chloride (1 mole) was added dropwise with stirring to 4 moles of 25% aqueous dimethylamine solution during two and seven-tenths hours. The temperature of the reaction mixture rose from 24 to 39° from the heat of reaction. The mixture was stirred for two hours, allowed to stand overnight, and made strongly alkaline with 6 *N* sodium hydroxide. The amine was extracted with ether, the ether solution was dried over sodium sulfate, and distilled through a 20 × 1.6 cm. helix-packed column. The yield of β-methylallyldimethylamine[6] was 81 g. (82%), b. p. 82–83.5°, $n^{25}D$ 1.4055. Reaction of 49.5 g. of β-methylallyldimethylamine with benzene in the presence of anhydrous aluminum chloride yielded 60.7 g. (69%) of N,N-dimethyl-(β-phenylisobutyl)-amine[6]; b. p. 89–90° (9 mm.), $n^{25}D$ 1.4973–1.4983. A picrate prepared from this amine in 95% ethanol and recrystallized from absolute ethanol had m. p. 176–178.5°.

Anal. Calcd. for $C_{18}H_{22}N_4O_7$: C, 53.20; H, 5.46; N, 13.79. Found: C, 53.31; H, 5.49; N, 13.59.

(13) Hepworth, *J. Chem. Soc.*, **119**, 256 (1921), reports m. p. 102°.

(14) Haller and Bauer, *Ann. chim.*, [9] **9**, 8 (1918).

(15) Baker and Ingold, *J. Chem. Soc.*, 263 (1927).

(16) See "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 280.

(17) Dunn and Stevens, [*J. Chem. Soc.*, 281 (1934)], report m. p. 205°.

(18) Perrot, *Compt. rend.*, **203**, 331 (1936), reports m. p. 122°.

N,N-Dimethyl-(β-phenylisobutyl)-amine Oxide (III).—N,N-Dimethyl-(β-phenylisobutyl)-amine (25 g.) was stirred with 33.5 g. of 35% aqueous hydrogen peroxide at room temperature until a clear solution was obtained (forty-eight hours). The excess hydrogen peroxide was destroyed by periodic addition of single drops of Catalase Sarett[19] until no more oxygen was evolved. The aqueous solution was extracted with ether to remove any unreacted amine and concentrated at 25 mm. pressure and a bath temperature of 45–55°. A portion of the white, crystalline solid residue was recrystallized from a mixture of absolute ethanol and ether with considerable loss. Analysis indicated that the solid so obtained was N,N-dimethyl-(β-phenylisobutyl)-amine oxide monohydrate.

Anal. Calcd. for $C_{12}H_{19}NO \cdot H_2O$: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.95; H, 9.68; N, 6.49.

Equivalent quantities of III in water and picric acid in 95% ethanol yielded 98% of the picrate of III, m. p. after recrystallization from absolute ethanol as fine yellow needles 171–172° (dec.).

Anal. Calcd. for $C_{18}H_{22}N_4O_8$: C, 51.18; H, 5.25; N, 13.27. Found: C, 51.01; H, 5.32; N, 13.38.

III prepared from 25 g. of N,N-dimethyl-(β-phenylisobutyl)-amine was decomposed in the apparatus described for decomposition of I, except that a trap cooled with liquid nitrogen was placed between the second receiver and the vacuum pump. The flask containing the amine oxide was immersed in an oil-bath at 95° and then evacuated. The bath was heated slowly to 148° during thirty minutes, at which time decomposition of the amine oxide began and the pressure rose to 30 mm. The heating bath was removed rapidly and replaced after five minutes, when the vigorous decomposition had subsided and the pressure in the system had again fallen to 3 mm. (In other experiments the sudden decomposition blew the wide-bore tube connecting the flask and condenser out of the flask, and it presumably would be safer to conduct the decomposition in an inert, high-boiling solvent to dissipate the heat of reaction.) The oil-bath was heated to 220° during two hours; the residue amounted to 1.6 g. The trap cooled with liquid nitrogen contained only a few drops of condensate, from which no dimethylamine picrate could be isolated.

The distillate was separated into neutral and basic fractions as described under decomposition of I. The residue obtained on concentration of the hydrochloric acid solution was made strongly basic with 6 *N* sodium hydroxide and extracted with ether. The ether extracts were dried over sodium sulfate and distilled through a 20 × 1.0 cm. helix-packed column. N,N-Dimethyl-(β-phenylisobutyl)-amine was recovered in a yield of 9.7 g. (39%), b. p. 91–94° (12.5 mm.), and identified by the m. p. of its picrate and mixed m. p. with a known sample, which was not depressed.

The residues from distillation of the recovered amine and from the neutral fraction described below appeared to be identical from preliminary distillations, and were combined and refractionated through a 30 × 0.8 cm. semimicro column.[20] In this way 1.19 g. of a compound was obtained; b. p. 111–115.5° (0.85 mm.), $n^{25}D$ 1.5322–1.5332. The compound was weakly basic and formed salts with picric acid and picrylsulfonic acid which crystallized poorly and could not be purified. Analytical results were in poor agreement with the formula for O-(β-phenylisobutyl)-N,N-dimethylhydroxylamine (IV), indicating the presence of an impurity if that structure is correct.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.56; H, 9.91; N, 7.25. Found: C, 74.69; H, 8.66; N, 7.57.

The pentane solution of the neutral product was dried over magnesium sulfate, concentrated, and distilled through a 20 × 1.0 cm. helix-packed column. α,α-Dimethylphenylacetaldehyde[21] was obtained in a yield of 1.6 g. (7.7%); b. p. 98.5° (17 mm.), 217–218° (Siwoloboff); $n^{25}D$ 1.5101, d^{25}_4 0.9854; M_D calcd., 44.80; found, 44.99.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.74; H, 8.11.

The semicarbazone prepared from the aldehyde had m. p. 169–173°, and a sample of the aldehyde which was oxidized with silver oxide yielded α,α-dimethylphenylacetic acid,[22] m. p. 76.5–78°. Mixed m. p. of the acid with an authentic sample, m. p. 77.5–78.5°, obtained by the alkaline hydrolysis of α,α,α-dimethylphenylacetamide, was not depressed.

Small samples of N,N-dimethyl-(β-phenylisobutyl)-amine oxide hydrate were decomposed by heating at atmospheric pressure and the relatively small amount of gas which was evolved was collected. It proved to contain carbon dioxide and oxygen, and not to contain dimethylamine (picric acid did not precipitate a picrate).

Benzyldiethylamine Oxide (V).—Benzyldiethylamine (50 g.) was stirred with 75 g. of 35% aqueous hydrogen peroxide for seventeen hours, until a homogeneous solution was obtained. Excess hydrogen peroxide was decomposed by stirring the solution with platinum foil. Benzyldiethylamine oxide picrate, prepared in 95% yield from an aliquot of a similar preparation and picric acid in 95% ethanol and recrystallized from the same solvent, had m. p. 124.5–125°.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 49.71; H, 5.07; N, 13.70.

The residual sirup of benzyldiethylamine oxide obtained on concentration was dried and decomposed by heating at 1 mm. in an oil-bath heated from 100 to 180° during one and one-half hours, in the manner described for decomposition of I. In a few cases the amine oxide crystallized before decomposition started. In such cases the flask containing the solid was heated momentarily with a free flame near the edge of the solid until decomposition started, as indicated by a pressure increase from 1 to 30 mm., to prevent a sudden decomposition. The temperature of the oil-bath was raised to 200° briefly; a residue of 1.5 g. remained. The distillate was combined with the material which was distilled during concentration of the amine oxide solution, and pentane was added. The dilute hydrochloric acid extract of the mixture was concentrated, made alkaline with 6 *N* sodium hydroxide, and extracted with ether, which was dried over sodium sulfate and distilled through a 20 × 1.0 cm. helix-packed column. The distillation yielded 2.7 g. (21%) of N,N-diethylhydroxylamine (VIII), 9.6 g. (19%) of O-benzyl-N,N-diethylhydroxylamine (VII) and 14.5 g. (34%) of N-benzyl-N-ethylhydroxylamine (VI).

The N,N-diethylhydroxylamine[23] had b. p. 48° (15 mm.), $n^{25}D$ 1.4173, d^{25}_4 0.8612; M_D calcd., 25.78; found, 26.04.

N,N-Diethylhydroxylamine picrate was prepared in 95% yield in 95% ethanol and recrystallized from benzene, m. p. 95–98°.

Anal. Calcd. for $C_{10}H_{14}N_4O_8$: C, 37.74; H, 4.43; N, 17.61. Found: C, 37.90; H, 4.76; N, 17.53.

N,N-Diethylhydroxylamine hydrochloride proved to be very hygroscopic and was not recrystallized satisfactorily. A sample prepared from VIII in ether and dry hydrogen chloride had m. p. 65–69.5° (sealed capillary).[24] The neutral oxalate had m. p. 137–140° after recrystallization from absolute ethanol.[25]

O-Benzyl-N,N-diethylhydroxylamine (VII) had b. p.

(19) Vita-Zyme Laboratories, Chicago, Ill.

(20) Gould, Holzman and Niemann, *Anal. Chem.*, **20**, 361 (1948).

(21) Tiffeneau and Orekhoff, *Bull. soc. chim.*, **29**, 809 (1921), report b. p. 215–218°; m. p. of the semicarbazone 176–177°.

(22) Tiffeneau and Dorlencourt [*Compt. rend.*, **143**, 1244 (1909)], report m. p. 78°; Bistrzycki and Mauron [*Ber.*, **40**, 4371 (1907)], report m. p. 80–81°.

(23) (a) Lachman [*Ber.*, **33**, 1027 (1900)] reports b. p. 47–49° (15 mm.); (b) Bewad [*J. prakt. Chem.*, [2] **63**, 100 (1901)] reports d^{20}_0 0.8670.

(24) Wieland [*Ber.*, **36**, 2317 (1903)] reports m. p. 63°; ref. 13 reports m. p. 63–64°, and ref. 23b reports m. p. 72–73°.

(25) Dunstan and Goulding [*J. Chem. Soc.*, **75**, 800 (1899)] report m. p. 136–137°; Wieland (ref. 24) reports m. p. 138°; ref. 13 reports m. p. 137–138°, and ref. 23b reports m. p. 134–138°.

70–71° (2.1 mm.), $n^{25}D$ 1.4891, d^{25}_4 0.9336; MD calcd. 54.62; found, 55.43.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.69; H, 9.64; N, 7.87.

O-Benzyl-N,N-diethylhydroxylamine picrate was prepared in 94% yield in 95% ethanol and had m. p. 115–116° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.06; H, 5.02; N, 13.66.

O-Benzyl-N,N-diethylhydroxylamine hydrochloride was prepared from VII and concentrated hydrochloric acid and recrystallized from a mixture of absolute ethanol and ether: m. p. 107–108°.

Anal. Calcd. for $C_{11}H_{18}NOCl$: C, 61.24; H, 8.41; N, 6.49; Cl, 16.44. Found: C, 61.55; H, 8.59; N, 6.41; Cl, 16.13.

N-Benzyl-N-ethylhydroxylamine (VI) had b. p. 88° (1.1 mm.); $n^{25}D$ 1.5232, d^{25}_4 1.0097; MD calcd., 45.27; found, 45.76.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.27. Found: C, 71.74; H, 8.94; N, 9.27.

N-Benzyl-N-ethylhydroxylamine picrate was prepared in 95% ethanol and recrystallized from aqueous ethanol, from which it separated as a monohydrate which was dried for five minutes at 35 mm. and room temperature for analysis, m. p. 79–81°.

Anal. Calcd. for $C_{15}H_{16}N_4O_8 \cdot H_2O$: C, 45.23; H, 4.55; N, 14.07; H_2O, 4.52. Found: C, 44.94; H, 4.74; N, 14.09; H_2O (by loss in weight at 55° and 35 mm.), 4.4.

The pentane solution containing weakly basic decomposition products was dried over magnesium sulfate and concentrated. The residue was fractionated through a 20 × 1.0 cm. helix-packed column and yielded an additional 6.0 g. (12%) of O-benzyl-N,N-diethylhydroxylamine (VII); b. p. 66° (1.4 mm.), $n^{25}D$ 1.4868–1.4872, making the total yield 31%. O,N-Dibenzyl-N-ethylhydroxylamine (IX) was separated as a higher boiling fraction; yield 5.3 g. (16%), b. p. 148° (4 mm.), $n^{25}D$ 1.5383, d^{25}_4 1.0105; MD calcd., 74.00; found, 74.64.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.81. Found: C, 79.78; H, 8.12; N, 5.74.

The picrate of O,N-dibenzyl-N-ethylhydroxylamine was prepared in 95% ethanol and recrystallized from absolute ethanol, m. p. 108.5–109.5°.

Anal. Calcd. for $C_{22}H_{22}N_4O_8$: C, 56.17; H, 4.72; N, 11.91. Found: C, 56.16; H, 4.83; N, 12.01.

A sample of benzyldiethylamine oxide, prepared from 20 g. of benzyldiethylamine and hydrogen peroxide, was decomposed by heating at atmospheric pressure in an oil-bath at 110–180° during one and eight-tenths hours. The ethylene which was formed was collected over sodium chloride solution in a gas buret, and amounted to 1.5 l. The ethylene was bubbled through bromine water and converted to ethylene dibromide, which was washed with water, dried over calcium chloride and distilled; yield 3.26 g. (14%), b. p. 128–130°.

Structure Proof of Compounds Formed by Decomposition of Benzyldiethylamine Oxide. (a) **N-Benzyl-N-ethylhydroxylamine (VI).**—A solution of 1.19 g. of VI in 10 ml. of 3 *N* hydrochloric acid was treated with 1.77 g. of stannous chloride dihydrate in 5 ml. of concentrated hydrochloric acid. The mixture was warmed on a steam-bath for six hours, diluted with water, and saturated with hydrogen sulfide. The precipitated tin sulfides were separated by filtration, and the filtrate and washings were concentrated under reduced pressure to yield 1.37 g. (102%) of benzylethylamine hydrochloride, m. p. 183–184°. Recrystallization from a mixture of absolute ethanol and ether gave white plates of the hydrochloride, m. p. and mixed m. p. with a known sample[26] 184–185°. A portion of the benzylethylamine hydrochloride was converted into the picrate, which after crystallization from aqueous ethanol had m. p. and mixed m. p. with a known sample[27] 122–123°.

(b) **O-Benzyl-N,N-diethylhydroxylamine (VII).**—A solution of 0.311 g. of VII in 10 ml. of absolute ethanol was hydrogenated in the presence of 0.3 g. of 10% palladium-on-Norite catalyst for thirty hours, in which time 1.45 molar equivalents of hydrogen was absorbed. The catalyst was separated by filtration, washed with ethanol and the filtrate and washings were distilled at atmospheric pressure until only a small residue remained. Addition of a solution of 0.40 g. of picric acid in 5 ml. of ethanol to the distillate precipitated diethylamine picrate as an oil which was crystallized from benzene. The yield of diethylamine picrate, m. p. 71–73°, was 0.412 g. (79%). A sample which was recrystallized from benzene had m. p. 73.5–74.5° and a mixed m. p. with a known sample was not depressed.

The residue remaining after distillation of the ethanol and diethylamine was warmed on a steam-bath for five minutes with 1 ml. of concentrated hydrochloric acid. The oil which separated was extracted with ether, dried over sodium sulfate and concentrated. Thiourea (0.13 g.) was added to a solution of the residue in 2 ml. of ethanol, and the mixture was warmed on a steam-bath for two minutes. Picric acid (0.4 g.) was added, and the mixture was cooled and diluted with water. Benzylisothiouronium picrate separated in a yield of 0.148 g. (22%), m. p. after recrystallization from aqueous ethanol 187–188.5°, which was not depressed on mixture with a known sample. The low yield of this derivative and the high hydrogen uptake in the catalytic reduction are presumed to be due to partial hydrogenolysis of the initially formed benzyl alcohol to toluene.

(c) **O,N-Dibenzyl-N-ethylhydroxylamine (IX).**—IX (0.13 g.) was heated under reflux with 25 ml. of 6 *N* hydrochloric acid for one and eight-tenths hours. The aqueous acid was distilled under reduced pressure, and the oily residue was treated with 0.13 g. of picric acid in 5 ml. of ethanol. After dilution with water to the point of turbidity, the picrate of O,N-dibenzyl-N-ethylhydroxylamine separated. Further dilution of the filtrate precipitated 0.062 g. (20%) of a second picrate, which after recrystallization melted at 76.5–79° and was identified as N-benzyl-N-ethylhydroxylamine picrate monohydrate by mixed m. p. with a known sample, which showed no depression.

In another similar hydrolysis of 0.38 g. of IX, the distillate of aqueous hydrochloric acid was extracted with ether. The extract was dried over sodium sulfate, concentrated, and the residue was warmed on a steam-bath with concentrated hydrochloric acid in the manner described under (b) above. Subsequent treatment with thiourea followed by picric acid as described in (b) yielded 0.10 g. (25%) of benzylisothiouronium picrate, m. p. 186.5–187.5°, which was not depressed by an authentic sample.

Summary

N,N-Dimethyl-(α-phenylethyl)-amine oxide (I) and N,N-dimethyl-(α,α-dimethylbenzyl)-amine oxide (II) undergo an elimination reaction rather than rearrangement on heating at 75–115°, forming N,N-dimethylhydroxylamine in both cases and styrene and α-methylstyrene, respectively. N,N-Dimethyl-(β-phenylisobutyl)-amine oxide (III) does not form an olefin on heating, indicating that the elimination reaction probably proceeds in a manner similar to the Hofmann reaction by attack of the amine oxide oxygen on β-hydrogen atoms (equation 1). Benzyldiethylamine oxide (V) rearranges in part on heating into O-benzyl-N,N-diethylhydroxylamine (VII), and also forms products of the elimination reaction, ethylene and N-benzyl-N-ethylhydroxylamine (VI). Additional products which are formed in this case

(26) Hoover and Hass [*J. Org. Chem.*, **12**, 508 (1947)] report m. p. 184°.

(27) Graymore *J. Chem. Soc.*, 41 (1941), reports m. p. 122–123°.

by the bimolecular alkylation of VI by V (equation 4) are O,N-dibenzyl-N-ethylhydroxylamine (IX) and N,N-diethylhydroxylamine (VIII).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Selective Oxidation with N-Bromosuccinimide. I. Cholic Acid[1]

BY LOUIS F. FIESER AND SRINIVASA RAJAGOPALAN[2]

The first objective of this work was to find an improved method for the conversion of cholic acid, the preponderant acid of available biles, into desoxycholic acid, the starting material for the only known synthetic routes to Kendall's Compound E, for which an important therapeutic use requiring greatly expanded supplies has recently been announced.[3] Wieland and Dane[4] discovered that 7α,12α-dihydroxycholanic acid can be converted into the 7-keto derivative in good yield by partial oxidation with chromic acid and thereby established the first of several instances of disparity between susceptibility of steroid alcoholic groups to acylation and to oxidation (except in Oppenauer oxidation, in which the first step is analogous to an acylation[5]). Iwasaki[6] effected the selective chromic acid oxidation of both 3α,7α- and 3α,7β-dihydroxycholanic acid to 3α-hydroxy-7-ketocholanic acid, and Kaziro and Shimada[7] demonstrated the selective oxidation of desoxycholic acid to 3α-hydroxy-12-ketocholanic acid. These Japanese workers thus established the order of susceptibility as $C_7 > C_{12} > C_3$ and correctly inferred that cholic acid should be convertible by chromic acid oxidation into the 7-keto derivative[7]; the failure of their own attempts to demonstrate the conversion is possibly attributable partly to the unfavorable melting point behavior of the 3α-hydroxy-7,12-diketocholanic acid that they isolated, as suggested by Gallagher and Long,[8] and partly to the difficulty in isolation of 3α,12α-dihydroxy-7-ketocholanic acid with high recovery even as the ester (Experimental part).

Haslewood[9] was the first to report the partial oxidation of cholic acid at C_7; by addition of aqueous chromate to cholic acid in acetic acid buffered with sodium acetate and Wolff–Kishner reduction of the crude oxidation mixture he obtained desoxycholic acid in yield of about 40%. Oxidation with chromic acid in acetic acid was studied by Gallagher and Long,[8] who isolated the 7-keto derivative as the methyl ester diacetate in 40% yield by chromatography, and by Hoehn and co-workers,[10] who obtained the ethyl ester in 41% yield; the latter workers report a yield of 41% (as ethyl ester) by oxidation of cholic acid with bromine in alkali at −5°.

As a means of evaluating various processes of partial oxidation, we adopted a standard procedure of conducting Wolff–Kishner reduction of the total oxidation mixture by the Huang-Minlon procedure[11] and isolating desoxycholic acid as the ether complex, from which pure desoxycholic acid can be quantitatively recovered.[12] The oxidation procedure of Haslewood[9] seemed the most promising, but in our experience the over-all yield from cholic acid was only 29.6%. Improved yields were obtained on applying the chromate oxidation procedure to the following pure derivatives: methyl cholate (47.5%); methyl cholate 3-acetate (85% yield); methyl 3-carbethoxycholate (83%). These derivatives were obtained in yields of 85, 39 and 80%, respectively, and hence the best route is through the methyl ester and its carbethoxy derivative, but the over-all yield is only 54%.

We then investigated with promising results oxidation with N-bromoacetamide in an aqueous medium, a method briefly applied in other instances by Reich and Reichstein.[13] The over-all yield of desoxycholic acid etherate from cholic acid by use of N-bromoacetamide in aqueous acetone was 57%, and the yields from various 3-derivatives were not sufficiently higher to compensate for the losses attending their preparation.

We then turned to the more readily prepared and commercially available N-bromosuccinimide which as far as we are aware has not been employed for the oxidation of secondary alcohols,[14] and found that it is a superior reagent for selective oxidations of substantially different character from N-bromoacetamide. Initial oxidations of cholic acid in aqueous acetone afforded, after usual reduction, pure desoxycholic acid etherate

(1) This work was supported in part by a grant from Research Corporation.

(2) Fellow of the National Cancer Institute.

(3) Hench, Kendall, Slocumb and Polley, *Proc. Staff Meetings Mayo Clinic*, **24**, 181 (1949).

(4) Wieland and Dane, *Z. physiol. Chem.*, **210**, 268 (1932).

(5) Gallagher and Long, *J. Biol. Chem.*, **165**, 365 (1946).

(6) Iwasaki, *Z. physiol. Chem.*, **244**, 181 (1936).

(7) Kaziro and Shimada, *ibid.*, **249**, 220 (1937).

(8) Gallagher and Long, *J. Biol. Chem.*, **147**, 131 (1943).

(9) Haslewood, *Nature*, **150**, 211 (1942); *Biochem. J.*, **37**, 109 (1943).

(10) Schneider and Hoehn, THIS JOURNAL, **65**, 485 (1943); Hoehn and Linsk, *ibid.*, **67**, 312 (1945); Hoehn and Schneider, U. S. Patent 2,321,598 (1943).

(11) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(12) White, *Biochem. J.*, **23**, 1165 (1929).

(13) Reich and Reichstein, *Helv. Chim. Acta*, **26**, 562 (1943).

(14) Hebbelynck and R. H. Martin, *Experientia*, **5**, 69 (1949), have reported the oxidation of benzyl alcohol and benzhydrol to the carbonyl compounds with N-chloroacetamide in neutral solvents or pyridine under illumination.

in 70% yield. We then found that the process can be simplified by conducting the oxidation in aqueous sodium bicarbonate solution. The best yields (68%) were obtained with 1.25–1.5 moles of N-bromosuccinimide, but a still larger excess had little deleterious effect. We then submitted pure desoxycholic acid to treatment with 1.25 moles of reagent under the same conditions and recovered the starting material unchanged. The reagent thus does not merely attack cholic acid preferentially at C_7 but attacks this position and leaves C_3 and C_{12} untouched. Chromic acid effects preferential oxidation at C_7 but effects successive oxidations at C_{12} and then C_3, and the same is true of bromine in aqueous alkali,[15] and even of microbiological oxidation.[16] Lardon[17] found that methyl etiocholate can be oxidized selectively to the 7-keto derivative with N-bromoacetamide in aqueous acetone in "good yield," but Reich and Reichstein[13] cite experiments showing that the same reagent (in aqueous *t*-butanol) effects oxidation of the following alcoholic groups at room temperature: 3α-, 12α-, 12β-, 17β-; thus desoxycholic acid was oxidized to the diketo acid. Sarett[18] observed the smooth oxidation of a 3α-hydroxysteroid with N-bromoacetamide in pyridine–*t*-butanol. The lack of reactivity of N-bromosuccinimide for 3α- and 12α-hydroxyl groups under the conditions that we have employed suggests a fundamental difference between the seemingly similar reagents. Direct comparison of the specificities of the various oxidizing agents under comparable conditions is in progress.

The unique specificity of the new oxidation procedure suggested an expedient for further increasing the availability of desoxycholic acid from bile. Since the desoxycholic acid present in the total acids from a bile hydrolyzate is not attacked by N-bromosuccinimide, and since adequate purification is accomplished in the course of the oxidation–reduction–etherate process outlined, the separation and purification of the component bile acids can be dispensed with and the total crude bile acids oxidized with excess N-bromosuccinimide in aqueous soda solution and the oxidation mixture reduced and processed as before. Lithocholic acid and other contaminants are removed in the ether solution, and pure desoxycholic acid is obtained very easily in yield estimated to be 34% higher than obtainable by separating the components by the usual procedures and processing the cholic acid by the present method, or in over twice the yield realizable by previous methods.

We are indebted to Dr. Max Tishler and his group at the Merck Laboratories for supplies and for friendly coöoperation.

(15) Charonnet and Horeau, U. S. Patent 2,244,328 (1941).
(16) Hoehn, Schmidt and Hughes, *J. Biol. Chem.*, **152**, 59 (1944).
(17) Lardon, *Helv. Chim. Acta*, **30**, 597 (1947).
(18) Sarett, THIS JOURNAL, **71**, 1165 (1949).

Experimental[19]

Methyl Cholate.—The melting points recorded for this ester differ widely: 147°,[20,21] 141–142°,[22] 156–158°,[23] 160–162°.[24] We prepared the ester by a combination of previous procedures[22,24] as follows: 100 g. of technical grade cholic acid (m. p. 195–197°) was dissolved by warming in 400 cc. of methanol containing 1 g. of hydrogen chloride per 100 cc. and the mixture allowed to stand overnight and then cooled in ice. The crystalline product that separated was found to be solvated; it was collected, air-dried, and dissolved in 250 cc. of toluene, and 200 cc. of solvent was removed by distillation with a free flame. Enough benzene was added to bring the solid into solution at the boiling point, and the solution was filtered and diluted with ether to the point of distinct turbidity and let stand overnight. The methyl cholate that crystallized was washed freely with ether and amounted to 73 g., m. p. 155–156°. The methanol and ethereal solutions afforded a further 15 g. of ester, m. p. 155–156°; yield 85%. A sample recrystallized from toluene–ether formed colorless needles, m. p. 155–156°.

Anal. Calcd. for $C_{25}H_{42}O_5$: C, 71.06; H, 10.01. Found: C, 71.00; H, 10.00.

Methyl Cholate 3-Acetate.—Although Meystre and Miescher[24] report difficulties in preparing this derivative, we found the directions of Grand and Reichstein[22] satisfactory and obtained nearly the yield specified; thus 88 g. of methyl cholate afforded 37.5 g. (39%) of the pure acetate, m. p. 149–150°. Attempts to raise the yield by conducting the acetylation with limited amounts of acetic anhydride in pyridine were unsuccessful.

Methyl 3-Carbethoxycholate.—This derivative was found to melt considerably higher than reported by Borsche,[25] who records the m. p. 147°. A solution of 42 g. of methyl cholate in 100 cc. of pyridine was treated gradually with 50 g. of ethyl choloformate with occasional cooling under the tap. The mixture was allowed to stand overnight, diluted with water, and the precipitated solid collected and washed. The yield of crude product, m. p. 173–175°, was 46 g. Crystallization from methanol afforded 39 g. (80%) of product, m. p. 176–177°, with slight shrinking at 148°.

Anal. Calcd. for $C_{28}H_{46}O_7$: C, 67.98; H, 9.38. Found: C, 67.95; H, 9.25.

Oxidation with Chromate.—Oxidations were conducted by the procedure of Haslewood,[9] the crude oxidation mixture was reduced according to Huang-Minlon,[11] and the desoxycholic acid was isolated as the etherate as described below and this derivative was dried at 90–100° in vacuum for one-half hour. Although the etherate is described as a 1:1 complex,[12] recovery experiments such as that cited below indicate that material dried in this manner is more nearly a 1:6 complex and we have calculated yields on the basis of the empirically determined molecular weight 400; the yields from 5-g. samples were: cholic acid, 1.45 g. (29.6%); methyl cholate, 2.25 g. (47.5%); methyl cholate 3-acetate, 3.66 g. (85%); methyl 3-carbethoxycholate, 3.2 g. (83%). The free desoxycholic acid melted at 171–173°.

Oxidation of N-Bromoacetamide.—A solution of 5 g. of cholic acid in 150 cc. of pure acetone was diluted with 50 cc. of water and treated at 25° with 2 g. of N-bromoacetamide (m. p. 108°) and 10 cc. of acetic acid. The solution turned yellow and then brown and in about fifteen minutes became colorless. After about three hours 50 cc. of water was added, solvent was removed at reduced pressure to the point of distinct turbidity, and a large volume of water was added to precipitate the product as a gum. This crude

(19) Melting points are uncorrected.
(20) Schotten, *Z. physiol. Chem.*, **10**, 175 (1886).
(21) Utaki, *ibid.*, **207**, 16 (1932).
(22) Grand and Reichstein, *Helv. Chim. Acta*, **28**, 344 (1945).
(23) Barnet, Lardon and Reichstein, *ibid.*, **30**, 1542 (1947).
(24) Meystre and Miescher, *ibid.*, **29**, 33 (1946).
(25) Borsche, *Ber.*, **57**, 1620 (1924).

material was reduced and the desoxycholic acid isolated as the etherate (mol. wt. assumed, 400) as described in detail below; yield 2.8 g. (57%). Yields of etherate from 5-g. samples of pure derivatives were as follows: methyl cholate, 3.3 g. (69%); methyl cholate 3-acetate, 3.0 g. (70%); methyl 3-carbethoxycholate, 3.1 g. (77%).

Methyl 3α-Acetoxy-7-keto-12α-hydroxycholanate.—The oxidation product from methyl cholate 3-acetate was a granular solid that on crystallization from methanol afforded colorless platelets, m. p. 175–176°.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 69.93; H, 9.15. Found: C, 70.01; H, 9.25.

Methyl 3-carbethoxy-7-keto-12α-hydroxycholanate also separated as a solid on dilution; it crystallized from methanol as either plates or needles, m. p. 181–182°.

Anal. Calcd. for $C_{28}H_{44}O_7$: C, 68.26; H, 9.00. Found: C, 68.57; H, 9.24.

Oxidation with N-Bromosuccinimide[26]; Preferred Procedure.—Eighty grams of technical cholic acid (Armour Laboratories, m. p. 195–197°) was dissolved by warming in a solution of 50 g. of sodium bicarbonate in 1.6 l. of tap water and the solution was cooled to 25°, treated with 43.7 g. (1.25 equiv.) of N-bromosuccinimide, and shaken occasionally until the reagent had all dissolved (about one and one-half hours). The yellow solution was allowed to stand at 25° for about seventeen hours, heated on the steam-bath for one hour, cooled in ice and acidified with dilute hydrochloric acid (1:2), added slowly with vigorous stirring and scratching. The keto acid separated as a white, granular solid and after cooling in ice for one-half hour it was collected, washed well with water, dried superficially between filter papers, transferred to a 1-l. round-bottomed flask with a ground joint and dried by evaporation to dryness with methanol (500 cc.; this saves time in the next step).

The flask was then charged with 600 cc. of triethylene glycol, 90 cc. of 86% hydrazine solution (the amount can be reduced to about 2 equivs.) and 70 g. of potassium hydroxide pellets, and heated cautiously under reflux in an oil-bath to a temperature of about 130° (thermometer suspended through condenser), when a vigorous exothermic reaction sometimes sets in (*e. g.*, when the starting acid is very impure). The flask was removed from the bath a few times until the frothing had subsided and then the mixture was refluxed gently for one-half hour; the condenser was removed and distillation conducted until the temperature had risen to 190°, and refluxing was continued for two to three hours at 190–200°. The solution was cooled, diluted with tap water to about 2 l., and acidified with 1:2 hydrochloric acid. On standing overnight the crude desoxycholic acid became granular and could be filtered easily. It was washed well, dried between filter papers, and then dried by evaporation with 500 cc. of methanol nearly to dryness (toward the end with a current of air). The residue while still warm was dissolved in 500 cc. of warm absolute ethanol and the solution allowed to stand at room temperature for one-half hour for separation of a trace of impurity, and filtered by gravity (100 cc. of ethanol for washing). The clear yellowish filtrate was evaporated to dryness as before (air current) and the slightly brown residual sirup was treated with 400 cc. of dry ether and alternately shaken and briefly heated until the gum had dissolved and given rise to a precipitate of desoxycholic acid etherate (unreacted lumps can be broken up with a flattened rod). After three or four hours with occasional shaking, the white etherate was collected, washed with 150–200 cc. of dry ether, and dried at 90–100° in vacuum for one-half hour. The etherate melts unsharply above 145°; some samples partly melted, resolidified, and remelted to a clear liquid at 170–173°. The average yield in three concordant experiments was 53 g. (68%, calculated for mol. wt. 400).

For conversion to free desoxycholic acid the above complex was heated on the steam-bath with 2.5 l. of tap water with stirring for one and one-half hours, when the solid partly melted and then resolidified. The mixture was cooled and the acid collected, triturated with cold water in a mortar, collected, and dried in vacuum at 100–110° for two hours. The white solid melted at 170–172°; average yield 51.8 g. (68%).

Ethyl 3α,12α-Dihydroxy-7-ketocholanate.[27]—The crude oxidation mixture from 80 g. of cholic acid was dehydrated by evaporation with 400 cc. of methanol, refluxed with 400 cc. of absolute ethanol and 12 cc. of boron fluoride etherate for three hours, and the solution concentrated to half its volume and poured into water. The dark-brown gummy product that separated was washed and rubbed repeatedly with water and with bicarbonate solution and evaporated with 300 cc. of methanol. The resulting solid was dissolved in 300 cc. of methanol, and the solution slowly deposited a crop of small crystals of the keto ester of high purity, m. p. 158–159°; yield 34 g. (40%).

The dark mother liquor and washings were evaporated and the dark-red gummy residue reduced according to Huang-Minlon and the mixture processed for recovery of desoxycholic acid etherate by the usual procedure. The yield of pure complex was 27 g. (34.5%). The combined yield corresponds to that of the above oxidation–reduction process and the experiment shows that the 7-keto acid can be isolated easily in a pure form as the ethyl ester but only in yield slightly better than half the amount actually present.

Other Oxidation Conditions.—Oxidation of cholic acid (40 g.) in acetone (1 l.)–water (400 cc.) with N-bromosuccinimide (21.8 g.) and processing as usual afforded 27.4 g. (70%) of desoxycholic acid etherate. Oxidation of methyl cholate in the same way with 1.25, 1.5 and 2.0 equivalents of the bromoimide gave the etherate in yields of 68, 68 and 63%, respectively; with 1.0 equivalent of reagent the product was contaminated with traces of cholic acid. Oxidation of methyl cholate in aqueous acetone with 1.25 equivalents of N-bromophthalimide gave the etherate in 68% yield. Attempted oxidation with chloramine-T was unsuccessful. Oxidation of cholic acid (5 g.) in aqueous bicarbonate solution at 25° as above but with use of 1.2 equivalents of bromine resulted in a lower yield of etherate (2.4 g., 49%).

Resistance of Desoxycholic Acid to N-Bromosuccinimide.—Five grams of technical desoxycholic acid or of the etherate (dried as above) was treated in 150 cc. of acetone and 50 cc. of water with 2.5 g. of N-bromosuccinimide and 10 cc. of acetic acid. The solution was allowed to stand for sixteen hours (the usual color changes occurred) and processed exactly as above, including Wolff–Kishner reduction. Desoxycholic acid etherate of usual purity was the only product recovered; yields 5.0 g. and 4.7 g.

Desoxycholic Acid from Total Bile Acids.—One hundred grams of the total acid precipitate prepared by saponification of 198 g. of a 75% sheep bile concentrate with refluxing alkali for eighteen hours and acidification was dissolved in 1.5 l. of water containing 65 g. of sodium bicarbonate and treated with 56 g. of N-bromosuccinimide at 25°. The initially dark solution improved in color as the oxidation progressed. After twenty-four hours the light greenish-yellow solution was filtered by gravity from a fine gray solid and acidified, and the rubbery precipitate was kneaded with water and submitted to reduction with 110 cc. of 85% hydrazine, 700 cc. of triethylene glycol and 85 g. of potassium hydroxide. The rest of the processing was done in the usual way except that the desoxycholic acid etherate was ground in a mortar with ether before the final collection. The complex was nearly colorless and melted at 175–177°, after shrinking at 145–155°; yield 41.5 g. The reddish-brown ethereal mother liquor was not worked up further. The yield corresponds

(26) Commercial material was most conveniently purified by adding 300 g. to 3 l. of boiling water, filtering the hot solution quickly through a conical funnel fitted with a small plug of absorbent cotton, and cooling the filtrate; the colorless plates that separated melted at 178–179°; yield 210 g.

(27) Haslewood, *Biochem. J.*, **38**, 108 (1944).

to 21.7 g. of free desoxycholic acid per 100 g. of sheep bile concentrate. By the usual methods of separation, 100 g. of concentrate yields about 4.4 g. of desoxycholic acid and 16.8 g. of cholic acid, convertible into 10.9 g. of desoxycholic acid by our process to give a total of 15.3 g. of the acid.

Summary

An improved method for the conversion of cholic acid into desoxycholic acid has been found in oxidation of the free acid at C_7 with N-bromosuccinimide in aqueous bicarbonate solution, followed by Wolff–Kishner reduction according to Huang-Minlon; the over-all yield is 68%. The oxidizing agent is more selective than chromic acid, bromine or even N-bromoacetamide, for the alcoholic groups at C_3 and C_{12} remain unattacked in the presence of an excess. In consequence, desoxycholic acid can be prepared with greater efficiency and ease than heretofore by direct application of the procedure to the total crude acids of saponified bile.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Selective Oxidation with N-Bromosuccinimide. II. Cholestane-3β,5α,6β-triol[1]

BY LOUIS F. FIESER AND SRINIVASA RAJAGOPALAN[1]

On exploring further possible applications of a method of oxidation found particularly effective for the selective oxidation of the 7α-hydroxyl group of cholic acid, we found that cholesterol (I) on oxidation with N-bromosuccinimide in aqueous acetone is converted in moderate yield into cholestane-3β,5α-diol-6-one (III).[2] The reaction could conceivably proceed through an intermediate oxide, but cholesterol α-oxide (Va) under the same conditions was found to yield a mixture containing only a small amount of the diolone III together with cholesterol 5,6-dibromide, and a bromo α,β-unsaturated ketone of analysis and absorption spectrum consistent with formula VI. We then found that cholestane-3β,5α,6β-triol can be oxidized to the diolone III in extraordinarily high yield in aqueous dioxane, acetone, or even methanol–ether or methanol. The triol II is known to be attacked preferentially at C_6 on chromic acid oxidation,[3] but an oxidation conducted by adding the reagent gradually over a ten-hour period afforded the 6-ketone as 3-acetate in only 65% yield, for without careful control the 3,6-diketone is easily formed.[2] No control is required in the present procedure, for the same high yield was obtained with 2.1 as with 1.05 equivalents of N-bromosuccinimide.

The best previous methods for preparation of cholestane-3β,5α,6β-triol are by reaction of cholesterol on the 3-acetate with hydrogen peroxide in acetic acid over a period of four days and saponification of the resulting acetate mixture, or hydrolysis of cholesterol α,β-oxide mixture.[2,4,5] Cleavage of the oxides by acetolysis with organic acids and hydrolysis with dilute sulfuric acid are attended with extensive or partial ester formation. An interesting incidental observation is that both cholesterol α-oxide and cholesteryl α,β-oxide acetate can be cleaved in high yield to the triol II or its 3-acetate by the action of periodic acid in refluxing aqueous acetone. This acid apparently functions as a satisfactory catalyst but is incapable of forming esters; the *trans*-triol suffers no appreciable glycol cleavage under the mild conditions required for hydrolysis (one-half hour).

Of more practical importance is the development of a reliable procedure for hydroxylating the double bond of cholesterol with hydrogen peroxide and formic acid.[6] Brief heating of cholesterol with 88% formic acid produces the 3-formyl derivative, and on addition of hydrogen peroxide to the resulting suspension a clear solution soon results and precipitation with water gives a mixture of esters from which cholestane-3β,5α,6β-triol 3,6-diformate can be isolated by crystallization. Brief saponification of the total mixture affords the pure triol in 91% yield.

Since cholestane-3β,5α-diol-6-one (III) can thus be prepared very easily in quantity from cholesterol in 85.5% over-all yield, it may serve as a useful intermediate to steroids of importance. However, two possible routes from this substance to 7-dehydrocholesterol have been investigated with negative results. The 3,5-diacetate (IV), known as a by-product of the chromic acid oxidation of cholesteryl acetate,[7] can be prepared readily by treatment of the diolone III with acetic anhydride and boron fluoride at room temperature. Since the tertiary acetoxyl group at C_5 when once formed is very resistant to saponification,[7] it seems possible that the ready acylation at this position may be the consequence of enol acetate formation and migration of the acetyl

(1) For acknowledgments, see Paper I, notes 1 and 2; THIS JOURNAL, **71**, 3935 (1949).

(2) Pickard and Yates, *J. Chem. Soc.*, **93**, 1678 (1908).

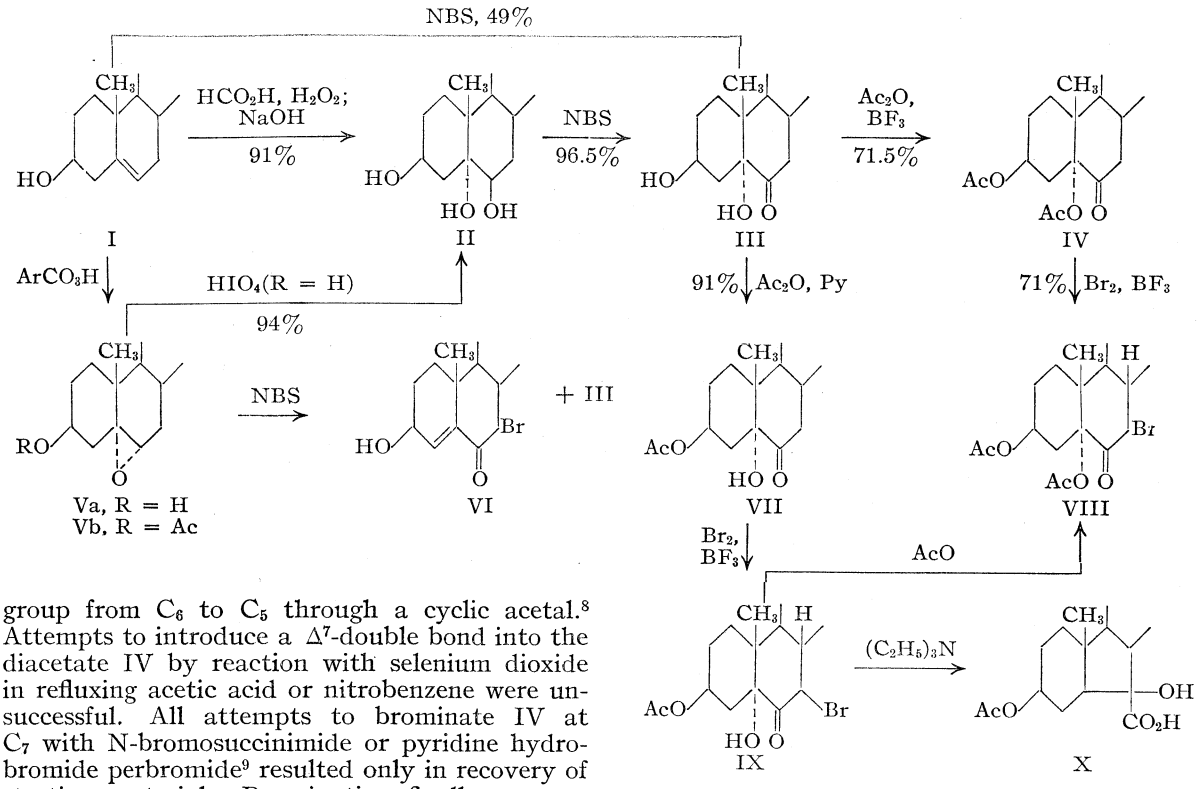
(3) Ellis and Petrow, *ibid.*, 1078 (1939).

(4) Westphalen, *Ber.*, **48**, 1064 (1915); Ruzicka and Bosshard, *Helv. Chim. Acta*, **20**, 244 (1937).

(5) Petrow, *J. Chem. Soc.*, 1077 (1937).

(6) Swern, Billen and Findlay, THIS JOURNAL, **67**, 1786 (1945); compare Roebuck and Adkins, *ibid.*, **70**, 4041 (1948); "Organic Syntheses," **28**, 35 (1948).

(7) Schenck, *Z. physiol. Chem.*, **243**, 119 (1936); Ellis and Petrow[3] prepared the compound from the 3-acetate with use of potassium acid sulfate as catalyst.



group from C_6 to C_5 through a cyclic acetal.[8] Attempts to introduce a Δ^7-double bond into the diacetate IV by reaction with selenium dioxide in refluxing acetic acid or nitrobenzene were unsuccessful. All attempts to brominate IV at C_7 with N-bromosuccinimide or pyridine hydrobromide perbromide[9] resulted only in recovery of starting material. Bromination finally was accomplished with use of bromine in hot acetic acid with boron fluoride as catalyst, but the chief product was contaminated with a difficultly separable isomer. More homogeneous material was obtained by similar bromination of cholestane-3β,5α-diol-6-one 3-acetate (VII), easily available by partial acetylation of the diolone (III) in pyridine. The bromo monoacetate (IX) on acetylation in the presence of boron fluoride yielded a pure diacetate (VIII) identical with the chief product of bromination of IV. This diacetate proved to be resistant to attempted dehydrobromination with triethylamine or pyridine, and hence the 7-bromo atom must have the β-configuration, *cis* to the hydrogen at C_8. The 3-monoacetate IX suffered slow dehydrobromination in refluxing triethylamine to give a mixture from which two isomers were isolated of composition corresponding to replacement of bromine by hydroxyl. The more abundant isomer, however, is acidic and probably results from a rearrangement, as in formula X. Such a rearrangement is analogous to that established[10] in the dehydrohalogenation of 5,7-dibromocholestane-3β-ol-6-one.[11] Further applications of the hydroxylation and oxidation procedures are under investigation.

(8) Compare Petrow, Rosenheim and Starling, *J. Chem. Soc.*, 135 (1943); Paige, *ibid.*, 437 (1943).

(9) Djerassi and Scholz, THIS JOURNAL, **70**, 417 (1948).

(10) Woodward and Clifford, *ibid.*, **63**, 2727 (1941).

(11) Heilbron and co-workers, *J. Chem. Soc.*, 801 (1937); 102 (1938).

Experimental[12]

Cholestane-3β,5α-diol-6-one[2] from Cholesterol (S.R.).—A suspension of 4.5 g. of cholesterol in 200 cc. of acetone and 25 cc. of water was treated with 2.5 g. (1.25 equiv.) of N-bromosuccinimide and 2.5 cc. of acetic acid and shaken occasionally at room temperature. In the course of forty-five minutes the mixture became yellow, orange, and then colorless and the solid all went into solution. After standing overnight the solution was diluted and extracted with ether, and the extract was washed with water and alkali, dried, and concentrated until crystals began separating. The material was collected and further small crops obtained by concentration of the mother liquor. Crystallization from chloroform gave colorless needles that separated in a fibrous mat and melted at 231–232°; yield 2.4 g. (49%).

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.45; H, 11.08. Found: C, 77.63, 77.75; H, 10.99, 10.76.

The identity was established by conversion to the *phenylhydrazone*,[2] m. p. 163–164°, and to the mono and diacetates as described below. When the oxidation was conducted with 3.25 equivalents of N-bromosuccinimide the yield dropped to 23%. The yield was also lower when dioxane was substituted for acetone or when no acetic acid was added. Processing of the combined ethereal mother liquors afforded a small amount of a substance that separated from ethanol in colorless needles, m. p. 122°, dec., that was identified as **5,6-dibromocholesterol** by mixed m. p. determination.

Oxidation of cholesteryl acetate (5 g.) by the same procedure gave an oil that when triturated with petroleum ether afforded 1.2 g. of crude solid, m. p. 160–170° (positive test for bromine). Several crystallizations from ligroin and methanol eventually gave a small crop of needles, m. p. 230–231°, identified as **cholestane-3β,-5α-diol-6-one 3-acetate**[2] by mixed melting point comparison.

(12) Melting points are uncorrected.

Cholestane-3β,5α,6β-triol (S.R.).—A suspension of 20 g. of technical cholesterol in 200 cc. of 88% formic acid was heated to 70–80° with stirring for five minutes to form a derivative that is evidently the 3-formate, which separated as an oily layer, and cooled to 25°. The resulting thick paste of solidified formate was treated with 20 cc. of 30% hydrogen peroxide and shaken occasionally. The temperature usually rose to 35–40°; sometimes there was an even more pronounced heat effect and in this case the temperature was controlled to 40° by cooling. After about forty-five minutes the solid dissolved, the foam subsided, and a blue fluorescent solution resulted, but the temperature remained a few degrees above that of the room for about four hours longer. After a total reaction time of six to fifteen hours, the mixture was treated with 300 cc. of boiling water, stirred, allowed to cool, and the granular white solid collected, dried superficially, dissolved in 600 cc. of methanol, and the solution treated with 20 cc. of 25% sodium hydroxide, warmed on the steam-bath for ten minutes, filtered, acidified and diluted with 200 cc. of water. The white solid that precipitated was collected after cooling, washed well with water and thoroughly dried. The triol so obtained was of high purity, m. p. 236–238°, and the yield, duplicated in several experiments, was 19.7 g. (91%). Crystallization from methanol gave needles, m. p. 237–239°.

Cholestane-3β,5α,6β-triol-3,6-diformate was isolated as the chief product of the reaction of cholesterol with performic acid by crystallization of the solid material prior to saponification. Several crystallizations from methanol gave colorless needles, m. p. 180–181°, $[\alpha]^{28}D$ − 47.5° (dioxane).

Anal. Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.54; H, 10.05.

Cholestane-3β,5α,6β-triol-3-acetate-6-formate (S.R.).—Hydroxylation of cholesteryl acetate with hydrogen peroxide in formic acid suspension as above proceeded sluggishly. There was little heat effect, and the solid did not go into solution on stirring the mixture at 40–50° for about eight hours. The precipitated product afforded triol of poor quality (m. p. 218–225°) in low yield (65%) on saponification; repeated crystallization of the unsaponified precipitate from methanol afforded colorless needles, m. p. 201–202°, $[\alpha]^{28}D$ − 43.9° (dioxane).

Anal. Calcd. for $C_{30}H_{48}O_5$: C, 73.74; H, 9.90. Found: C, 73.72; H, 9.97.

Reaction of Cholesterol α-Oxide with N-Bromosuccinimide (L.F.F.).—The α-oxide[13] was prepared by reaction of cholesterol with perphthalic acid in ether solution at room temperature. The precipitation of phthalic acid was complete in about two hours; the alkali-washed filtrate was dried, evaporated to a small volume and diluted with petroleum ether, and the α-oxide, m. p. 138–139.5°, separated in yield of 59%; recrystallized material melted at 147–148°.

A solution of 2 g. of the oxide in 80 cc. of acetone was treated with 2 cc. of acetic acid and 10 cc. of water, the precipitated material was brought into solution by gentle warming, and 1.07 g. (1.2 equiv.) of N-bromosuccinimide was added. This soon dissolved to a yellow solution and after a time long needles of the oxide separated and then, within about five hours, began to dissolve. Brief shaking resulted in a clear solution, and in a few hours a total of 0.7 g. of crystals of a different form separated. Recrystallization of this material from ethyl acetate gave large rectangular prisms, m. p. 158° dec. On further crystallization from benzene the substance, which is provisionally regarded as **7-bromo-Δ⁴-cholestene-3β-ol-6-one** (VI), formed clusters of cottony needles, m. p. 158–159°, dec., $[\alpha]^{28}D$ −33.3° (dioxane), λ_{alc}^{max} 238–243 mμ (log ε 4.2).

Anal. Calcd. for $C_{27}H_{43}O_2Br$: C, 67.62; H, 9.04. Found: C, 67.39; H, 8.84.

The mother liquor on concentration and addition of water afforded a total of 0.88 g. of material melting above 200°, but a component of constant m. p. was obtained only after several crystallizations from methanol in yield of 0.2 g. This substance formed large, flat needles, m. p. 231–232°, and gave no depression when mixed with **cholestane-3β,5α-diol-6-one.**

Cleavage of 5,6-Oxides with Periodic Acid (L.F.F.).—A solution of 1 g. of cholesterol α-oxide in 30 cc. of hot acetone was treated with a solution of 0.625 g. of periodic acid dihydrate in 10 cc. of water. Before all of the precipitated oxide had redissolved, thin plates of the cleavage product began to separate. The mixture was refluxed for one-half hour, cooled, and the product collected and washed with acetone–water (1:1). The thoroughly dried material (0.83 g.) melted at 231–232° and showed no depression when mixed with cholestane-3β,5α,6β-triol. Dilution of the mother liquor at the boiling point afforded a second crop of 0.14 g. of crystals, m. p. 225–226° (total yield, 94%). Recrystallization of the combined crops from methanol afforded flat needles, m. p. 234–235°.

Cholesteryl α,β-oxide acetate (8 g.) was refluxed for one hour in acetone solution (140 cc.) with 2 g. of periodic acid dihydrate in 20 cc. of water and the solution was filtered and concentrated to the point of saturation. A first crop of cholestane-3β,5α,6β-triol-3-acetate, m. p. 205–206°, amounted to 5.93 g. Concentration of the mother liquor afforded three further crops that separated either as plates or prisms and melted in the range 203–206°. The total yield of 3-acetate was 7.24 g. (87%).

Cholestane-3β,5α-diol-6-one (III) from the *trans*-Triol (S.R. and L.F.F.).—The selective oxidation of the triol at C_6 by N-bromosuccinimide proceeds readily in aqueous acetone or methanol with either a small or large excess of reagent. The following procedures were found particularly satisfactory.

(a) **In Aqueous Dioxane.**—A solution of 10 g. of triol in 90 cc. of dioxane was diluted with 10 cc. of water, cooled to 25° and treated with 4.5 g. (1.05 equiv.) of N-bromosuccinimide, which promptly dissolved. In the course of three to four minutes the color changed to yellow, deep orange, light yellow, and colorless, and the reaction product began to separate. The temperature was kept at 25° by cooling, and after ten minutes the mixture was cooled in ice and the diolone collected and washed with 50% methanol; the fully dried material weighed 6.7 g., m. p. 232–233°, dec. The mother liquor was diluted with water and extracted with ether, and the washed and dried solution was concentrated until crystals of the diolone began to separate, and a further crop of 2.5 g. of ketone of satisfactory purity was obtained; total yield of material, m. p. 231–233°, dec., 9.2 g. (93%).

In an experiment conducted without the addition of water the reaction was slow and the reaction product was obtained in low yield and very inferior quality.

(b) **In Aqueous Methanol–Ether.**—A 1-liter separatory funnel was charged with 23 g. of the triol, 450 cc. of ether, 75 cc. of methanol, 75 cc. of water and 10.8 g. (1.05 equiv.) of N-bromosuccinimide and shaken to effect solution. Oxidation was over in a few minutes and gave an orange-yellow solution. On addition of water the color became lighter and the bulk of the diolone separated from the organic phase as colorless, shiny needles. The water phase was tapped off and the suspension in ether washed with bisulfite solution, with alkali and with water. The ketone was then collected on a Buchner funnel and washed with ether to give a first crop of 19 g., m. p. 232–233°, dec. Successive concentrations of the mother liquor afforded two additional crops amounting to 3 g., m. p. 232–233°, dec.; total yield 22 g. (96.5%).

In parallel experiments on one-tenth the above scale with 1.05 and with 2.1 equivalents of N-bromosuccinimide, the yield of product in the first crop was 1.94 g. (m. p. 231–232°) and 1.91 g. (m. p. 231–232°), respectively.

Cholestane-3β,5α-diol-6-one 3-Acetate.[2] (a) **By Acetylation (S.R.).**—A mixture of 10 g. of the diolone, 50 cc. of acetic anhydride and seven drops of pyridine was heated to the boiling point, allowed to cool to room temperature and treated with water. The reaction product consisting

(13) Hattori, *J. Pharm. Soc., Japan*, **60**, 334 (1940) (*C. A.*, 7294 (1940)).

of colorless needles was washed with a little methanol and dried; yield 10.7 g. (91%). Material recrystallized from methanol melted at 232–233° and did not depress the sample (b).

(b) **By Oxidation (L.F.F.).**—A mixture of 400 mg. of cholestane-3β,5α,6β-triol 3-acetate and 200 mg. (1.3 equiv.) of N-bromosuccinimide was dissolved in 15 cc. of acetone by slight warming, cooled to 25° and treated with 1 cc. of water. The solution turned pale yellow in one or two minutes, crystals began to separate in ten minutes and the yellow color disappeared in twenty-five minutes. After a total of one and one-half hours 10 cc. of water was added and the precipitated solid collected; yield 370 mg. (93%), m. p. 229–230°; recrystallized: m. p. 232–233°.

Cholestane-3β,5α-diol-6-one 3,5-Diacetate[2,3] **(L.F.F. and S.R.).**—A suspension of 10 g. of the diolone in 50 cc. of acetic anhydride was treated with six drops of boron fluoride etherate, stirred, and the lumps broken up with a stirring rod. The bulk of the solid rapidly dissolved with a slight rise in temperature, and complete solution was effected by brief warming on the steam-bath. After fifteen minutes water was added and the crystalline yellow solid that soon separated was collected and the color removed by washing with a little methanol. Crystallization from methanol afforded 8.5 g. (71.5%) of the diacetate as prismatic needles, m. p. 170–171°.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.04; H, 10.02. Found: C, 74.25; H, 10.14.

A sample of the diacetate (5 g.) was refluxed with selenium dioxide (2.5 g.) in acetic acid (50 cc.) for six hours, but was recovered unchanged (4.7 g.). A similar experiment conducted in refluxing nitrobenzene (2 g. diacetate, seven hours) led to extensive tar formation, and the only product isolated was starting material (0.8 g., m. p. 169–170°).

7β-Bromocholestane-3β,5α-diol-6-one 3-acetate (L. F.F.).—A solution of 3.23 g. of cholestane-3β,5α-diol-6-one 3-acetate in 70 cc. of acetic acid was treated at 60° with a solution of 1.23 g. of bromine in 35 cc. of acetic acid and 1 cc. of boron fluoride etherate, kept at 60° for fifteen minutes, when the solution had become light yellow, let stand for one hour and diluted with 100 cc. of water. The dried precipitate (3.71 g., m. p. 88–100°) was ground in a mortar with a little methanol, when initially a part dissolved and a part formed a gum. Further trituration produced a thick paste of white solid, which when collected, washed and dried weighed 2.90 g. (71%).

The bromo derivative is very readily soluble in ether, fairly soluble in petroleum ether and moderately soluble in hot methanol (about 30 cc./g.). On repeated crystallization from methanol it formed a cottony mat of fine needles of the constant m. p. 170–171°; $[\alpha]^{28}D$ +7.5° (dioxane).

Anal. Calcd. for $C_{29}H_{47}O_4Br$: C, 64.55; H, 8.78. Found: C, 64.60; H, 8.63.

Dehydrobromination was accomplished by refluxing a solution of 1 g. of the 3-acetate in 10 cc. of triethylamine. The amine hydrobromide is insoluble in the boiling amine; the amount collected after seven hours and washed with ether represented 28% of the theory, and after twenty-four hours of refluxing the total yield of salt was 267 mg. (93%). The only slightly discolored filtrate and washing were evaporated at reduced pressure and the residue was washed in ether with acid and water and the solution dried and evaporated. The resulting light brown gum was chromatographed in petroleum ether (30–60°) by Dr. Huang-Minlon. Elution with petroleum ether–benzene (1:3; 1:1; 2:1) and with pure benzene gave fourteen fractions, the first five of which were oily. The next three fractions melted in the range 150–172° and were halogen-free, and crystallization of the total from acetone–ligroin (70–90°) afforded a few milligrams of isomer A, m. p. 173–175°.

Fraction 11 afforded 125 mg. of halogen-free crystals, m. p. 167–168°. Recrystallization from methanol (m. p. 168–169°) and then from acetone–petroleum ether gave isomer B (probably X), m. p. 170–171°. The substance is only slightly soluble in boiling dilute soda solution, but the cooled and filtered solution gives a definite precipitate on acidification.

Anal. Calcd. for $C_{29}H_{48}O_5$: C, 72.97; H, 10.19. Found, A: C, 73.36, 73.28; H, 10.00, 10.15. B: C, 73.24; H, 10.30.

7β-Bromocholestane-3β,5α-diol-6-one 3,5-Diacetate (L.F.F.).—A solution of 1.5 g. of the 7β-bromo 3-acetate in 13 cc. of hot acetic anhydride was treated with five drops of boron fluoride etherate and let cool, when 1.5 g. (79.5%) of the diacetate separated in crystalline form, m. p. 214–216°. Recrystallization from 250 cc. of methanol afforded 1.29 g. of needles, m. p. 216.5–217.5°, $[\alpha]^{25}D$ +37.0° (dioxane).

Anal. Calcd. for $C_{31}H_{49}O_5Br$: C, 64.01, H, 8.49. Found: C, 64.09; H, 8.42.

Attempts to brominate the diolone 3,5-diacetate with N-bromosuccinimide with and without irradiation and peroxide resulted only in recovery of unchanged starting material. Bromination of the diacetate (503 mg.) in acetic acid (5 cc.) with a solution of bromine (0.176 g.) in acetic acid (5 cc.) was effected by adding boron fluoride etherate (6 drops) and warming the solution to 75° for twenty-five minutes, when the color had faded to light yellow. On addition of 3 cc. of water and cooling a solid product was obtained; 450 mg., m. p. 201–203°, dec. One crystallization from 45 cc. of methanol gave long spars, m. p. 205–207°, dec. (325 mg.), and further purification gave material of the expected composition; m. p. 210–211°, dec., $[\alpha]^{25}D$ +27° (dioxane).

Anal. Calcd. for $C_{31}H_{49}O_5Br$: C, 64.01; H, 8.49. Found: C, 63.74; H, 8.44.

This material apparently consists chiefly of the above 7β-bromo diacetate containing a small amount of a less dextrorotatory isomer (7α-epimer ?), but several further crystallizations raised the m. p. only to 213–214°; a mixture of this with the 216.5–217.5° material melted at 214–215°.

The 216.5–217.5° diacetate (1.3 g.) was refluxed with triethylamine (80 cc.) for fifty-eight hours, but only about 100 mg. of triethylamine hydrobromide separated and the only product encountered was starting material (0.6 g.). The 210–211° product was recovered unchanged after being boiled with pyridine for six hours; this was also true when silver benzoate was added, but the recovery was in this case lower.

Summary

1. A procedure for the hydroxylation of the double bond of cholesterol by brief treatment with performic acid and saponification affords cholestane-3β,5α,6β-triol in 91% yield.

2. The above triol can be selectively oxidized to the 6-ketone with N-bromosuccinimide in 94% yield, even in the presence of methanol.

3. The 5,6-oxido derivatives of cholesterol and cholesteryl acetate can be cleaved to the glycols by reaction with periodic acid in acetone.

4. Bromination of the mono- or diacetate of cholestane-3β,5α-diol-6-one was accomplished with use of boron fluoride catalyst, but the chief products are evidently the 7β-bromo derivatives, since that from the diacetate resists dehydrohalogenation and that from the 3-monoacetate yields an acidic product of rearrangement.

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Studies of Imidazole Compounds. IV. Derivatives of 4-Ethylimidazole

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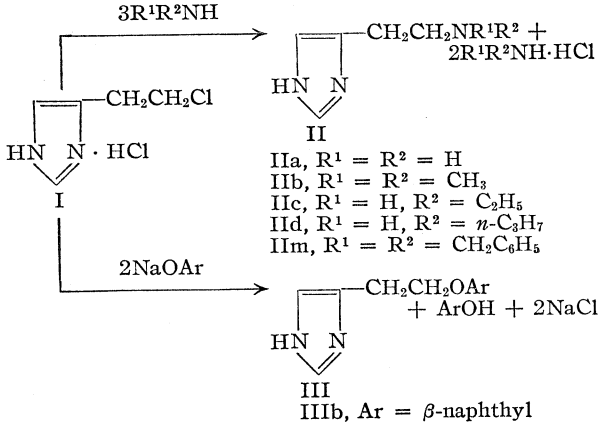
In the first paper of this series certain derivatives of 4-methylimidazole[1] were discussed; a practicable synthesis of 4-(2-chloroethyl)-imidazole hydrochloride (I)[2] was reported in a later paper. In the present paper derivatives of 4-ethylimidazole related to histamine and prepared from I are described.

Several histamine derivatives bearing alkyl substituents on the side chain nitrogen-atom have been prepared, thus extending the work of Garforth and Pyman[3] who described three lower members of the series. The 4-(2-alkylaminoethyl)-imidazoles (II) were prepared by the addition of I to an excess of an amine in boiling anhydrous *n*-propanol. Some of the condensation products could then be isolated as the dihydrochloride or dihydrobromide. Usually, however, this procedure was not possible; instead, the sirupy dihydrochloride was converted into the crystalline dipicrate, which after suitable purification was reconverted into the crystalline dihydrochloride.

Two substituted 4-ethyl-imidazoles containing oxygen in the side chain (III) were synthesized by reaction of I with a sodium phenolate.



A detailed report on the pharmacology of these imidazoles will be published elsewhere. However, a few remarks in regard to their activity may be in order. In group II, the larger the N-alkyl substituent, the smaller is the histamine activity as measured by the spasm produced on the isolated guinea-pig ileum strip. Following this generalization, the most potent derivatives are 4-(2-dimethylaminoethyl)-imidazole (IIb) and 4-(2-ethylaminoethyl)-imidazole (IIc), each being 75% as active as histamine (IIa).[4] A compound of intermediate activity is IId with 5% of the activity of histamine, whereas IIm, containing the N-benzyl substituent, the largest in the series, is totally inactive at the levels tested (200 times the level at which histamine gave a standard response). Moreover, an interesting example of competitive inhibition is presented by IIm, since it possesses weak but definite antihistaminic activity [0.5% of the activity of N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)-ethylenediamine hydrochloride].

In the series containing an oxygen substituent in the side chain, the pharmacological properties of 4-[2-(2-naphthoxy)-ethyl]-imidazole (IIIb) are worthy of note. It displays a high histamine-like activity, 50% that of histamine, but unlike the latter's action the spasm produced on the ileum strip is only momentary.

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Experimental[5]

Physical and analytical data and the methods of preparation are summarized in Table I.

4-(2-Ethylaminoethyl)-imidazole Dihydrochloride (IIc). Procedure A.—A solution of 3.5 g. of I[2] in 30 ml. of a 30% ethanolic ethylamine solution was heated in a sealed tube at 100° for fourteen hours. The product was treated with a solution of 5 g. of sodium carbonate in 25 ml. of water and concentrated *in vacuo*. The residue was heated at 90° *in vacuo* for one hour and then digested with 50 ml. of absolute ethanol and filtered. After several more digestions the combined alcohol solutions were concentrated *in vacuo*. The resulting brown sirup was acidified (congo paper) with 1 *N* hydrochloric acid and added with stirring to a solution of 11.5 g. of picric acid in 150 ml. of water. The crystalline picrate which formed on cooling was recrystallized from water after a treatment with charcoal (Nuchar); yield 8.0 g.; m. p. 185°, with loss of water of crystallization at 104°.

The picrate was converted into the hydrochloride by treating it with 20 ml. of 5 *N* hydrochloric acid and removing the picric acid by repeated extractions with ether. The aqueous layer was concentrated *in vacuo* to a sirup, which after solution in hot methanol crystallized as platelets on careful addition of methyl ethyl ketone; after another crystallization the dihydrochloride weighed 1.5 g., m. p. 162–163°.

4-(2-Diethylaminoethyl)-imidazole Dihydrochloride. Procedure B.—To a stirred solution of 13.4 g. of anhydrous diethylamine in 25 ml. of anhydrous *n*-propanol, boiling under reflux, was added a solution of 3.4 g. of I in 25 ml. of *n*-propanol during one-half hour with exclusion of moisture. After further boiling under reflux for six hours, a solution of 5 g. of sodium carbonate in 25 ml. of water was added and the crude, brown sirupy base isolated as described above. It was treated with a 3 *N* solution of hydrogen chloride in absolute ethanol until strongly acid and crystallization induced by the slow addition of dry ethyl acetate. Recrystallization from dry ethanol–ethyl acetate yielded 0.60 g. of the dihydrochloride, m. p. 219–220°.

(1) Turner, Huebner and Scholz, THIS JOURNAL, **71**, 2801 (1949).

(2) Turner, *ibid.*, **71**, 3476 (1949).

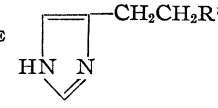
(3) Garforth and Pyman, *J. Chem. Soc.*, 489 (1935).

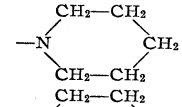
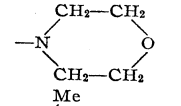
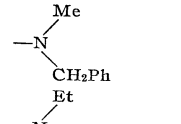
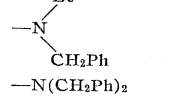
(4) Vartiainen, *J. Pharm. and Exp. Thera.*, **54**, 265 (1935), reported the former to be 20% and the latter 5 % as potent as histamine.

(5) The microanalyses were carried out by Mr. Joseph Alicino, Metuchen, N. J.

TABLE I

DERIVATIVES OF 4-ETHYL-IMIDAZOLE



No.	R^3	Salts	M. p.,[a] °C.	Yield, %	Recrystn. solvent	Procedure	Empirical formula	Analyses, % Calculated C	Calculated H	Found C	Found H
IIb	$-NMe_2$	Dihydrochloride	183–184[b]	25	Ethanol		$C_7H_{13}N_3 \cdot 2HCl$	39.63	7.12	39.95	7.18
		Dipicrate	215[c]	40	Water	A	$C_7H_{13}N_3 \cdot 2C_6H_3O_7N_3$	38.19	3.22	38.01	3.25
IIc	$-NHEt$	Dihydrochloride	162–163[d]	35	Ethanol–acetone	A	$C_7H_{13}N_3 \cdot 2HCl$	39.63	7.12	39.55	7.20
		Dipicrate	(104) 185[e]	60	Water		$C_7H_{13}N_3 \cdot 2C_6H_3O_7N_3$	38.19	3.22	37.93	3.00
IId	$-NHPr$	Dihydrochloride	96–100	50	Ethanol–butanone	A	$C_8H_{15}N_3 \cdot 2HCl$	42.56	7.61[f]	42.68	7.72
		Dipicrate	165		Water		$C_8H_{15}N_3 \cdot 2C_6H_3O_7N_3$	39.27	3.47	39.16	3.50
IIe	$-NHCH(CH_3)_2$	Dihydrochloride	195–196[g]	35	Ethanol–butanone	A	$C_8H_{15}N_3 \cdot 2HCl$	42.56	7.61[h]	42.84	7.69
		Dipicrate	175		Water						
IIf	$-NEt_2$	Dihydrochloride	219–220	15	Ethanol–ethyl acetate	B	$C_9H_{17}N_3 \cdot 2HCl$	45.00	7.97[i]	44.75	7.71
IIg	$-NPr_2$	Dihydrochloride	(Sirup)								
		Dipicrate	190	45	Water	B	$C_{11}H_{21}N_3 \cdot 2C_6H_3O_7N_3$	42.25	4.18	42.16	3.92
IIh		Dihydrochloride	276–278	55	Ethanol–butanone		$C_{10}H_{17}N_3 \cdot 2HCl$	47.60	7.63	47.46	7.24
		Dipicrate	188–191		Water	B	$C_{10}H_{17}N_3 \cdot 2C_6H_3O_7N_3$	41.44	3.64	41.72	3.91
IIi		Dihydrochloride	238–243	55	Ethanol–ether	B	$C_9H_{15}N_3O \cdot 2HCl \cdot {}^1/_2 H_2O$	41.04	6.92	41.26	6.41
IIj		Dihydrobromide	178–179	20	Propanol	C	$C_{13}H_{17}N_3 \cdot 2HBr$	41.40	5.08[j]	41.26	4.83
IIk		Dihydrobromide	82–83	5	Ethanol–butanone	C	$C_{14}H_{19}N_3 \cdot 2HBr$	42.86	5.42	42.70	5.41
IIm	$-N(CH_2Ph)_2$	Dihydrochloride	155–156	15	Propanol	D	$C_{19}H_{21}N_3 \cdot 2HCl \cdot {}^3/_4 H_2O$	60.40	6.54	60.44	6.64
IIIa	$-OPh$	Hydrochloride	136–137[k]	40	Ethanol–ether						
		Picrate	118–120[l]	60	Water	E	$C_{11}H_{12}N_2O \cdot C_6H_3O_7N_3$	48.91	3.63	49.05	3.67
IIIb	$-O(2)C_{10}H_7$	.....	151–152								
			(free base)	25	Ethanol	E	$C_{15}H_{14}ON_2$	75.60	5.89	75.61	6.07

[a] Melting points are uncorrected and were taken in a capillary. [b] Reported[3] m. p. 188° cor. [c] Reported[3] m. p. 233° cor. [d] Reported by Garforth and Pyman[3] as m. p. 169° cor. [e] Change in crystalline form at 104° with loss of water of crystallization. Reported m. p. 186° changing at 100° cor. [f] *Anal.* Calcd.: Cl, 31.37. Found: Cl, 31.63. [g] Since the completion of this work, this compound has been synthesized by another method by Sheehan and Robinson, THIS JOURNAL, **71**, 1436 (1949), who report a melting point of 197.5–199° cor. [h] *Anal.* Calcd.: Cl, 31.37. Found: Cl, 31.63. [i] *Anal.* Calcd.: N, 17.50; Cl, 29.52. Found: N, 17.24; Cl, 29.89. [j] *Anal.* Calcd.: N, 11.14; Br, 42.38. Found: N, 11.03; Br, 42.17. [k] Reported m. p. 136–137° cor. [l] Reported m. p. 122° cor.

4-(2-Benzylmethylaminoethyl)-imidazole Dihydrobromide. Procedure C.—The mixture resulting from the reaction of 3.4 g. of I with 10.0 g. of benzylmethylamine, carried out as described under procedure B, was concentrated *in vacuo*. The residue was treated with 50 ml. of 10% aqueous sodium carbonate and extracted with 100 ml. of ether. The ether was removed and the resulting oil distilled at 15 mm. in a bath held at 140–150°. This served to remove most of the benzylmethylamine. A solution of the residue in 10 ml. of 48% hydrobromic acid was taken to dryness *in vacuo*, then dissolved in a few ml. of hot absolute ethanol. The crystalline dihydrobromide obtained after several days in the cold was recrystallized from anhydrous *n*-propanol to yield 1.5 g., m. p. 178–179°.

4-(2-Dibenzylaminoethyl)-imidazole Dihydrochloride Procedure D.—The reaction mixture obtained from 3.4 g. of I and 12.0 g. of dibenzylamine according to procedure B was boiled under reflux for twenty-four hours. The cooled solution ultimately deposited 6.2 g. of dibenzylamine hydrochloride (m. p. 257–258°), which was filtered. After evaporation of the filtrate to dryness, the residue was digested briefly with 1.86 g. of sodium carbonate in 30 ml. of water. Repeated extraction of the aqueous suspension with petroleum ether removed dibenzylamine, and the crude imidazole was extracted with diethyl ether. Following distillation of the ether, the residue was dissolved in 10 ml. of concentrated hydrochloric acid, evaporated to dryness, and dissolved in 10 ml. of ethanol. When this solution was left in the cold for several hours, it deposited 1.4 g. of dibenzylamine hydrochloride, which was filtered. The evaporated filtrate was taken up in 5 ml. of hot anhydrous *n*-propanol. The solution yielded 1.5 g. of crude 4-(2-dibenzylaminoethyl)-imidazole dihydrochloride; after two more recrystallizations 0.36 g. of the pure hydrochloride remained, m. p. 155–156°.

4-(2-Phenoxyethyl)-imidazole Dihydrochloride. Procedure E.—To a solution of 2.8 g. of phenol in 23.0 ml. of 1.30 *N* methanolic sodium methoxide, boiling under reflux, was slowly added a solution of 2.5 g. of I in 25 ml. of *n*-propanol. After six hours the cooled reaction mixture was treated with an excess of 3 *N* hydrogen chloride in ethanol, the precipitated sodium chloride was collected, and the filtrate was taken to dryness *in vacuo*. The residue was suspended in water and extracted several times with ether to remove excess phenol. The aqueous phase was added to a boiling solution of 8.5 g. of picric acid in 130 ml. of water. The picrate was filtered and recrystallized from water; yield 4.2 g., m. p. 118–120°. The picrate was converted into the hydrochloride by treating it with 12 *N* hydrochloric acid and extracting with ether in the usual manner. The sirupy hydrochloride was recrystallized from absolute ethanol–ether; m. p. 129–131°; yield 1.3 g.

Summary

A series of 4-(2-alkylaminoethyl)-imidazoles

related to histamine and two 4-(2-aryloxyethyl)-imidazoles have been prepared from 4-(2-chloroethyl)-imidazole hydrochloride. A few of these substances resembled histamine in their pharmacodynamic actions but all were less active. Weak antihistaminic activity was shown by 4-(2-dibenzylaminoethyl)-imidazole.

SUMMIT, N. J. RECEIVED JUNE 18, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, GENERAL MILLS, INC.]

Polyglycerols. III.[1] Synthesis of Triglycerol[2]

BY J. ROBERT ROACH AND HAROLD WITTCOFF

The synthesis of a crystalline isomer of linear triglycerol[3] is described in this paper.

Probably the first reference to triglycerol was made by Lourenco[4] who reported it as a distillable reaction product from the interaction of glycerol and gaseous hydrogen chloride. Levene and Walti[5] hydrolyzed the reaction products resulting from the action of potassium acetate on epichlorohydrin to obtain several distillable products including a small quantity of triglycerol (b. p. 200–205° (0.1 mm.)). The same boiling range was reported by Istin[6] who distilled triglycerol directly from a polyglycerol mixture. Isolation of crude triglycerol from a polyglycerol mixture by distillation of the acetates[7,8] and the allyl ethers[3] has also been reported. In none of this work has the crystalline pentahydric triglycerol been isolated.

The present synthesis involves the hydroxylation of O-α,α'-diallylglycerol[9] by action of either performic acid or potassium permanganate. The requisite diallylglycerol was prepared by the interaction of allyl alcohol and glycerol-α,α'-dichlorohydrin in the presence of sodium hydroxide. The homogeneity of this product, on which depends the linear structure of the triglycerol, follows from the oft-recorded observation that chlorohydrins such as glycerol dichlorohydrin are dehydrohalogenated in strong basic medium to epoxides. These, in turn, react with alcohols to yield ethers in which the ether linkage is primary.[10] Furthermore, it was not possible by careful fractional distillation to detect the presence of any isomeric substance.

Since the triglycerol could not be readily distilled from the reaction mixtures in which it was formed, acetonation was employed. On treatment of the crude mixtures with acidic acetone, there resulted a mixture of isopropylidenetriglycerol and diisopropylidenetriglycerol which on hydrolysis yielded the pure triglycerol.

Separation of isopropylidenetriglycerol and diisopropylidenetriglycerol was difficult. By careful fractional distillation, however, samples which analyzed properly were obtained.

The triglycerol obtained by hydrolysis of the isopropylidene derivatives was probably a sirupy mixture of stereoisomers. Crystallization from anhydrous *n*-butanol of the product resulting from performic acid hydroxylation yielded 25–33% of a crystalline isomer of melting point 98–99°. The sirup from the mother liquor could not be induced to crystallize. For linear triglycerol there are theoretically possible a *dl*-mixture and two *meso*-forms. The presence of isomers was perhaps indicated by the fact that the sirupy triglycerol from the performic acid hydroxylation demonstrated proper elementary analyses. That permanganate hydroxylation provided a different ratio of isomers was inferred from the observation that the sirupy triglycerol yielded, on crystallization, 50% of crystalline isomer of identical melting point.

The solid triglycerol was converted to the penta-(*p*-nitrobenzoate) derivative. Attempts to prepare similar derivatives of the sirupy isomers from which the crystalline triglycerol had been removed led only to uncrystallizable oils.

Experimental

O-α,α'-Diallylglycerol.—Allyl alcohol (1161 g., 20 moles) was added, with stirring, to 50% aqueous sodium hydroxide (880 g., 11 moles) whereupon the temperature rose spontaneously to 52°. Glycerol dichlorohydrin (644.8 g., 5 moles) was added dropwise over a period of three and one-fourth hours, while the temperature was maintained at 70–80° by the exothermic reaction. After completion of the addition, stirring was continued at 70–80° for one and one-fourth hours, whereupon the excess allyl alcohol was removed by distillation *in vacuo*. The product was washed successively with water, dilute acetic acid, and again with water until the washings were neutral. All of the aqueous solutions were combined and extracted with ether, after which the ether solution was washed with water and was combined with the product. The mixture was dried (sodium sulfate) and after removal of the ether, the product was distilled through a 15-inch Vigreux column. No forerun was obtained. The material of constant refractive index ($n^{25}D$ 1.4520, d^{25}_4 0.9810) distilled at 112–113° (14 mm.) and weighed 524.4 g. (60.8%). Redistillation at high reflux ratio through a 12-inch column packed with stainless steel helices gave a series of

(1) Paper II, THIS JOURNAL, **71**, 2666 (1949).

(2) Paper No. 100, Journal Series, Research Laboratories, General Mills, Inc.

(3) For a discussion of nomenclature *cf.* H. Wittcoff, J. R. Roach and S. E. Miller, THIS JOURNAL, **69**, 2655 (1947), footnote 2.

(4) A. V. Lourenco, *Ann. chim. phys.*, [3] **67**, 257 (1863).

(5) P. A. Levene and A. Walti, *J. Biol. Chem.*, **77**, 685 (1928).

(6) M. Istin, *Ann. faculté sci. Marseille*, **13**, 5 (1940); *C. A.*, **41**, 2392 (1947).

(7) M. Rangier, *Compt. rend.*, **187**, 345 (1928); *C. A.*, **22**, 4468 (1928).

(8) H. J. Wright and R. N. DuPuis, THIS JOURNAL, **68**, 446 (1946).

(9) N. Kishner, *J. Russ. Phys.-Chem. Soc.*, [1] 31 (1892); Beilstein, "Handbuch der organische Chemie," 4th ed., J. Springer, Berlin, 1918, Vol. I, p. 513.

(10) A. Fairbourne, G. P. Gibson and D. W. Stephens, *J. Chem. Soc.*, 1965 (1932).

fractions, all of which boiled at 68–69° (0.9–1.0 mm.) and 93% of which possessed a $n^{25}D$ of 1.4510.

Anal. Calcd. for $C_9H_{16}O_3$: I_2 number, 294.8; hydroxyl %, 9.87. Found: I_2 number, 293.9; hydroxyl %, 9.7.

In addition of the diallylglycerol there was obtained an unidentified higher boiling product (93 g.) which distilled at approximately 135° (0.6 mm.).

Isopropylidenetriglycerol and Diisopropylidenetriglycerol from the Oxidation of O-α,α'-Diallylglycerol with Performic Acid.—A mixture of O-α,α'-diallylglycerol (172 g., 1 mole), formic acid (87%, 700 cc.) and hydrogen peroxide (28%, 229 g., 2 moles) was stirred mechanically (safety glass shield). The temperature rose to 40° in twenty minutes and was maintained there first by external cooling and then by heating for a total time of five hours. The mixture was allowed to stand overnight whereupon titration of a test sample indicated the presence of about 0.5 g. of hydrogen peroxide. This was destroyed with sodium bisulfite (20 g.) and the mixture was evaporated *in vacuo* to a thick sirup. A methanol solution of the sirup was filtered and evaporated, and the sirup was dissolved in absolute ethanol (300 cc.). The solution was made slightly alkaline with alcoholic sodium hydroxide and the ethyl alcohol and ethyl formate were removed by slow distillation. The residue was dissolved in methanol (200 cc.) which contained sodium hydroxide (15 g.), and the solution was heated on the steam-bath for one hour to saponify any formate groups not removed by the alcoholysis. The mixture was made slightly acid with concentrated hydrochloric acid, after which it was concentrated. Most of the sodium chloride was removed by dissolving the residue in methanol, filtering and removing the solvent under reduced pressure. This sequence of operations was carried out twice. Thereupon the residue was dissolved in absolute ethanol (200 cc.) and the solution was allowed to stand twelve hours over sodium sulfate. Concentration of the ethanol solution yielded a theoretical quantity (240 g.) of sirup.

The hydroxylation product (240 g.) together with a solution of hydrogen chloride (9.0 g.) in acetone (1500 cc.) was stirred overnight with anhydrous sodium sulfate (90 g.). After the reaction mixture was made slightly basic with alcoholic sodium hydroxide, it was filtered and concentrated. The acetonated product (113 g.) was obtained in low yield, indicating that much of the original product had not been acetonated. Accordingly, the sodium sulfate was extracted well with methanol, and from the alcohol solution there was obtained 90 g. of sirup. This was subjected to acetonation as above (500 cc. of acetone, 9 g. of hydrogen chloride, 100 g. of sodium sulfate) to obtain more product (98 g.). The total yield of acetonated derivative was thus 211 g. (approximately 70% overall yield). This was a mixture of isopropylidene- and diisopropylidenetriglycerol. For purposes of preparing triglycerol, the distilled product was hydrolyzed directly according to the procedure indicated below.

In order to separate the isopropylidene derivatives, 70 g. of the mixture was distilled through a short column, and the course of the distillation was followed by refractive index measurements.

Sixty-three grams of distillate was obtained in two fractions. The second fraction will be discussed below. The first fraction (47 g.) distilled at 146–196° (0.3 mm.) (major portion 150–165° (0.3 mm.)). As already indicated, it was difficult to separate pure diisopropylidenetriglycerol from small amounts of isopropylidenetriglycerol by fractional distillation.

In one experiment a material which analyzed properly was obtained by distilling the diisopropylidene fraction several times, at high reflux ratio, through a 12-inch, monel metal helices-packed column. The product distilled at 157–158° (0.6 mm.) and had a $n^{25}D$ of 1.4530.

Anal.[11] Calcd. for $C_{15}H_{28}O_7$: C, 56.24; H, 8.75. Found: C, 55.9, 55.9; H, 8.7, 9.0.

(11) The authors are indebted to Mr. James Kerns for micro carbon and hydrogen analyses.

The second fraction (16 g.) referred to above, distilling at 196–240° (0.3 mm.), was fractionally distilled to yield isopropylidenetriglycerol of boiling point 172–175° (0.25 mm.) and $n^{25}D$ of 1.4691.

Anal. Calcd. for $C_{12}H_{24}O_7$: C, 51.41; H, 8.63. Found: C, 51.6, 51.4; H, 8.6, 8.9.

Sirupy Triglycerols from Isopropylidene- and Diisopropylidenetriglycerol.—The first fraction of the preceding experiment (30 g.) was dissolved in water (30 cc.) and concentrated hydrochloric acid (3 cc.). The solution was heated on the steam-bath for one-half hour. During this time acetone (12 cc. of the theoretical 13.5 cc.) distilled. The solution was then concentrated *in vacuo* to obtain a theoretical quantity (22.5 g.) of sirup. This was distilled to yield sirupy triglycerol (20 g.) which collected over a range of 190–230° (0.1 mm.), although most of the product distilled at 215–220° (0.1 mm.). The product had a $n^{25}D$ of 1.4902. This value varies with the ratio of isomers obtained by the different preparative procedures used, as shown by subsequent data.

Anal. Calcd. for $C_9H_{20}O_7$: C, 44.99; H, 8.39. Found: C, 45.1, 44.9; H, 8.7, 8.7.

Crystalline Triglycerol from the Performic Acid Hydroxylation.—The sirupy triglycerol described above (8 g.) was dissolved in warm anhydrous *n*-butanol (8 cc.). After several days of refrigeration there resulted 2 g. of crystalline triglycerol which, after three crystallizations from butanol, melted at 98–99°. Accordingly, from this and other experiments it appears that 25–33% of the crystalline isomer is present in the triglycerol which results from the hydroxylation of O-α,α'-diallylglycerol with performic acid.

Anal. Calcd. for $C_9H_{20}O_7$: C, 44.99; H, 8.39. Found: C, 45.1, 44.9; H, 8.1, 8.3.

The sirup remaining in the mother liquor, when distilled at about 225° (0.3 mm.), yielded fractions varying in $n^{25}D$ from 1.4758 to 1.4870. These values are considerably lower than the value of 1.4902 demonstrated by the original mixture from which the crystalline triglycerol was removed. None of these fractions could be crystallized, nor could they be converted to crystalline *p*-nitrobenzoates.

In an attempt to gain further insight into the composition of the unfractionated sirupy triglycerol, a quantity of it was separated by distillation at 206–275° (1 mm.) into 4 fractions. The first, second and fourth fractions weighed 4.0 g. each and had $n^{25}D$ of 1.4855, 1.4899 and 1.4935, respectively. The third fraction weighed 21.5 g. and had a $n^{25}D$ of 1.4920. The last two fractions crystallized readily to yield a total of 13 g. of crystalline product. The first two fractions and the sirupy portions of the last two could be induced neither to crystallize nor to yield solid *p*-nitrobenzoates. The crystalline triglycerol, on the other hand, could be converted to a solid *p*-nitrobenzoate. These data show that it is possible to obtain partial separation of the diastereoisomers of triglycerol by fractional distillation.

Penta-(*p*-nitrobenzoate) of the Crystalline Isomer of Triglycerol.—This derivative could be prepared either from crystalline triglycerol or from the unfractionated sirupy mixture of triglycerols. The melting point of the product was 134–134.5° regardless of its source, although the yield from the sirupy mixture was considerably lower and the product was purified with greater difficulty, as would be expected. Mixed melting points of the samples of *p*-nitrobenzoate derivative prepared from sirupy or crystalline triglycerol demonstrated no depression.

The unfractionated sirupy triglycerol was converted to the *p*-nitrobenzoate derivative by the conventional procedure employing anhydrous pyridine. The amorphous solid obtained by precipitation from water was crystallized from acetone to obtain the impure derivative melting at 95–102°. The product was crystallized once more from acetone, three times from mixtures of acetone and absolute ethanol (1:1) and twice from ethyl acetate. The resulting white needles melted sharply at 134–134.5°.

Anal. Calcd. for $C_{44}H_{35}O_{22}N_6$: C, 53.60; H, 3.57; N, 7.10. Found: C, 53.6, 53.7; H, 3.6, 3.6; N, 7.4, 7.5.

Triglycerol from the Oxidation of O-α,α'-Diallylglycerol with Potassium Permanganate.—To a mixture of O-α,α'-diallylglycerol (86.0 g., 0.5 mole) and water (600 cc.) cooled to 3° was added, with stirring, a solution of potassium permanganate (160 g., 1.01 mole) in water (3200 cc.) over a period of five hours. The temperature was kept at 3–5°. At the end of the addition the mixture was allowed to stand at room temperature for one and one-half hours, during which time the reaction temperature rose to 10°. The mixture was subsequently warmed to 25° and allowed to stand one hour longer after which the manganese dioxide was removed and the filtrate and washings were neutralized with concentrated hydrochloric acid (21.8 cc.). The aqueous solution was evaporated *in vacuo* to dryness and the residue was extracted with methanol. Removal of the methanol yielded a viscous sirup which was dissolved in ethyl alcohol. Benzene was added and the solvents were distilled in an attempt to remove the last trace of water azeotropically. A solution of the resulting sirup in absolute methanol was dried over anhydrous sodium sulfate. Filtration and removal of the methanol from the filtrate yielded 126.1 g. of a viscous water-white sirup (theoretical yield 121.1 g.). Undoubtedly impurities such as higher oxidation products were present as evidenced by the yield of isopropylidene derivatives.

The crude triglycerol (90 g.) was acetonated according to the procedure described above (750 cc. of acetone, 7.5 g. of anhydrous hydrogen chloride, 100 g. of anhydrous sodium sulfate). There resulted 75 g. (65.6% over-all yield based on diallylglycerol) of crude material which on distillation yielded 54 g. (approximately 47.2%) of a mixture of isopropylidene- and diisopropylidenetriglycerols. The mixture of isopropylidene derivatives was separated by fractional distillation into one fraction which was chiefly diisopropylidenetriglycerol (b. p. 162° (2 mm.)) and a higher boiling fraction (distillation range 190–220° (4–9 mm.)) which was primarily isopropylidenetriglycerol.

The first fraction (29 g.) was hydrolyzed to triglycerol as described above, yielding a viscous liquid (21.7 g., 100%) which on distillation gave 16.2 g. of sirupy triglycerol having a $n^{25}D$ of 1.4931. This value was higher than that shown by the sirupy triglycerol from the performic acid hydroxylation, probably because the proportion of isomers present was different, as shown by the following crystallization studies. The isolation of the crystalline isomer was effected as detailed above. Approximately 50% of the triglycerol prepared by this procedure was isolated as crystalline material as compared to 25–33% isolated from the sirupy triglycerol mixture resulting from the performic acid hydroxylation. The crystalline triglycerol prepared by the two methods had identical melting points (98–99°) which were not depressed on admixture. In this preparation, as in the previous one, the sirupy residue isolated from the mother liquor ($n^{25}D$ 1.4800) could not be induced to crystallize, nor could it be converted to a crystalline derivative.

Anal. Calcd. for $C_9H_{20}O_7$: C, 44.99; H, 8.39. Found: C, 45.1, 44.9; H, 8.1, 8.2.

Summary

1. Triglycerol has been synthesized by the hydroxylation of O-α,α'-diallylglycerol by the action of performic acid and by the action of permanganate.

2. Crystalline triglycerol of melting point 98–99° has been isolated and identified.

3. Triglycerol was isolated from the reaction mixtures by conversion to its isopropylidene derivatives and subsequent distillation.

MINNEAPOLIS, MINNESOTA RECEIVED MAY 16, 1949

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Steroid Analogs Lacking Ring C. I. The Synthesis of 6-Cyclohexyl-Δ^{1-9}-octalone-2 by the Robinson–Mannich Base Method

BY CLIFFORD H. SHUNK[1,2] AND A. L. WILDS

For some time we have been interested in the synthesis of certain analogs of the steroid hormones progesterone, desoxycorticosterone and testosterone lacking ring C. The first stage in this work, started in 1941 and interrupted during the war, has been to apply the Robinson–Mannich base synthesis[3] of cyclic α,β-unsaturated ketones to 4-cyclohexylcyclohexanone (I), obtaining 6-cyclohexyl-Δ^{1-9}-octalone-2 (VIII). Since we were interested in extending the reactions to less readily available derivatives of the ketone I, we have looked in some detail into several methods of applying this synthesis.

The best yields in the Robinson–Mannich base synthesis have been obtained with ketones having the adjacent methylene group activated, and accordingly we first investigated the carbomethoxy derivative III, as in our previous work in the chrysene series.[4] This was prepared from the ketone I *via* the glyoxylate II, although in poor yield (*ca.* 12%) primarily because of the decarbonylation step. The next reaction with the methiodide of 1-diethylaminobutanone-3 proceeded in good yield to the diketo ester IV, and the latter could be cyclized to 6-cyclohexyl-Δ^{1-9} octalone-2 (VIII) in fair yield (48%) with aqueous alkali or acid. With sodium methoxide the carbomethoxy group was retained giving IX.

Because of the poor over-all yields by this method, and particularly in the decarbonylation of the glyoxylate II, the latter derivative itself was used for condensation with the Mannich base methiodide. However, cyclization of the resulting product gave the octalone VIII in less than 20% yield.

It seemed attractive to try the hydroxymethyl-

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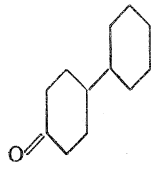
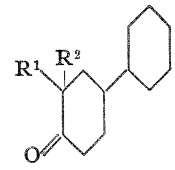
(3) *Cf.* du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937), and subsequent papers.

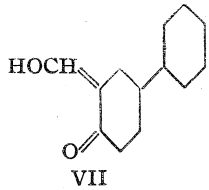
(4) Wilds and Shunk, THIS JOURNAL, **65**, 469 (1943).



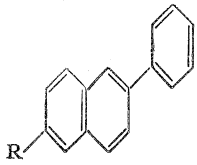
I



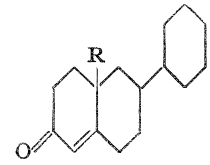
II, R^1 = H; R^2 = —COCOOCH$_3$
III, R^1 = H; R^2 = —COOCH$_3$
IV, R^1 = $CH_3COCH_2CH_2$—; R^2 = —$COOC_6H$
V, R^1 = $CH_3COCH_2CH_2$—; R^2 = —CHO
VI, R^1 = $CH_3COCH_2CH_2$—; R^2 = H



VII



X, R = H
XI, R = —OH



VIII, R = H
IX, R = —COOCH$_3$

ene derivative VII, since this group can be introduced into ketones in excellent yield[5] and after alkylation is very easily eliminated.[6] Apparently hydroxymethylene ketones have not been employed previously in the Mannich base condensation. As high as 87% of the derivative VII could be obtained from the ketone I employing an excess of ethyl formate and sodium methoxide. There was no indication of any bis-hydroxymethylene derivative being formed[7]; the ultraviolet absorption spectrum showed a single maximum at 281 mμ.[8]

Reaction of the hydroxymethylene ketone VII with 1-diethylaminobutanone-3 methiodide resulted in introduction of the γ-ketobutyl group in excellent yield; the product consisted of V, in which the formyl group was retained, and VI in which this had been eliminated, the ratio of the two varying with the reaction conditions. Each was cyclized smoothly with acid, or preferably with dilute methanolic alkali at room temperature for two to three hours. The over-all yield of 6-cyclohexyl-Δ^{1-9}-octalone-2 from 4-cyclohexylcyclohexanone was about 60–65%. By following the ultraviolet absorption spectrum it was possible to determine rather easily the relative effectiveness of various cyclizing reagents and the optimum conditions for maximum yield.[9]

(5) *Cf.* Johnson, Anderson and Shelberg, THIS JOURNAL, **66**, 220 (1944); Johnson and Shelberg, *ibid.*, **67**, 1745 (1945).

(6) *Cf.* Wilds and Djerassi, *ibid.*, **68**, 1715 (1946).

(7) This is in agreement with the findings of Prelog and Metzler with cyclopentanone, *Helv. Chim. Acta.*, **30**, 878 (1947).

(8) This illustrates the fact that a β-OH group results in a greater shift of the maximum for α,β-unsaturated ketones than an alkyl group [*cf.* Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942)], amounting to about 50 mμ compared to 35 mμ for an α-OH [Fieser, Fieser and Rajagopalan, *J. Org. Chem.*, **13**, 800 (1948)].

(9) Although the octalone VIII can exist in two racemic isomers which would be expected to be in equilibrium under the conditions of cyclization (due to ready shift of the double bond), only one isomer could be obtained, with no direct evidence for the presence of the other form.

Evidence confirming the structure of the octalone was obtained by dehydrogenation to 2-phenylnaphthalene (X) and 6-phenyl-2-naphthol (XI).

Experimental[10]

4-Cyclohexylcyclohexanone (I).—4-Hydroxybiphenyl was hydrogenated[11] in absolute ethanol at 140° and 2000 p. s. i. using W-6 Raney nickel catalyst[12]; the mixture of isomeric 4-cyclohexylcyclohexanols was obtained in 96% yield, m. p. in the range 80–105°. Forty grams of this mixture was dissolved in 500 ml. of glacial acetic acid and stirred at 15–18° while a solution of 30 g. of chromium trioxide in 40 ml. of water and 100 ml. of acetic acid was added slowly over a period of one hour. After an additional hour at the same temperature 50 ml. of methanol was added, the mixture allowed to stand one-half hour and then the solvent was removed under reduced pressure. The gummy residue was dissolved in dilute hydrochloric acid and ether, and the ether layer washed thoroughly with acid, dilute sodium hydroxide and water. From the ether extract was obtained 34.6 g. (87%) of the ketone, b. p. 98–100° (0.1 mm.), m. p. 30–31° (reported,[13] 31°). The semicarbazone melted at 215–216° (reported[13] 216°).

From the alkaline extract was obtained an oily acid which crystallized from ether–petroleum ether, 0.97 g. (2%), m. p. 92–93°. Further recrystallization from carbon tetrachloride did not change the m. p. of the product, evidently β-cyclohexyladipic acid. The yield of this acid was increased using higher temperatures during the oxidation.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.1; H, 8.8. Found: C, 62.9; H, 8.8.

2-Hydroxymethylene-4-cyclohexylcyclohexanone (VII).—The following modification of the general procedure of Johnson, Anderson and Shelberg,[5] employing three moles of sodium methoxide and five moles of ethyl formate per mole of ketone, gave the best yields. The sodium methoxide prepared from 4.8 g. of sodium and 50 ml. of dry methanol was freed of excess solvent, finally heating at 160° under reduced pressure for one-half hour, cooled under nitrogen, 25 ml. of dry benzene added and distilled again to dryness. The solid was broken up, suspended in 50 ml. of dry, thiophene-free benzene and stirred while 30 ml. of dry ethyl formate was added. After one-half hour at room temperature the mixture was cooled in an ice-bath, a solution of 13.0 g. of 4-cyclohexylcyclohexanone in 100 ml. of benzene was added and the ice-bath removed. To the yellow gelatinous mixture was then added 150 ml. of benzene and stirring was continued overnight at room temperature. Ice-cold water was added and the benzene layer extracted with two portions of cold 2% sodium hydroxide. After washing the combined alkaline layers with ether and acidifying, the resulting oil was extracted thoroughly with chloroform, washed and dried over sodium sulfate. The light orange oil remaining after the chloroform was removed under reduced pressure was distilled (capillary tube attached to a source of nitrogen) giving 13.1 g. (87%) of nearly colorless hydroxymethylene derivative, b. p. 114–116° (0.1 mm.).[14] Redistillation gave material, b. p. 113° (0.1 mm.), which had an absorption maximum at 281 mμ (E = 8,690).[15,16] The compound, which gave a purple color with alcoholic ferric chloride, was unstable and decomposed after a few days even when sealed in an ampule.

(10) All melting points are corrected.

(11) *Cf.* Musser and Adkins, THIS JOURNAL, **60**, 664 (1938).

(12) Adkins and Billica, *ibid.*, **70**, 695 (1948).

(13) v. Braun, *Ann.*, **472**, 60 (1929).

(14) When equivalent amounts of sodium methoxide, ethyl formate and ketone were used the yield was only 66%.

(15) Absorption spectra were determined in 95% ethanol using a Beckman quartz spectrophotometer; E = molecular extinction coefficient.

(16) There was no indication of a peak at longer wave lengths corresponding to the bis-hydroxymethylene derivative.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 75.0; H, 9.7. Found: C, 74.6; H, 9.5.

The **copper enolate**, prepared in 88% yield by shaking an ether solution of the hydroxymethylene ketone with a saturated solution of cupric acetate, was recrystallized from benzene to give clusters of fine green needles that decomposed at 228–229°.

Anal. Calcd. for $C_{26}H_{38}O_4Cu$: C, 65.3; H, 8.0; Cu, 13.3. Found: C, 65.7; H, 8.1; Cu,[17] 13.4.

The **aniline derivative** was prepared by adding 90 mg. of aniline to 100 mg. of hydroxymethylene ketone in 1 ml. of methanol. After one hour at room temperature 99 mg. (73%) of solid was obtained, m. p. 114–118°. Recrystallization from methanol gave light yellow prisms, m. p. 115–117°.

Anal. Calcd. for $C_{19}H_{25}ON$: C, 80.5; H, 8.9. Found: C, 80.5; H, 8.9.

2-Formyl-2-(γ-ketobutyl)-4-cyclohexylcyclohexanone (V).—To a solution of 1.45 g. of sodium in 50 ml. of dry methanol was added 13.07 g. of the hydroxymethylene ketone VII dissolved in 50 ml. of methanol. The solution was cooled in an ice-bath and then treated with 50 ml. of methanol containing the methiodide prepared from 18 g. of 1-diethylaminobutanone-3.[18] The solution was allowed to come to room temperature as the ice melted and after standing overnight 12.94 g. (67%) of white needles was collected, washing with methanol. This material, m. p. 121–123° (gas evol.), was found to contain one molecule of methanol even after drying at 65° (0.1 mm.) overnight; the melting point was not changed by further recrystallization.[19]

Anal. Calcd. for $C_{17}H_{26}O_3 \cdot CH_3OH$: C, 69.7; H, 9.7. Found: C, 69.7; H, 9.7.

After the above solid was filtered from the reaction mixture, the filtrate was poured into ice-cold dilute sodium hydroxide, extracted with benzene–ether, washed with cold dilute acid, water and dried over sodium sulfate. Distillation gave 4.84 g. of an oil, b. p. 140–155° (0.1 mm.), which from analysis appeared to consist of approximately two parts of VI, from which the formyl group had been eliminated (21%) to one part of V retaining the formyl group (9%), corresponding to a total yield of 97%.

Anal. Calcd. for $C_{16}H_{26}O_2$ (formyl group eliminated): C, 76.7; H, 10.5. Calcd. for $C_{17}H_{26}O_3$: C, 73.3; H, 9.4. Found: C, 75.6, 75.4; H, 10.2, 10.2.

The ratio of solid to oily product varied in different experiments. In one run using two parts methanol to one of benzene for the solvent, there resulted 7% of the solid, m. p. 112–114°, and 92% of oil, evaporatively distilling below 170° (0.1 mm.), corresponding in analysis to the solvent-free formyl derivative V.

Found: C, 73.2, 73.1; H, 9.5, 9.5.

6-Cyclohexyl-Δ^{1-9}-octalone-2 (VIII) from 2-Formyl-2-(γ-ketobutyl)-4-cyclohexanone (V). (a) Acid Cyclization.—Preliminary cyclization experiments were carried out by dissolving 100 mg. of the formyl derivative (V, containing one molecule of methanol) in 25 ml. of acetic acid, adding 5 ml. of concentrated hydrochloric acid and allowing to stand at room temperature. At intervals samples were withdrawn, evaporated under reduced pressure and the extent of cyclization determined from the ultraviolet absorption in ethanol at 239 mμ, with the following results: one hour, 45%; two hours, 59%; four hours, 70%; six and one-half hours, 80%; thirty-seven hours, 82%. At reflux, the cyclization appeared to be complete in less than one-half hour (one-half hour, 82%; one and one-half hour, 82%; two and one-half hours, 78%).

On the basis of these preliminary results, a solution of 2.0 g. of the solid formyl derivative V in 190 ml. of acetic acid was treated with 40 ml. of concentrated hydrochloric acid and allowed to stand at room temperature for sixteen hours. The solvent was then removed under reduced pressure followed by several portions of alcohol, leaving 1.55 g. of a red oil, E_{239} = 12,900 (corresponding to a 79% yield). The oil was partially crystallized from 10 ml. of petroleum ether (40–60°) by cooling with Dry Ice, giving 0.29 g., m. p. 37–39°. Evaporative distillation of the filtrate at 145° (0.1 mm.) gave 1.13 g. of colorless distillate which yielded another 0.25 g. of the solid, m. p. 34–37°. Chromatographic adsorption of the remaining oil on alumina gave in the ether–petroleum ether (1:4 and 2:3) eluates an additional 0.16 g. of solid, m. p. 36–39° and 0.097 g. of oily ketone (E_{239} = 10,700). The total yield of solid ketone was 47%. Further recrystallization yielded colorless prisms, m. p. 41.5–42.5°, with an absorption maximum at 239 mμ, E = 17,000.[15]

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.7; H, 10.4. Found: C, 82.8; H, 10.5.

The **semicarbazone**, prepared in 95% yield by the alcohol–pyridine procedure, was recrystallized from ethanol, m. p. 223–224°. The same semicarbazone was obtained whether the solid ketone or the oily filtrates were used.

Anal. Calcd. for $C_{17}H_{27}ON_3$: C, 70.6; H, 9.4. Found: C, 70.7; H, 9.2.

The **2,4-dinitrophenylhydrazone**, prepared in methanol containing a drop of hydrochloric acid, crystallized from ethyl acetate–ethanol as a red solid, m. p. 202–203°.

Anal. Calcd. for $C_{22}H_{28}O_4N_4$: C, 64.1; H, 6.8. Found: C, 63.8; H, 6.7.

In another run as above, acid cyclization of 2 g. of the solid formyl derivative gave 1.55 g. of oil (E_{239} = 12,800, indicating a 78% yield) which was converted directly to the semicarbazone. Digestion of the crude derivative (1.57 g., m. p. 210–215°) gave with hot alcohol 1.34 g., m. p. 223–224°, corresponding to a 72% yield.

(b) Alkaline Cyclization.—Preliminary experiments with 200 mg. of the solid formyl derivative V in 50 ml. of methanol and 4 ml. of water containing 2 g. of potassium hydroxide (nitrogen atmosphere), indicated alkaline cyclization to be rapid at room temperature (fifteen minutes, 55%; one hour, 84%; two and one-half hours, 90%; three and one-half hours, 88%; five hours, 81%).

On this basis, to 500 ml. of methanol through which nitrogen was bubbling was added 20 g. of potassium hydroxide in 40 ml. of water followed by 5.29 g. of the solid formyl derivative V (containing methanol). After two and one-quarter hours at room temperature the slightly yellow solution was poured into 1500 ml. of saturated sodium chloride solution and extracted with four portions of ether, washing the latter with water and drying over sodium sulfate. Removal of the solvent left 3.83 g. of light yellow oil, E_{239} = 14,400, which corresponded to an 82% yield. By crystallization from petroleum ether using Dry Ice 2.68 g. (68%) of solid, m. p. 35–37°, was obtained. Evaporative distillation of the filtrate at 165° (0.1 mm.) yielded 0.96 g. of oil. Conversion of the latter to the semicarbazone, m. p. 215–217°, indicated it contained 0.55 g. of the ketone, bringing the total yield to 82%.

A similar alkaline cyclization of 3.87 g. of the oil (found above to correspond to two parts of the formyl derivative V to one part of the derivative VI with the formyl group eliminated) gave 3.17 g. of oily ketone (E_{239} = 12,000 or 65% yield) from which 2.03 g. (59%) of the crystalline ketone, m. p. 33–36°, could be obtained.

Dehydrogenation of 6-Cyclohexyl-Δ^{1-9}-octalone-2.—A solution of 1 g. of the octalone derivative VIII in 6 ml. of *p*-cymene and 0.2 g. of 30% palladium on carbon[20] was

(17) Determined by weighing residual cupric oxide in boat after carbon–hydrogen analysis.

(18) The methiodide was prepared as described previously (ref. 4) adding the methyl iodide in small portions with cooling (vigorous reaction) and allowing each to react before adding more.

(19) When 200 mg. of the solid was heated at 150°, 17 mg. of distillate was obtained and shown to be methanol by conversion to methyl 3,5-dinitrobenzoate, m. p. 106–107°, undepressed when mixed with a known sample. That the methanol might not be merely solvent of crystallization was indicated by repeated failure to induce the solvent-free compound (see below) to crystallize from methanol.

(20) Linstead and Thomas, *J. Chem. Soc.*, 1130 (1940).

heated to reflux under nitrogen. After nineteen hours an additional 0.1 g. of catalyst was added and heating continued for a total of forty-three hours. Since only 182 ml. of hydrogen had been evolved, the mixture was filtered after diluting with benzene, evaporated and the residue heated with 0.1 g. of fresh catalyst at 320° for one hour (260 ml. of hydrogen evolved). The product was dissolved in ether and extracted with several portions of 10% potassium hydroxide. The residue from the ether was evaporatively distilled at 160° (0.1 mm.) and crystallized from methanol to give 0.04 g. (5%) of **2-phenylnaphthalene (X)**, m. p. 96–98°. The m. p. was raised to 101–102° by further recrystallization (reported,[21] 101.5°). From the alkaline extracts after evaporative distillation at 150–165° (0.1 mm.) and crystallization from benzene was obtained 0.27 g. (28%) of **6-phenyl-2-naphthol (XI)**, m. p. 176–177°. Recrystallization from benzene raised the m. p. to 177–178° (reported,[22] 175–176°).

Anal. Calcd. for $C_{16}H_{12}O$: C, 87.2; H, 5.5. Found: C, 87.1; H, 5.3.

The **methyl ether of 6-phenyl-2-naphthol**, prepared with alkali and methyl sulfate and recrystallized from methanol, melted at 148–149° (reported,[22] 148°).

2-Methoxalyl-4-cyclohexylcyclohexanone (II).—To the methanol-free sodium methoxide prepared from 0.86 g. of sodium was added 30 ml. of dry benzene and 4.4 g. of dimethyl oxalate. The mixture was refluxed for ten minutes under nitrogen with stirring, then cooled in an ice-bath and 6.72 g. of 4-cyclohexylcyclohexanone (I) added in 20 ml. of benzene. After standing at room temperature for one and one-half hours, the light orange solution was extracted with three portions of ice-cold 2% sodium hydroxide, the latter acidified and extracted with ether. The ether extract was washed with sodium bicarbonate solution, water, dried over sodium sulfate and evaporated, leaving 6.0 g. (60%) of a light yellow oil which gave a purple color with alcoholic ferric chloride solution.

One gram of this oil in 10 ml. of ether gave 0.66 g. (59%) of the green **copper enolate derivative** (dec. at 220–222°). Recrystallization from benzene raised the decomposition point to 224–225°.

Anal. Calcd. for $C_{30}H_{42}O_6Cu$: C, 60.6; H, 7.1; Cu, 10.7. Found: C, 60.5; H, 7.1; Cu,[17] 10.6.

From the bicarbonate extract of the crude glyoxylate was obtained 1.3 g. of a viscous red oil from which was crystallized 0.28 g. of a solid, m. p. 110–114°, using carbon tetrachloride–petroleum ether. Triturating this solid with hot benzene and filtering gave 0.03 g. of material m. p. 213–215°.[23] From the filtrate was obtained 0.19 g. of a different compound, m. p. 115–116°. Recrystallization of the lower melting compound from benzene did not change its melting point. The analysis of compound, which gave a red color with alcoholic ferric chloride, indicated it to be the free glyoxylic acid derivative (corresponding to II).

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.6; H, 8.0. Found: C, 66.3; H, 8.1.

2-Carbomethoxy-4-cyclohexylcyclohexanone (III).—A 11.4-g. sample of the 2-methoxalyl derivative II, not purified by extraction with bicarbonate, was heated at 180° with 10 g. of powdered soft glass for thirty minutes. The red oil was dissolved in ether and extracted with cold dilute sodium hydroxide. From the ether after washing and drying was obtained 6.3 g. of a red oil from which was obtained 4.85 g. (48%) of colorless distillate boiling below 140° (0.5 mm.). Redistillation gave 1.2 g., b. p. 84–90° (0.1 mm.), which proved to be largely 4-cyclohexylcyclohexanone, 1.1 g., b. p. 90–115° (0.1 mm.), and 2.3 g. (23%) of the carbomethoxy derivative, b. p. 115–118° (0.1 mm.), or b. p. 134° (0.6 mm.).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.6; H, 9.3. Found: C, 70.9; H, 9.2.

When methoxalyl derivative which had been washed with bicarbonate was employed, 37% of crude material distilling below 160° (0.5 mm.) was obtained.

The **pyrazolone derivative, 5-cyclohexyl-4,5,6,7-tetrahydro-3-indazolone** was prepared by heating 1.0 g. of the crude undistilled oil with 0.8 g. of hydrazine sulfate, 1 ml. of pyridine and 10 ml. of methanol for four hours. Treatment with water and ether yielded 0.44 g. of white solid, m. p. 234–238°. Recrystallization of the derivative from ethyl acetate–acetic acid raised the m. p. to 239–243°.

Anal. Calcd. for $C_{13}H_{20}ON_2$: C, 70.9; H, 9.2. Found: C, 70.9; H, 9.2.

2-Carbomethoxy-2-(γ-ketobutyl)-4-cyclohexylcyclohexanone (IV).—To 0.23 g. of sodium dissolved in 10 ml. of methanol was added 2.4 g. of the 2-carbomethoxy derivative III in 10 ml. of benzene. After refluxing for ten minutes the solution was cooled in ice and a solution of the methiodide from 2.90 g. of 1-diethylaminobutanone-3 in 10 ml. of methanol was added. After standing overnight at room temperature and refluxing for one hour, the cooled mixture was diluted with water and extracted with ether, washing the latter with dilute acid and drying over sodium sulfate. The oil (2.90 g.) remaining after removal of the solvent solidified after standing for three months. Recrystallization from ether–petroleum ether (40–60°) gave colorless platelets, m. p. 74–75°.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.1; H, 9.2. Found: C, 70.3; H, 8.9.

10-Carbomethoxy-6-cyclohexyl-Δ^{1-9}-octalone-2 (IX).—To a solution of 250 mg. of sodium in 25 ml. of methanol was added 149 mg. of the above oily 2-carbomethoxy diketone IV, and the mixture was refluxed under nitrogen for two hours, cooled, diluted with water and extracted with benzene-ether. From the washed and dried extract was obtained a yellow oil which was evaporatively distilled at 165° (0.05 mm.) giving 86 mg. of oil which yielded 24 mg. (17%) of colorless needles, m. p. 110–111°. Recrystallization from methanol did not raise the m. p.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.4; H, 9.0. Found: C, 74.4; H, 8.9.

The **semicarbazone** was prepared by the alcohol-pyridine procedure and recrystallized from chloroform–methanol, m. p. 204–206°.

Anal. Calcd. for $C_{19}H_{29}O_3N_3$: C, 65.7; H, 8.4. Found: C, 65.3; H, 8.6.

6-Cyclohexyl-Δ^{1-9}-octalone-2 (VIII) from 2-Carbomethoxy-2-(γ-ketobutyl)-4-cyclohexylcyclohexanone (IV).—Alkaline cyclization[24] of 250 mg. of the oily carbomethoxy derivative IV was carried out by refluxing and stirring under nitrogen with 25 ml. of 5% aqueous potassium hydroxide for twenty hours. After isolation and evaporative distillation at 165° (0.1 mm.), 110 mg. of distillate was obtained which yielded 113 mg. of crude semicarbazone of the octalone derivative, m. p. 209–211°, mixed m. p. 210–213°. This corresponds to a 48% yield.

Acid cyclization[24] of 270 mg. of the carbomethoxy derivative IV by heating at reflux for twenty hours with 25 ml. of acetic acid and 5 ml. of hydrochloric acid gave 220 mg. of oily octalone after evaporative distillation.

When 2.0 g. of the 2-methoxalyl derivative II was allowed to react with the methiodide of 1-diethylaminobutanone-3 and a 240-mg. portion of the product (1.67 g. of neutral oil) cyclized[24] by refluxing with 25 ml. of methanol containing 2.5 ml. of 45% potassium hydroxide for four hours, 60 mg. of evaporatively distilled, oily octalone derivative VIII was obtained, which yielded 39

(21) Chattaway and Lewis, *J. Chem. Soc.*, **65**, 872 (1894).

(22) Hey and Lawton, *J. Chem. Soc.*, 383 (1940).

(23) Recrystallization of this higher melting compound from acetone–benzene raised the m. p. to 214–215°. The compound gave an orange color with alcoholic ferric chloride; from the analysis it is suggested, tentatively, that it may be 5-phenyl-2-ketosuberic acid, arising from a trace of 4-phenylcyclohexanone in the starting ketone. Calcd. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.1. Found: C, 63.6; H, 6.2.

(24) These undoubtedly are not the best conditions for cyclization.

mg. of semicarbazone, m. p. 219–221° (mixed m. p. undepressed), and 22 mg., m. p. 185–190°. The total amount of crude semicarbazone corresponded to a 12–20% over-all yield.

Summary

6-Cyclohexyl-Δ^{1-9}-octalone-2 (VIII) has been prepared from 4-cyclohexylcyclohexanone by the Robinson–Mannich base synthesis. The use of hydroxymethylene ketones in this synthesis has been found to be advantageous, with over-all yields of 60–65% in this example.

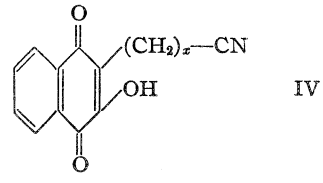
MADISON 6, WISCONSIN RECEIVED JULY 1, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of 2-Alkyl-3-hydroxy-1,4-naphthoquinones with Oxygenated Side Chains[1]

BY DONALD J. CRAM[2]

The syntheses and testing of a large number of naphthoquinones[3] as antimalarials has shown that the potency of the drug is a function of the lipophilic character of the molecule, and that resistance to metabolic degradation of the side chain is dependent on the presence of oxygen in the side chain. The present study is concerned with the development of methods of synthesis of 2-alkyl-3-hydroxy-1,4-naphthoquinones of structures I, II and III, in which x, y and z can be varied independently. Such methods would permit a systematic approach to the balance of lipophilic character of the quinone against resistance to metabolic degradation of the molecule, these two variables working in opposition to each other.



IV

The synthesis of IV ($x = 10$) by Fieser, *et al.*,[4] suggested the approach to the problem which has been worked out in the following fashion. Treatment of reductively acetylated nitrile quinones (V) with Grignard reagents produced ketones (I) in which x and y could be varied independently: x, by either starting with different nitriles or by applying the Hooker oxidation[5] to the ketones themselves; y, by using Grignard reagents prepared from different alkyl halides. The ketones were reductively acetylated and the ketonic group of the side chain reduced with aluminum isopropoxide to produce II, in which x could be reduced one unit at a time through the Hooker oxidation. Alternately, the reductively acetylated ketones were treated with Grignard reagents of varying types to produce tertiary alcohols of type III.

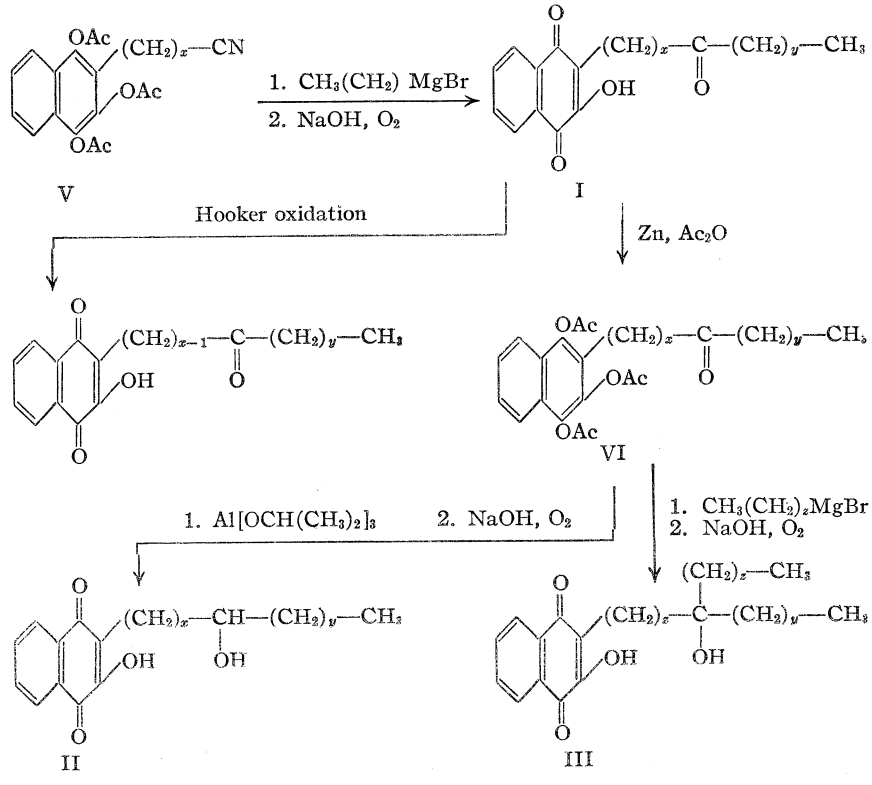


Table I records the physical properties and analytical data obtained for the new compounds that were prepared as well as a reference to the procedure employed (typical procedures are given in the experimental section). All of the quinones were prepared from compound of type IV as a

(1) This problem was assigned to the author by Louis F. Fieser.

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(3) Fieser, *et al.*, THIS JOURNAL, **70**, 3151–3244 (1948).

(4) Fieser, *et al.*, *ibid.*, **70**, 3208 (1948).

(5) Fieser, *et al.*, *ibid.*, **70**, 3215 (1948).

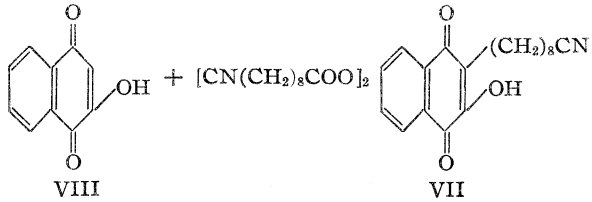
TABLE I

2-ALKYL-3-HYDROXY-1,4-NAPHTHOQUINONES AND DERIVATIVES

Compound		Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
IV	$x = 8$	A	55	100–101	$C_{19}H_{21}O_3N$	73.29	6.80	73.44	6.74
IV[4]	$x = 10$	A	51	96–97	.....	...	..	...	..
V	$x = 8$	B	46	98–99	$C_{25}H_{29}O_6N$	68.32	6.65	68.62	6.47
V	$x = 10$	B	89	101	$C_{27}H_{33}O_6N$	69.36	7.11	69.48	6.95
I	$x = 8, y = 7$	C[a]	72	106–107	$C_{27}H_{38}O_4$	76.02	8.98	76.30	8.72
I	$x = 9, y = 0$	D	54	108–109	$C_{21}H_{26}O_4$	73.65	7.65	73.39	7.85
I	$x = 9, y = 7$	D	68	108–109	$C_{28}H_{40}O_4$	76.32	9.15	76.42	8.90
I	$x = 10, y = 0$	C	72	105–106	$C_{22}H_{28}O_4$	74.13	7.92	74.36	8.36
I	$x = 10, y = 1$	C	73	104–105	$C_{23}H_{30}O_4$	74.55	8.16	74.36	8.42
I	$x = 10, y = 2$	C	82	103–104	$C_{24}H_{32}O_4$	74.96	8.39	74.76	8.15
I	$x = 10, y = 3$	C	87	91–92	$C_{25}H_{34}O_4$	75.35	8.59	75.10	8.80
I	$x = 10, y = 7$	C	75	107–108	$C_{32}H_{42}O_4$	76.61	9.31	76.91	9.38
VI	$x = 8, y = 7$	B	81	81–82	$C_{33}H_{46}O_7$	71.71	8.39	71.70	8.46
VI	$x = 9, y = 0$	B	84	73–74	$C_{27}H_{34}O_7$	68.92	7.28	69.51	7.53
VI	$x = 10, y = 7$	B	92	79–80	$C_{35}H_{50}O_7$	72.13	8.65	72.07	8.42
II	$x = 8, y = 7$	E	88	95–96	$C_{27}H_{40}O_4$	75.66	9.41	75.52	8.33
II	$x = 9, y = 7$	D	25	109–110	$C_{28}H_{42}O_4$	75.97	9.56	76.25	9.86
II	$x = 10, y = 7$	E	86	95–96	$C_{29}H_{44}O_4$	76.27	9.71	76.37	9.91
III	$x = 8, y = 7, z = 0$	F	92	Oil	$C_{28}H_{42}O_4$	75.97	9.56	76.02	9.60
III	$x = 9, y = 7, z = 0$	F[b]	90	Oil	$C_{29}H_{44}O_4$	76.27	9.76	76.39	9.78
III	$x = 10, y = 7, z = 0$	F	93	Oil	$C_{30}H_{46}O_4$	76.55	9.85	76.37	9.91

[a] Also prepared by D, yield 53%, m. p. 106–107°. [b] Prepared by the action of octylmagnesium bromide on VI, $x = 9, y = 0$.

primary starting material. Compound VII was synthesized by methods analogous to the preparation of IV ($x = 10$).[4] The compound 9-amidononanoic acid,[6] was dehydrated and the product hydrolysed to give 9-cyanononanoic acid. This substance was converted to its solid peroxide (VIII), which was used to alkylate lawsone by procedures that have been developed by Fieser, *et al.*[3]



VIII VII

Experimental

9-Cyanononanoic Acid.—A mixture of 50 g. of the ethyl ester[6] of 9-amidononanoic acid and 25 g. of phosphorus pentachloride were heated at 100° under reduced pressure for one-half hour. The liquid was cooled, dissolved in benzene, and the solution was washed first with water, then with sodium carbonate solution, and again with water. The organic layer was dried, and evaporated under reduced pressure to an oil, which was dissolved in 245 cc. of a 0.78 *N* barium hydroxide solution in methanol; the mixture was allowed to stand for fifteen hours. The barium salt was then collected, dissolved in a minimum amount of water, and acidified with an excess of acetic acid. The product was crystallized from an ether–petroleum ether mixture; yield of half acid, 26 g., m. p. 49–50°. The melting point did not change on recrystallization.

Anal. Calcd. for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35. Found: C, 65.72; H, 9.22.

(6) This substance was prepared according to the procedure of Flaschentrager, *Z. physiol. Chem.*, **159**, 297–308 (1926).

2-(8′-Cyanoöctyl)-3-hydroxy-1,4-naphthoquinone (Procedure A).—A solution of 72 g. of 9-cyanononanoic acid, 70 g. of thionyl chloride (Eastman White Label), and two drops of pyridine in 300 cc. of dry ether was refluxed for three hours. The solution was evaporated to an oil under reduced pressure. Dry ether (300 cc.) was added to the oil, and the mixture was again evaporated to an oil, which was dissolved in 300 cc. of dry ether, treated with 10 g. of Darco and filtered.

The filtrate was cooled to −15°, and to the chilled solution, 97 g. of a cold solution of 33% hydrogen peroxide was added. The temperature was again brought to −15°, and a solution of 34 g. of sodium hydroxide in 165 cc. of water was added at such a rate that the temperature of the stirred mixture never went above −5°. When the addition was complete, the mixture was stirred for one-half hour at −10°, and the white solid that separated was collected, washed with cold water, and pressed as dry as possible. This substance was dissolved in a minimum amount of chloroform, the solution dried with magnesium sulfate and filtered. The filtrate was evaporated to one-third of the original volume, and five volumes of low-boiling petroleum ether was added. The peroxide that separated was dried (45 g.).

The peroxide was mixed with 23 g. of lawsone and 450 cc. of glacial acetic acid, and the mixture was heated to 95° for two hours. The solvent was then evaporated under reduced pressure, and the residue was dissolved in ether. The ether solution was washed first with a solution of sodium bicarbonate, then with water, and the quinone was extracted into a 2% sodium hydroxide solution, which was washed with petroleum ether and acidified. Crystallization of the quinone that separated (glacial acetic acid) produced 22.5 g. of yellow needles, m. p. 99–100°. The substance formed yellow staffs, m. p. 100–101°, when crystallized from ethanol.

This quinone formed a red color in alkaline solution (addition of sodium hydrosulfite dispelled the color), and a red-orange color in a solution of concentrated sulfuric acid.

2-(10′-Cyanodecyl)-1,3,4-triacetoxynaphthalene (Procedure B).—A mixture of 22.5 g. of 2-(10′-cyanodecyl)-3-hydroxy-1,4-naphthoquinone, 22.5 g. of zinc dust,

135 cc. of acetic anhydride and two drops of triethylamine were mixed, and allowed to stand for two days at room temperature. The mixture was warmed to 50°, filtered, and the cake was washed with boiling acetic acid. To the combined filtrates was added enough water to decompose the excess acetic anhydride, the mixture was cooled, and the product was crystallized; 27.5 g. of hard white granules, m. p. 101°.

2-(11′-Ketononadecyl)-3-hydroxy-1,4-naphthoquinone (Procedure C).—Octylmagnesium bromide Grignard reagent was made in the usual way from 21.2 g. of magnesium turnings, 170 g. of octyl bromide, and 300 cc. of dry ether. To this mixture, stirred in an atmosphere of nitrogen, 27.5 g. of 2-(10′-cyanodecyl)-1,3,4-triacetoxynaphthalene (dissolved in 300 cc. of dry benzene) was added over a period of one-half hour. Ether was distilled from the reaction mixture until the volume had dropped to 400 cc. and the solution was refluxed for three hours, cooled, and poured into a mixture of ice and 50% hydrochloric acid. The two layers were well mixed, separated, and the ether–benzene layer was extracted with a sodium hydroxide-saturated solution of 50% methanol and water. The aqueous layer was washed with petroleum ether, and an excess of brine was added. The sodium salt that separated was collected, washed with water and suspended in glacial acetic acid; 20 g. of canary-yellow needles separated: m. p. 107–108°. Further crystallization of the quinone did not alter the melting point. The color reactions of this substance are identical with those of other 2-alkyl-3-hydroxy-1,4-naphthoquinones.

2-(10′-Ketoöctadecyl)-3-hydroxy-1,4-naphthoquinone (Procedure D).—This procedure is modeled after that developed by Fieser[5] as an improvement of the Hooker reaction.

A solution of 1.2 g. of sodium carbonate in 25 cc. of water was mixed with 50 cc. of dioxane, the solution was warmed to 70°, and 4.54 g. of 2-(11′-ketononadecyl)-3-hydroxy-1,4-naphthoquinone was added. Nitrogen was swept over the surface of the liquid, and after five minutes, 2 cc. of a 33% solution of hydrogen peroxide was added. The solution was held at 70° with nitrogen sweeping over the surface until it turned colorless. The solution was then cooled, acidified with 30% hydrochloric acid (3 cc.), mixed with 3 cc. of water saturated with sulfur dioxide, and the excess sulfur dioxide was removed by bubbling nitrogen through the mixture. Ethanol (100 cc.), 35 cc. of 25% sodium hydroxide solution, and 10 g. of cupric sulfate dissolved in 50 cc. of water were added. This mixture was stirred for one hour, heated to 60° for ten minutes, filtered and acidified with acetic acid. The product was crystallized twice from glacial acetic acid; 3.0 g. (fine canary-yellow needles), m. p. 108–109°.

2-(11′-Hydroxynonadecyl)-3-hydroxy-1,4-naphthoquinone (Procedure E).—To a solution (130 cc.) of 1 *M* aluminum isopropoxide through which nitrogen was bubbling, 13 g. of 2-(11′-ketononadecyl)-1,3,4-triacetoxynaphthalene was added. The solution was heated to the boiling point and then slowly fractionated through a short column. Both acetone and isopropyl acetate, as well as some isopropyl alcohol, distilled. A total of 50 cc. of distillate was collected in a period of six hours. At the end of that time the solution in the flask was cooled, and poured into a mixture of 35 cc. of concentrated hydrochloric acid, 100 cc. of water and 100 g. of ice. After the aluminum salt had decomposed, the mixture was extracted with 150 cc. of ether, and the ether layer was washed with water. To the ether layer, 100 cc. of a 50% ethanol–water mixture saturated with sodium hydroxide was then added. Oxygen was bubbled through the solution for one-half hour, an excess of glacial acetic acid was added, and the product that separated was crystallized (glacial acetic acid); 8.7 g. (86% yield) of fine yellow needles of product was obtained; m. p. 95–96°. Further recrystallization of the compound did not alter the melting point. The color reactions of the substance are the same as those of other 2-alkyl-3-hydroxy-1,4-naphthoquinones.

2-(9′-Hydroxy-9′-methylheptadecyl)-3-hydroxy-1,4-naphthoquinone (Procedure F).—The methyl Grignard reagent was prepared in the usual way from 2 g. of magnesium turnings, 12 g. of methyl iodide and 200 cc. of dry ether. To this solution (stirred in an atmosphere of nitrogen), 3 g. of 2-(9′-ketoheptadecyl)-1,3,4-triacetoxynaphthalene dissolved in 200 cc. of dry benzene was added over a period of one-half hour. The mixture was refluxed for four hours, cooled and poured slowly into a mixture of saturated ammonium chloride solution and ice. The two layers were well shaken, and the ether–benzene layer was washed with dilute alkaline solution. The ether–benzene solution was then extracted with several portions of a 65% ethanol–water mixture saturated with sodium carbonate. The extracts were combined and washed three times with low-boiling petroleum ether. To this alkaline solution was then added two volumes of brine, and the quinone was extracted into pure ethyl ether. The ether layer was washed twice with distilled water, then with two portions of 5% sulfuric acid solution, and finally with four portions of distilled water. The solution was dried thoroughly with magnesium sulfate and filtered through hard paper into a weighed flask. The ether was evaporated under reduced pressure, and the last traces of solvent were removed by heating the oil under 1 mm. of pressure at 50° for three hours. The product (2.2 g.) was obtained in the form of a viscous yellow-orange oil. The color reactions of this compound are the same as those of other 2-alkyl-3-hydroxy-1,4-naphthoquinones.

Acknowledgment.—The author is indebted to Dr. L. F. Fieser for many suggestions regarding this problem.

Summary

Procedures have been developed for the preparation of 2-alkyl-3-hydroxy-1,4-naphthoquinones in which ketonic carbonyl groups, and secondary and tertiary hydroxyl groups can be placed in the alkyl side chains in any desired position, the alkyl side chains being of any desired length.

LOS ANGELES, CALIFORNIA RECEIVED MARCH 26, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

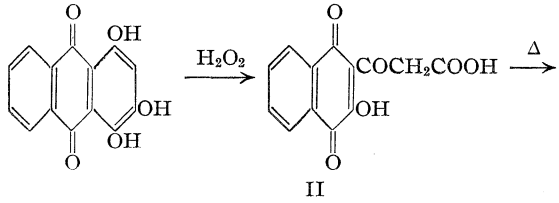
Preparation and Reactions of 2-Acyl-3-hydroxy-1,4-naphthoquinones[1]

BY DONALD J. CRAM[2]

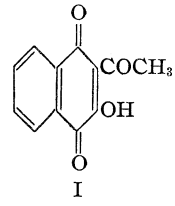
The growing importance of quinones as compounds of pharmaceutical and biological interest stimulated the present investigation of the preparation and reactions of 2-acyl-3-hydroxy-1,4-naphthoquinones. These substances, as well as compounds from which they are prepared, offer starting points from which a large variety of other quinones can be prepared, and the polyfunctional character of these substances has led in some cases to unexpected and interesting chemical reactions.

After the present study had been completed, several methods of synthesis of this type of compound were reported.[3] Previous to this work, only the simplest member, 2-acetyl-3-hydroxy-1,4-naphthoquinone (I), was known and had been prepared by the oxidation of purpurin.[4]

Repetition of the oxidation of purpurin resulted in a small yield of quinone I, as well as one of the precursors of this substance, the acid, II, which was converted to I through the action of heat.



II



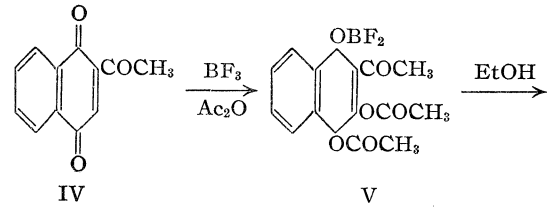
I

Treatment of 1,2,4-triacetoxynaphthalene with aluminum chloride resulted in a small yield of 2-acetyl-3-acetoxy-1,4-naphthohydroquinone (III), whose structure was demonstrated by synthesis from I. The hydroxyl group in I was acetylated by treatment of the silver salt with acetyl chloride to give 2-acetyl-3-acetoxy-1,4-naphthoquinone, reduction of which produced III. Compound III was also produced by reduction of I to 2-acetyl-3-hydroxy-1,4-naphthohydroquinone, which in turn was partially acetylated to give III. Further acetylation of III as well as the reductive acetylation of I produced 2-acetyl-1,3,4-triacetoxynaphthalene.

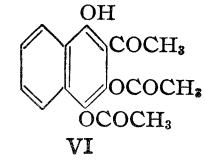
A Fries rearrangement of 1,4-diacetoxynaphthalene resulted in a poor yield of 2-acetyl-4-acetoxy-1-naphthol, which was also synthesized by the reduction of 2-acetyl-1,4-naphthoquinone[5] (IV) and partial acetylation of the product. Complete acetylation of 2-acetyl-4-acetoxy-1-naphthol produced 2-acetyl-1,4-diacetoxynaphthalene, which was also obtained by the reductive acetylation of 2-acetyl-1,4-naphthoquinone.

The most generally applicable approach to the synthesis of 2-acyl-3-hydroxy-1,4-naphthoquinones is illustrated by the following series of reactions. The compound 2-acetyl-4-acetylamino-1-naphthol[6] was oxidized with concentrated nitric acid in glacial acetic acid solution to produce good yields of 2-acetyl-1,4-naphthoquinone (IV).[7] An attempt was made to introduce a hydroxyl group into quinone IV by oxidation with hydrogen peroxide, but the oxide was obtained in only poor yields.

A new and general procedure for the introduction of a hydroxyl group into the 3-position of 2-acyl-1,4-naphthoquinones has been developed. When IV was subjected to a modified Thiele[8] reaction (boron trifluoride etherate as catalyst), the boron fluoride containing compound V separated from the reaction mixture, and was converted



IV V



VI

with boiling ethanol into VI. The structure of this diacetate was demonstrated in the following manner. Acetylation of 2-acetyl-3-acetoxy-1,4-naphthohydroquinone under mild conditions pro-

(1) This problem was assigned to the author by Dr. Louis F. Fieser.

(2) National Research Predoctoral Fellow, 1946–1947; present address: Department of Chemistry, University of California at Los Angeles, California.

(3) Spruit, *Rec. trav. chim.*, **66**, 655–672 (1947).

(4) Dimroth and Schultz, *Ann.*, **411**, 343 (1916); see also Kuhn and Wallenfels, *Ber.*, **74**, 1594 (1941).

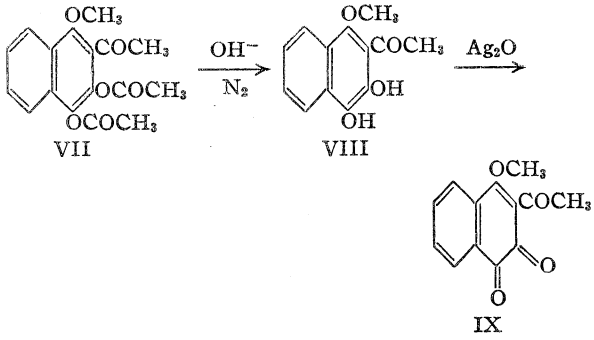
(5) The preparation of this substance is described further on in the investigation.

(6) Friedlaender, *Ber.*, **28**, 1950 (1895).

(7) This substance was obtained by Friedlaender[6] by the oxidation of 2-acetyl-4-amino-1-naphthol with ferric chloride, but the yield was poor and the product difficult to purify.

(8) This reaction has been used with sulfuric acid as catalyst for the conversion of naphthoquinone to 1,2,4-triacetoxynaphthalene [Thiele and Winter, *Ann.*, **311**, 347 (1900)], and more recently Fieser [THIS JOURNAL, **70**, 3165 (1948)] employed boron trifluoride as catalyst.

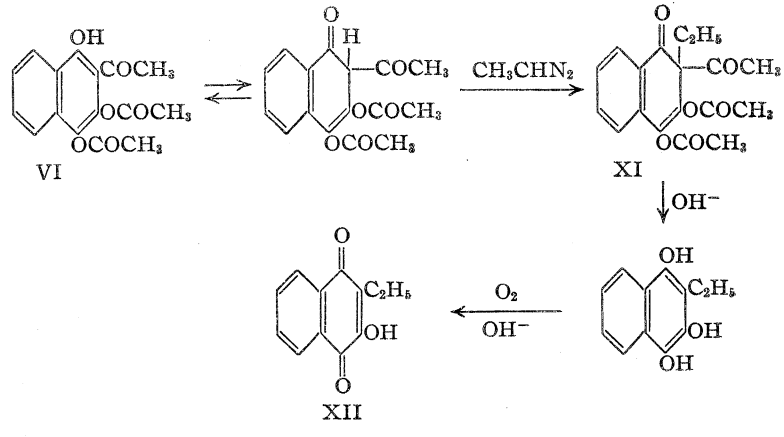
duced VI, indicating that one of the acetoxyl groups of the diacetate is in the 3-position. Methylation of VI with either dimethyl sulfate and sodium carbonate or diazomethane produced a monomethylated diacetate VII, which when hydrolyzed under carefully controlled conditions produced VIII. This substance was oxidized with silver oxide under anhydrous conditions (dry ether) to the *o*-quinone IX. Although unstable to acid or base, IX reacted with *o*-phenylenediamine to yield a diazine X.



Condensation of I with *o*-phenylenediamine produced an azine, which on methylation yielded X.

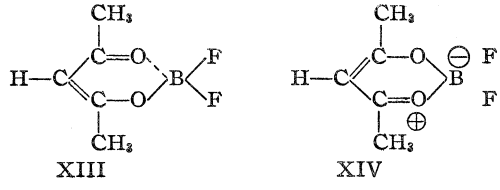
The above series of reactions proves that the diacetate VI contains two acetoxyl groups in the 3- and 4-positions and a free hydroxyl group in the 1-position.

It is interesting to note that on treating VI with diazoethane, carbon alkylation occurred to give XI, possibly *via* the ketonic tautomer of VI. The structure of XI was demonstrated by hydrolysis and oxidation to 2-ethyl-3-hydroxy-1,4-naphthoquinone (XII) which was shown to be identical with an authentic sample.[9]

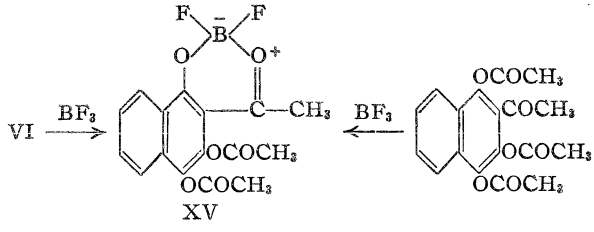


The structure of the boron fluoride containing compound V was established in the following way. The analytical values for carbon and hydrogen were high, probably owing to the passage of volatile boron fluoride compounds into the absorption train. Therefore, a method of fluorine analysis was developed, based on the conversion of fluorine to fluoride ion by fusion of the compound with alkali, and determination of the ion by the usual procedure.[10]

The analysis indicated that V contained a BF_2-group in place of a proton. There are several cases in the literature where a BF_2-group replaced a phenolic or enolic hydrogen. Morgan, *et al.*,[11] and Sugden, *et al.*,[12] prepared the boron difluoride derivative of acetylacetone by the addition of boron trifluoride to a solution of acetylacetone in benzene. The former authors assigned structure XIII to the compound, whereas the latter authors, on the basis of parachor determinations, advanced the structure XIV.



By analogy with the above observations the structure of the boron-difluoride-containing product of the Thiele reaction (V) was assigned the dipolar structure XV, which is preferred over the



alternate non-polar structure because of the strong electrophilic character of the boron atom, and because of the resonance of stabilization inherent in the dipolar form, and because of the energy gained by the formation of a new bond. Compound XV was also prepared by the addition of boron trifluoride to VI or to 2-acetyl-1,-3,4-triacetoxynaphthalene. The identity of the products of the three methods of preparation of XV was proved by (a) fluorine analysis, (b) decomposition points and (c) ultraviolet absorption spectra comparisons. To prove that the acetoxyl groups in the 3- and 4-positions of XV were not involved in the fixation of the BF_2-groups in the molecule, 2-acetyl-1-naphthol was allowed to react with boron trifluoride etherate in glacial acetic acid solution to give a com-

(9) S. C. Hooker, THIS JOURNAL, **58**, 1174 (1936).

(10) See Scott, "Standard Method of Chemical Analysis," fifth edition, Vol. I, D. Van Nostrand Co., Inc., New York, N. Y., 1939, p. 405.

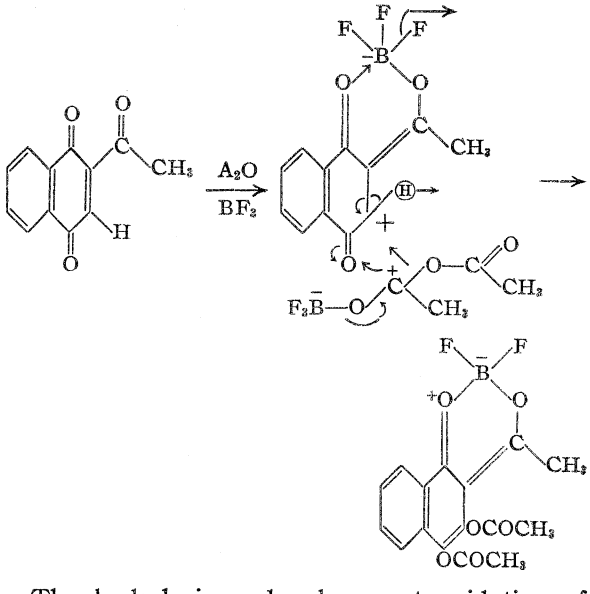
(11) Morgan and Tunstall, *J. Chem. Soc.*, **124**, 1965 (1924).

(12) Sugden, *J. Chem. Soc.*, 321 (1929); Sugden and Waloff, *J. Chem. Soc.*, 1492–1497 (1932).

pound containing a boron difluoride group in place of a hydrogen. Treatment of this substance with warm ethanol produced starting material.

Figure 1 records the ultraviolet absorption spectra of 2-acetyl-1-naphthol and its boron difluoride derivative, and Fig. 2 records the ultraviolet absorption spectra of VI and its boron difluoride derivative, XV. Examination of these spectra indicates a marked similarity between all four curves.

The elucidation of the structure of V demonstrates that 2-acyl-1,4-naphthoquinones undergo a modified Thiele reaction to give not the expected triacetate but a diacetate containing a BF_2-group on the phenolic oxygen in the 1-position. Although 1,4-naphthoquinone undergoes the normal Thiele reaction, 2-methyl-1,4-naphthoquinone does not. This fact suggests that the addition of acetic anhydride to quinone IV is a reaction involving the acetyl group in the side-chain. A possible mechanism for the reaction is presented.



The hydrolysis and subsequent oxidation of diacetate VI was carried out by procedures developed by Fieser,[13] and quinone I was the final product.

The procedures discussed above proved to be general, and were used in the present investigation for the preparation of 2-(4′-cyclohexylbutyryl)-3-hydroxy-1,4-naphthoquinone and 2-(3′-phenylpropionyl)-3-hydroxy-1,4-naphthoquinone. The substance, 2-benzalacetyl-3-hydroxy-1,4-naphthoquonine, was prepared through the base catalyzed condensation of 2-acetyl-3-hydroxy-1,4-naphthoquinone with benzaldehyde.

When compound VI was treated with a large excess of cetyl magnesium bromide in benzene solution, the two acetoxyl groups were cleaved, and the acetyl group reacted normally with the

(13) L. F. Fieser, THIS JOURNAL, **70**, 3174 (1948).

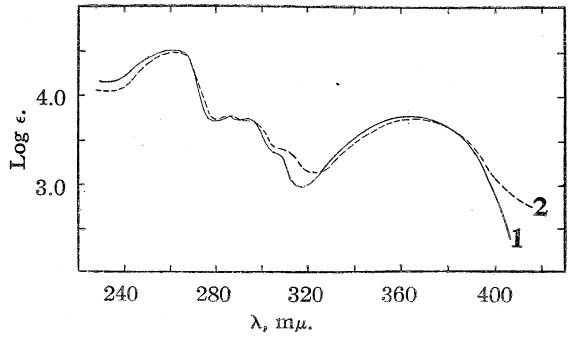


Fig. 1.—The ultraviolet absorption spectra (Beckman quartz spectrophotometer) in dioxane of: 2-acetyl-1-naphthol, curve 1; and the boron difluoride derivative of 2-acetyl-1-naphthol, curve 2.

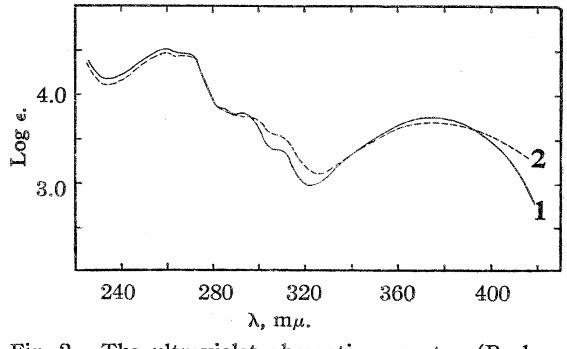
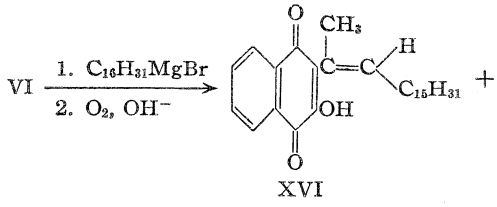
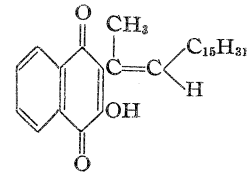


Fig. 2.—The ultraviolet absorption spectra (Beckman quartz spectrophotometer) in dioxane of: 2-acetyl-3,4-diacetoxy-1-naphthol, curve 1; and the boron difluoride derivative of 2-acetyl-3,4-diacetoxy-1-naphthol, curve 2.

Grignard reagent. When the reaction mixture was decomposed, the tertiary alcohol lost a molecule of water, and the product proved to be a mixture of *cis* and *trans* isomers, XVI and XVII.



XVI

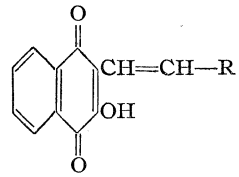


XVII

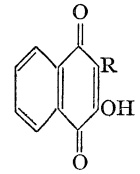
Each isomer was converted into a mixture of the two isomers when heated at 120° for half an hour. The structures of the two compounds were confirmed by oxidation to palmitic aldehyde which was identified as the *p*-nitrophenylhydrazone.

Quinones of structure XVIII give a purple color in alkaline solution, and compounds of structure XIX produce a red color.[9] Compounds

XVI and XVII both give a red color in alkaline solution.



XVIII



XIX

The steric inhibition of resonance implicit in structures XVI and XVII (the bulk of the methyl and methylene groups of the side-chain forbid coplanarity) provides an explanation for the similarity of the color reactions of these molecules and XIX.

Careful examination of Fisher–Hershfelder models of XVI indicates that the planar configuration of this molecule involves interference between the bulk of the C_{15} side-chain and the hydroxyl group in the 3-position, whereas this particular interference is absent in XVII. Determinations of the ultraviolet absorption spectra of the two isomers show that the positions of the maxima and minima as well as the extinction coefficients are all comparable, except for the maxima that occur at the longest wave length. The isomer melting at 91–92° has a maximum at 405 mμ, whereas the isomer melting at 82° has a maximum at 395 mμ. Since the isomer that presents the lesser hindrance to coplanarity of the two unsaturated systems should absorb light at the longer wave length, and since models indicate that configuration XVII gives less hindrance to coplanarity than XVI, formula XVII is assigned to the isomer melting at 91–92°, and XVI to the isomer melting at 82°.

Table I records the wave lengths and logarithms of the molecular extinction coefficients of the maxima and minima of the ultraviolet absorption spectra of isomers XVI and XVII in ethanol.

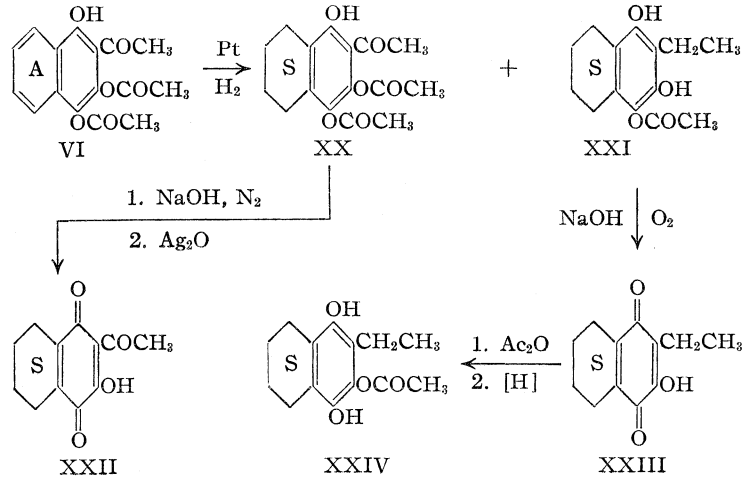
TABLE I

ULTRAVIOLET ABSORPTION SPECTRA DATA PERTAINING TO THE GEOMETRIC ISOMERS, XVI AND XVII (BECKMAN QUARTZ SPECTROPHOTOMETER) IN ETHANOL

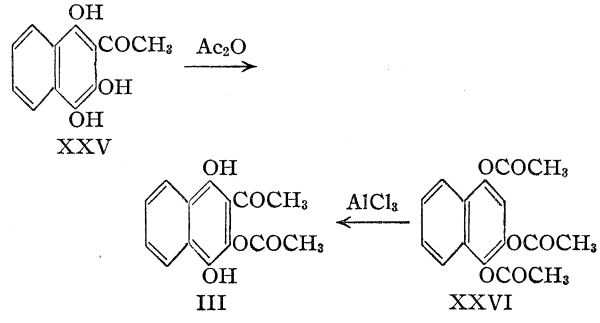
Max. mμ	Max. log ε	Min. mμ	Min. log ε	Max. mμ	Max. log ε	Min. mμ	Min. log ε
Isomer XVI, m. p. 82°				Isomer XVII, m. p. 91–92°			
252	4.265	232	3.990	254	4.228	232	4.026
276	4.236	266	4.138	274	4.204	262	4.187
330	3.452	308	3.360	330	3.424	312	3.397
395	3.148	370	3.116	405	3.193	368	3.110

In an attempt to reduce the ketone in the side-chain of VI to the corresponding alcohol, VI was submitted to hydrogenation in a solution of glacial acetic acid with platinum oxide catalyst. Two compounds, XX and XXI, were isolated and converted to the corresponding quinones, XXII and XXIII. The position of the acetoxyl group in XXI was demonstrated by synthesis of the other possible isomer, XXIV.

The structures of these substances indicate that the reduction of VI took place in three directions: (a) ring A of the nucleus was reduced; (b) the ketonic group in the side-chain was reduced to a methylene group; (c) the acetoxyl group in the 3-position was removed by reduction. The removal by reduction of the acetoxyl group from position three of VI contrasts with the preferential acetylation of the hydroxyl group in the 3-position



of XXV, and with the selective deacetylation that must take place in the conversion of XXVI to III.



In an attempt to avoid the complications experienced in the reduction of 2-acyl-3,4-diacetoxy-1-naphthols with platinum oxide and hydrogen, compound XXVII was reduced over copper chromite catalyst in dioxane at 150° under 150 atmospheres of hydrogen. In this reduction the carbonyl group of the side-chain was reduced to a methylene group, and conversion of the substance XXVIII to quinone XXIX, a known compound,[14] confirmed the identity of the substance.

Table II records the physical properties and analyses of those of the above compounds whose detailed preparation can be adequately described by reference to the procedure used for an anal-

(14) Fieser, *et al.*, THIS JOURNAL, **70**, 3181 (1948).

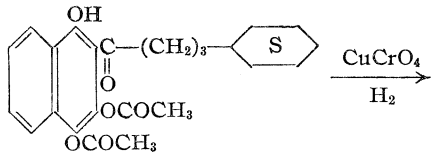
TABLE II

METHODS OF PREPARATION AND PHYSICAL PROPERTIES OF INTERMEDIATES OF, DERIVATIVES OF, AND 2-ACYL-3-HYDROXY-1,4-NAPHTHOQUINONES

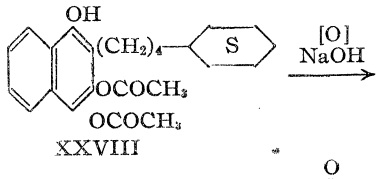
N = naphthalene. NQ = 1,4-naphthoquinone. NHQ = 1,4-naphthohydroquinone. NL = 1-naphthol. PP = 3′-phenylpropionyl. CHB = 4′-cyclohexylbutryl.

Starting material	Product[1]	Prd.	Yield, %	M. p., °C.	Crys. solv.	Crys.[2] form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-Acetyl-3-acetoxyNHQ	2-Acetyl-1,3,4-tri-acetoxyN	A	33	138–139	Alc.	W. pr.	$C_{18}H_{19}O_7$	62.79	62.94	4.68	4.94
2-Acetyl-3-hydroxyNQ	2-Acetyl-1,3,4-tri-acetoxyN	B	66	138–139	Alc.	W. pr.	.....	...	...	...	...
2-Acetyl-3-acetoxyNQ	2-Acetyl-3-acetoxyNHQ	C	49	196–197	Alc.	Y. n.	.....	...	...	...	...
2-Acetyl-3-hydroxyNQ	2-Acetyl-3-hydroxy-NHQ[3]	C	54	190–192	Eth.	O.-r. n.	$C_{12}H_{10}O_4$	66.05	66.25	4.62	4.85
2-Acetyl-3-hydroxyNHQ	2-Acetyl-3-acetoxyNHQ	A[4]	57	196–197	Alc.	Y. n.	.....	...	...	...	...
2-Acetyl-4-acetoxyNL	2-Acetyl-1,4-diacetoxyN	A	74	102–103	Alc.	W. pr.	$C_{16}H_{14}O_8$	67.12	66.81	4.93	5.19
2-AcetylNQ	2-Acetyl-1,4-diacetoxyN	B	74	102–103	Alc.	W. pr.	.....	...	...	...	...
2-AcetylNQ	2-AcetylNHQ[5]	C	80	216–217	Eth.	Y. n.	.....	...	...	...	...
2-AcetylNHQ	2-Acetyl-4-acetoxyNL[5]	A[4]	81	103–104	Alc.	Y. n.	.....	...	...	...	...
2-Acetyl-4-acetoxyNL	2-Acetyl-4-aminoNL	D	83	126–127[6]	Alc.	Y. pl.	.....	...	...	...	...
2-Acetyl-4-aminoNL	2-Acetyl-4-acetylamino-NL	A[7]	84	217–218[8]	Alc.	L. y. n.	$C_{14}H_{13}O_3N$	69.12	69.24	5.39	5.29
2-Acetyl-4-acetylaminoNL	2-AcetylNQ	E	88	80–81[9]	Pet.	Y. n.	.....	...	...	...	...
2-AcetylNQ	BF_2-deriv. of VI	F	82	232–236 (d.)	Acet.	Y. n.	$C_{16}H_{13}O_6BF_2$			F, 10.85	10.79
2-Acetyl-3,4-diacetoxyNL	BF_2-deriv. of VI	G	72	232–236 (d.)	Acet.	Y. n.	$C_{16}H_{13}O_6BF_2$			F, 10.85	10.87
2-Acetyl-1,3,4-tri-acetoxyNL	BF_2-deriv. of VI	G	77	232–236 (d.)	Acet.	Y. n.	$C_{16}H_{13}O_6BF_2$			F, 10.85	10.68
BF_2-deriv. of VI	2-Acetyl-3,4-diacetoxy-NL	H	85	184–185	Acet.	Y. n.	$C_{16}H_{14}O_6$	63.57	63.69	4.67	4.81
2-AcetylNL	BF_2-deriv.-2-acetylNL[10]	G	63	245–248 (d.)	Acet.	Y. p.	$C_{12}H_9O_2BF_2$			F, 16.24	16.18
2-Acetyl-3,4-diacetoxy-NL	2-Acetyl-3-hydroxyNQ	I	70	134–135	Acet.	Y. p.	.....	...	...	...	...
2-Acetyl-3-acetoxyNHQ	2-Acetyl-3,4-diacetoxy-NL	A[4]	64	184–185	Acet.	Y. n.	.....	...	...	...	...
2-Acetyl-3,4-diacetoxy-NL	2-Acetyl-1,3,4-tri-acetoxyN	A	78	138–139	Alc.	W. pr.	.....	...	...	...	...
2-Acetyl-2-ethyl-3,4-di-acetoxy-1-naphthone	2-Ethyl-3-hydroxyNQ[11]	I	93	139–140	Acet.	Y. n.	.....	...	...	...	...
2-Benzalacetyl-4-nitroNL[12]	2-(PP)-4-aminoNL[13]	D	56	140–141	Alc.	O. pl.	$C_{19}H_{17}O_2N$	78.32	78.59	5.88	5.64
2-(PP)-4-aminoNL	2-(PP)-4-acetylaminoNL	A[7]	76	184–185	Acet.	Y. n.	$C_{21}H_{19}O_3N$	75.65	75.73	5.74	5.67
2-(PP)-4-acetylaminoNL	2-(PP)NQ	E	76	94–95	Acet.	Y. n.	$C_{19}H_{14}O_3$	78.60	78.51	4.86	4.91
2-Benzal-4-nitroNL	2-(PP)NQ	J	68	94–95	Acet.	Y. n.	.....	...	...	...	...
2-(PP)NQ	2-(PP)-3,4-diacetoxyNL	F + H[14]	54	116–117	Acet.	Y. n.	$C_{23}H_{20}O_6$	70.40	70.62	5.14	5.23
2-(PP)-3,4-diacetoxyNL	2-(PP)-3-hydroxyNQ	I	71	97–98	Benz. + Pet.	Y. n.	$C_{19}H_{14}O_4$ $C_{21}H_{18}O_6$[15]	74.50 68.84	74.60 68.94	4.61 4.95	4.81 5.05
2-(CHB)-4-nitroNL	2-(CHB)NQ	J	72	52–53	Acet.	Y. n.	$C_{20}H_{22}O_3$	77.39	77.40	7.15	7.26
2-(CHB)NQ	2(CHB)-3,4-diacetoxy-NL	F + H[14]	71	171–172	Acet.	Y. n.	$C_{24}H_{28}O_6$	69.88	69.83	6.84	6.97
2-(CHB)-3,4-diacetoxy-NL	2-(CHB)-3-hydroxyNQ	I	85	134–135	Acet.	Y. pl.	$C_{20}H_{22}O_4$	73.60	73.40	6.80	6.91
2-Acetyl-3,4-diacetoxy-NL	2-Acetyl-3,4-diacetoxy-5,6,7,8-tetrahydroNL[16]	K	44	124–125	Eth.	Y. gr.	$C_{16}H_{18}O_6$	62.74	62.51	5.92	5.92
2-(CHB)-3,4-diacetoxy-NL	2-(CHB)-3,4-diacetoxy-5,6,7,8-tetrahydroNL	K	36	115–116	Alc.	Y. n.	$C_{24}H_{32}O_6$	69.21	69.44	7.75	7.67
2-Acetyl-3,4-diacetoxy-5,6,7,8-tetrahydroNL	2-Acetyl-3,4-dihydroxy-5,6,7,8-tetrahydroNL	L	89	180–182 (d.)	Eth.	Y. n.	$C_{12}H_{14}O_4$	64.85	65.11	6.35	6.53
2-Acetyl-3,4-dihydroxy-5,6,7,8-tetrahydroNL	2-Acetyl-3-hydroxy-5,6,7,8-tetrahydroNQ	M	83	87–88	Eth.	O. pl.	$C_{12}H_{12}O_4$	65.44	65.56	5.49	5.73
2-(CHB)-3,4-diacetoxy-5,6,7,8-tetrahydroNL	2-(CHB)-3-hydroxy-5,6,7,8-tetrahydroNQ	L + M[17]	75	66–67	Pet.	O. n.	$C_{20}H_{26}O_4$	72.70	73.12	7.93	8.12

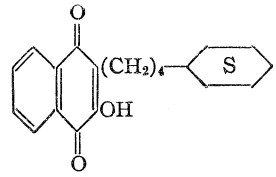
[1] In all cases where two different methods of preparation of the same compound are reported, admixture of samples produced no depression of melting point. [2] y. = yellow, n. = needles, w. = white, pr. = prisms, o. = orange, r. = red, pl. = plates, gr. = granules, l = light. [3] Forms a deep purple color in alkaline sol., deep red color in concd. sulfuric acid. [4] The procedure was modified by not heating the reaction mixture, but allowing it to stand ten hours at room temp. [5] Admixture with same substance produced from Fries rearrangement (see expl.) gave no m. p. depression. [6] Friedlaender (ref. 6) prepared this compound by a different procedure but reported neither melting point nor yield. [7] The sodium acetate and heating period were unnecessary. [8] Friedlaender (ref. 6) reported a m. p. of 107° for a monoacetylated amine, and Torrey and Cardarelli [THIS JOURNAL, 32, 1477 (1910)] reported a m. p. of 212°. [9] Friedlaender (ref. 6) reported a m. p. of 78° for this compound prepared by a different procedure. [10] This substance when warmed with ethanol reverts to the starting material. [11] Hooker reported a m. p. of 138–139° for this compound. The m. p. of a mixture of the two samples is 138–139°. [12] This substance [Torrey and Cardarelli (ref. 18) reported m. p. 202–208°] was prepared in a 92% yield, m. p. 210°. [13] The double bond in the side-chain was also reduced. [14] In this reaction the BF_2-derivative was treated directly with ethanol to give the phenol. [15] When crystallized from glacial acetic acid this quinone contains one mole of acetic acid of crystallization (yellow needles, m. p. 85–86 (dec.)). [16] 2-Ethyl-3-hydroxy-4-acetyl-5,6,7,8-tetrahydro-1-naphthol was isolated as a by-product (see expl.). [17] The intermediate hydroquinone was not isolated.



XXVII



XXVIII



XXIX

ogous reaction described in the experimental section.

Experimental

2-Acetyl-3-hydroxy-1,4-naphthoquinone (I) from Purpurin.—The reaction was run according to the procedure of Dimroth and Schultze,[4] but since the products were isolated from the reaction mixture by a method different than that reported by these workers, the procedure is repeated here.

To a cooled solution of 6 g. of purpurin in 150 cc. of water and 18 cc. of 5 *N* sodium hydroxide solution, 15 drops of a 1% cobalt sulfate solution and 10 cc. of a 30% hydrogen peroxide solution were added. The temperature rose to 40° in about three minutes and was maintained by placing the mixture in an ice-bath. After five minutes the solution turned red-brown, and 7.5 cc. of concentrated hydrochloric acid was added; the precipitate was collected and washed with water. The solid was triturated twice with saturated sodium carbonate solution and filtered. From the solid residue 2 g. of purpurin was recovered. The filtrate was acidified; the yellow precipitate was collected, dissolved in ethanol and passed through a small alumina column. The filtrate was evaporated to a small volume, and 50 mg. (11% yield) of I was obtained as yellow plates by crystallization of the oil from glacial acetic acid; m. p. 134–135°.

This quinone gives an orange color in alkaline solution, a yellow color in concentrated sulfuric acid solution, and a deep purple color in alkaline sodium hydrosulfite solution. Dimroth and Schultze[4] reported a yield of 79% and a melting point of 128–129°.

The original filtrate of the reaction mixture was extracted with ether, and the ether solution was dried and evaporated to a small volume from which yellow crystals slowly separated. Two recrystallizations from acetone and petroleum ether furnished 100 mg. of 2-(2′-carboxyacetyl)-3-hydroxy-1,4-naphthoquinone (II) in the form of orange needles; m. p. 119–120°. This substance produces a yellow color in alkaline solution, a yellow color in concentrated sulfuric acid solution and a purple color in alkaline sodium hydrosulfite solution.

Anal. Calcd. for $C_{13}H_8O_6$: C, 60.01; H, 3.10. Found: C, 60.20; H, 3.38.

The carboxylic acid II (50 mg.) was dissolved in 2 cc. of glacial acetic acid, and the solution was heated to 90° for five minutes. When cooled and diluted with water, the yellow quinone I crystallized; m. p. 134–135°. The melting point was not depressed by the addition of an authentic sample of I.

2-Acetyl-3-acetoxy-1,4-naphthohydroquinone (III).—A mixture of 1,3,4-triacetoxynaphthalene, 5 g. of anhydrous aluminum chloride and 100 cc. of *o*-dichlorobenzene was stirred at 80° for four hours, cooled, and mixed with 200 g. of ice and 50 cc. of 50% hydrochloric acid. A yellow solid was collected, and three recrystallizations (ethanol) produced 0.15 g. (3% yield) of III in the form of yellow needles, m. p. 196–197°. The compound forms an orange color changing to purple in alkaline solution, and a green color changing to yellow in an ethanol solution containing a drop of ferric chloride solution.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.37; H, 4.66.

The substance 2-hydroxy-1,4-naphthoquinone[13] (2.5 g.) was recovered from the filtrate.

Procedure A. 2-Acetyl-1,3,4-triacetoxynaphthalene from 2-Acetyl-3-acetoxy-1,4-naphthohydroquinone (III).—To 25 mg. of III, 1.0 g. of acetic anhydride and a trace of sodium acetate were added. The mixture was warmed to 100° and diluted with 100 cc. of water, cooled, and two recrystallizations (ethanol) of the substance that separated afforded 10 mg. of white prisms; m. p. 138–139°.

Procedure B. 2-Acetyl-1,3,4-triacetoxynaphthalene from 2-Acetyl-3-hydroxy-1,4-naphthoquinone (I).—A mixture of 100 mg. of I, 200 mg. of zinc dust,[15] 2 g. of acetic anhydride and a trace of sodium acetate was heated on a steam-bath for one-half hour, filtered and the filtrate was stirred into 10 cc. of water. The product that separated was crystallized from ethanol; 105 mg., m. p. 138–139°.

2-Acetyl-3-acetoxy-1,4-naphthoquinone.—To 10 cc. of a solution of 2% ammonia in a 50% water–ethanol mixture 0.4 g. of I was added. The ammonium salt crystallized immediately. An excess of 50% silver nitrate solution was added to the mixture; the silver salt was filtered, digested with ethanol, and thoroughly dried. This salt was suspended in dry ether, and acetyl chloride was added drop by drop until all the quinone salt was decomposed. The precipitated silver chloride was collected; the filtrate was evaporated to a small volume in vacuum, cooled, and the quinone acetate was collected. Two recrystallizations of the product from dry ether produced 0.32 g. of light-yellow needles; m. p. 123–124°. This acetate hydrolyzes readily into the free quinone, and for this reason cannot be crystallized from ethanol.

Anal. Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found: C, 65.28; H, 4.09.

Procedure C. 2-Acetyl-3-acetoxy-1,4-naphthohydroquinone (III) from 2-Acetyl-3-acetoxy-1,4-naphthoquinone.—An ether solution of 0.20 g. of 2-acetyl-3-acetoxy-1,4-naphthoquinone was shaken successively with three fresh portions of a solution of sodium hydrosulfite in water.[16] The ether solution was thoroughly washed with water, dried, and filtered through a small mat of Darco that had been washed with ether. The filtrate was evaporated to a small volume, cooled, and the product collected. Recrystallization of the substance from ethanol furnished 0.10 g. of yellow needles, m. p. 196–197°.

2-Acetyl-4-acetoxy-1-naphthol and 2-Acetyl-1,4-naphthohydroquinone.—A mixture of 3.0 g. of 1,4-diacetoxynaphthalene, 3.0 g. of anhydrous aluminum chloride and 30 cc. of nitrobenzene was heated for two hours at 70°, cooled, and decomposed with a mixture of ice and hydrochloric acid. The nitrobenzene was steam distilled, the black tar that remained was extracted into ether, and a brown insoluble precipitate was collected. The filtrate was dried, evaporated to dryness, and the residue repeatedly extracted with low-boiling petroleum ether. The extracts were combined, treated with Darco, evaporated to a small volume, and cooled. The product crystallized, and two recrystallizations (ethanol) furnished 0.25 g. (8.4% yield) of light yellow needles of 2-acetyl-4-

(15) This procedure is patterned after that described by Fieser, "Experiments in Organic Chemistry," 2nd Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 399.

(16) This procedure is patterned after that developed by Fieser, *loc. cit.*, p. 190.

acetoxy-1-naphthol, m. p. 103–104°. The acetate forms a red solution with concentrated sulfuric acid, an orange solution with aqueous alkali, and a green solution with ethanol containing a drop of ferric chloride solution.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.56; H, 4.71.

The material left from the petroleum ether extractions was dissolved in ether and shaken with sodium hydrosulfite solution, washed with water, dried, and filtered through a small ether-washed pad of Darco. When the filtrate was evaporated to a small volume and cooled, a solid separated, which after two recrystallizations from ether afforded 0.2 g. (8.1% yield) of 2-acetyl-1,4-naphthohydroquinone, m. p. 216–217°. The compound forms a red solution with concentrated sulfuric acid, an orange solution (which darkens) in aqueous alkali, and a green color changing to red in an ethanol solution containing a drop of ferric chloride solution.

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.20; H, 5.04.

Procedure D. 2-Acetyl-4-amino-1-naphthol.—A mixture of 10 g. of 2-acetyl-4-nitro-1-naphthol,[17] 0.10 g. of platinum oxide, 100 cc. of methanol and 5 cc. of concentrated hydrochloric acid was shaken under 25 lb. of hydrogen until six equivalents of hydrogen had been absorbed (four hours). The salt that separated was filtered and washed with methanol. This substance was mixed with 50 cc. of ethanol, and 10 cc. of a saturated sodium bicarbonate solution was added. The free amine was collected and recrystallized from ethanol; 7.3 g. (83% yield), m. p. 126–127°. Friedlaender prepared this substance by a different procedure, but he did not report a melting point or a yield.

Procedure E. 2-Acetyl-1,4-naphthoquinone (IV).—To a mixture of 16 g. of 2-acetyl-4-acetylamino-1-naphthol[18] and 140 cc. of glacial acetic acid at 15°, 6 g. of 70% nitric acid dissolved in 20 cc. of glacial acetic acid was added. The solid dissolved when the mixture was stirred. When 200 cc. of water was added to the solution, IV crystallized in fine yellow needles; 10.2 g. (88% yield), m. p. 80–81°.

2-Acetyl-1,4-naphthoquinone Oxide.—A solution made up of 0.1 g. of sodium carbonate, 0.4 cc. of dioxane, 2.5 cc. of dioxane, 2.5 cc. of water and 0.5 cc. of 30% hydrogen peroxide solution was added to 0.5 g. of IV dissolved in 15 cc. of ethanol. The mixture turned black. After ten minutes 100 cc. of water was added, and the precipitated solid collected. Two recrystallizations of the product from ethanol produced white needles of the oxide; 0.2 g. (37% yield), m. p. 125–126°.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 66.67; H, 3.73. Found: C, 66.52; H, 3.96.

Boron Difluoride Derivative (V) of 2-Acetyl-3,4-diacetoxy-1-naphthol (VI)

Procedure F. From 2-Acetyl-1,4-naphthoquinone (IV).—A mixture of 4.0 g. of IV, 12.0 g. of acetic anhydride and 2.0 g. of a solution of boron trifluoride in ether (45% by weight) was allowed to stand for twenty-four hours at room temperature.[19] Brilliant yellow needles of V separated, were collected and washed with cold glacial acetic acid; 6.0 g. (82% yield), m. p. 232–236° dec. Recrystallization of the substance from glacial acetic acid did not alter the melting properties.

This compound burns with a green flame and leaves a black ash; it is insoluble in water, decomposes in alkali and shows only a slight solubility in non-polar organic solvents. If heated with any organic solvent containing water, it decomposes. Solutions fluoresce strongly in the sunlight.

Procedure G. From 2-Acetyl-3,4-diacetoxy-1-naphthol (VI).—To a saturated solution of 5.0 g. of VI in glacial acetic acid, 3 g. of boron trifluoride etherate was added. A heavy precipitate of fine, yellow crystals separated immediately.[19] Recrystallization of the substance from glacial acetic acid furnished 4.2 g. of yellow needles, m. p. 232–236° dec.

Procedure H. 2-Acetyl-3,4-diacetoxy-1-naphthol (VI).—When 10 g. of V and 100 cc. of a 90% ethanol–water mixture were boiled for one-half hour, the boron fluoride compound decomposed to give orange-yellow crystals of VI. The mixture was cooled, the product collected and recrystallized from glacial acetic acid to yield 7.3 g. of lustrous yellow needles, m. p. 184–185°. This substance forms an orange solution with concentrated sulfuric acid, a yellow solution changing to deep red and finally to brown with aqueous alkali, and a green color in a solution of ethanol containing a drop of ferric chloride.

Procedure I. 2-Acetyl-3-hydroxy-1,4-naphthoquinone (I).—A solution (10 cc.) of a 30% potassium hydroxide was added to a mixture of 4 g. of VI and 40 cc. of ethanol (both mixtures had been previously flushed with nitrogen).[13] The mixture was allowed to stand for one-half hour. At the end of this time the purple solution was cooled, acidified with a cold solution of 8 cc. of concentrated hydrochloric acid in 25 cc. of water, and a cold solution of 8.7 g. of ferric chloride hexahydrate in 2.5 cc. of concentrated hydrochloric acid and 12 cc. of water was added. A crop of yellow needles separated, which crystallized from glacial acetic acid as gold-colored plates; 2.0 g. (70% yield), m. p. 134–135°. Admixture of the substance with an authentic sample of I (prepared from purpurin) did not depress the melting point.

1-Methoxy-2-acetyl-3,4-diacetoxynaphthalene (VII).—To a solution of 4.0 g. of VI in 300 cc. of dry benzene, an ether solution of diazomethane prepared from 10 g. of N-methyl-N-nitrosourea was added. The mixture after standing at room temperature for three hours, was evaporated in vacuum to an oil, which was dissolved in 30 cc. of ethanol, treated with charcoal and cooled in a Dry Ice–acetone mixture for several hours. The white solid that separated was filtered, washed with cold ethanol, and recrystallized twice from glacial acetic acid; 1.8 g. (white prisms), m. p. 106–107°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.33; H, 5.21.

Compound VII was also prepared in the usual manner by the action of dimethyl sulfate on VI, but the yield was inferior.

1-Methoxy-2-acetyl-3,4-dihydroxynaphthalene (VIII).—Solutions of 2.2 g. of VII in 30 cc. of ethanol and 7.5 cc. of 20% potassium hydroxide were flushed with nitrogen, mixed, and allowed to stand under nitrogen for two and one-half hours (the mixture was shaken frequently). Acidification with acetic acid yielded yellow crystals which, after thorough washing with water and recrystallization from glacial acetic acid afforded 0.65 g. of light yellow needles, m. p. 227–228°. The compound formed a green solution with ethanol containing a drop of ferric chloride solution, and a red solution with concentrated sulfuric acid, and an orange solution turning to brown with aqueous alkali. The substance was not identified.

Anal. Found: C, 69.84; H, 4.38.

The mother liquors of the original reaction mixture were saturated with sodium chloride, and cooled to 0° for twelve hours. The substance that separated was recrystallized twice from an ether–petroleum ether mixture; 0.4 g. of deep red-orange needles, m. p. 92–93°. The substance produced an orange solution with aqueous alkali, and a green color changing quickly to orange with an aqueous solution containing a drop of ferric chloride.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.15; H, 5.38.

1-Methoxy-2-acetyl-3,4-naphthoquinone (IX).—A solution of 0.15 g. of VIII in 20 cc. of anhydrous ether was stirred for one hour with 0.25 g. of anhydrous magnesium

(17) Acetylation of 1-naphthol (Friedlaender, ref. 6, reported a quantitative yield and a m. p. of 103°) gave an 80% yield of 2-acetyl-1-naphthol, m. p. 101–102°. Nitration of this compound produced an 82% yield, m. p. 157–158°, of 2-acetyl-4-nitro-1-naphthol (Friedlaender, ref. 6, reported no yield and m. p. 157°).

(18) Torrey and Cardarelli, THIS JOURNAL, **32**, 1477 (1910).

(19) A small amount of etching of the glass of the reaction flask occurred.

sulfate and 0.25 g. of silver oxide. The solid was collected, and the quinone that had crystallized during the oxidation was dissolved in dry acetone and filtered. The combined filtrates were evaporated to a small volume under reduced pressure, and cooled. The solid when recrystallized twice from acetone formed rich orange-yellow needles; 75 mg., m. p. 166–167°. This ortho quinone is slightly soluble in ether and soluble in acetone. The substance forms a yellow solution with sulfuric acid, a deep red solution with aqueous alkali (after two minutes) and a deep purple solution with a mixture of aqueous alkali and sodium hydrosulfite, if the alkali is added first and allowed to stand for two minutes before the hydrosulfite is added. If sodium hydrosulfite is added first, and then the alkali, a deep red solution results.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: C, 67.72; H, 4.67.

O-Methyl-2-acetyl-1-naphtheurhodol.—A mixture of 50 mg. of IX, 35 mg. of *o*-phenylenediamine, and 1 cc. of glacial acetic acid was allowed to stand at room temperature for one-half hour. When the solution was cooled, a solid separated which was crystallized from ethanol; 20 mg. (light yellow needles), m. p. 157–158°.

Anal. Calcd. for $C_{19}H_{14}O_2N_2$: C, 75.48; H, 4.67. Found: C, 75.51; H, 4.65.

2-Acetyl-1-naphtheurhodol.—A solution of 0.5 g. of I and 0.18 g. of *o*-phenylenediamine in 2 cc. of glacial acetic acid was heated to the boiling point for one minute, and cooled. The product that separated was recrystallized twice from glacial acetic acid; 0.45 g. of orange needles, m. p. 206–207°.

Anal. Calcd. for $C_{18}H_{12}O_2N_2$: C, 74.99; H, 4.20. Found: C, 74.83; H, 3.90.

O-Methyl-2-acetyl-1-naphtheurhodol from 2-Acetyl-1-naphtheurhodol.—To a solution of 0.2 g. of 2-acetyl-1-naphtheurhodol in 20 cc. of a 50% acetone–water solution saturated with sodium carbonate, 2 cc. of dimethyl sulfate was added over a period of one-half hour. The mixture was stirred and kept basic by the addition of more sodium carbonate. Crystallization of the substance that separated (ethanol and water) produced light yellow needles; 0.15 g., m. p. alone and mixed with an authentic sample (see above), 157–158°.

2-Acetyl-2-ethyl-3,4-diacetoxy-1-naphthone (XI).—An ethereal solution of diazoethane was prepared from 15 g. of N-ethyl-N-nitrosourea, and added to a solution of 8 g. of VI in one liter of dry benzene. The reaction mixture was allowed to stand overnight at room temperature, and was concentrated under reduced pressure to a volume of 100 cc. The solution was then filtered through a heavy mat of Darco, and when the filtrate was cooled, 4 g. of starting material crystallized. The mixture was filtered, and the filtrate was concentrated to an oil, which was dissolved in a small amount of ethanol, mixed with a generous portion of Darco, and filtered; the filtrate was allowed to stand in an ice-chest for forty-eight hours. At the end of this period the substance that precipitated was crystallized twice from ethanol; 1.2 g. of white needles, m. p. 130–131°. This product forms a red color when allowed to stand in an aqueous alcoholic alkaline solution, and an orange color in concentrated sulfuric acid.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.47; H, 5.68.

Procedure J. 2-(3′-Phenylpropionyl)-1,4-naphthoquinone by a Condensed Procedure.—Glacial acetic acid (200 cc.), acetic anhydride (100 cc.), 0.35 g. of platinum oxide and 34 g. of 2-benzalacetyl-4-nitro-1-naphthol were mixed and shaken under twenty-five pounds of hydrogen until eight equivalents had been absorbed (eighteen hours). To the mixture 6 g. of 70% nitric acid was then added. The suspended solid went into solution in about two minutes, and the catalyst was collected. Water (one volume) was added to the filtrate, the mixture was cooled, and a crop of fine yellow needles was collected; 21 g. (68% yield), m. p. 94–95°, not depressed by addition of an authentic sample of the quinone.

2-Benzalacetyl-3-hydroxy-1,4-naphthoquinone.—A mixture of quinone I (1 g.), 0.8 g. of benzaldehyde, 10 cc. of ethanol and 5 cc. of a 30% sodium hydroxide solution was stirred for twelve hours (the mixture turned black as soon as the components were added to one another). The solution was then acidified with acetic acid and oxidized with a solution of 1 g. of ferric chloride hexahydrate in 5 cc. of water and 1 cc. of concentrated hydrochloric acid. The oil that separated was dissolved in glacial acetic acid and set aside for several days. A small crop of crystals separated, and three recrystallizations from glacial acetic acid produced 0.1 g. of tan needles, m. p. 181–182°. The quinone formed a yellow solution with aqueous alcoholic alkali, a red-orange solution with concentrated sulfuric acid, a blue solution changing to purple and finally to red with an alkaline sodium hydrosulfite solution, and a yellow-orange solution with ethanol containing a drop of ferric chloride solution.

Anal. Calcd. for $C_{19}H_{12}O_4$: C, 74.99; H, 3.98. Found: C, 74.67; H, 4.09.

2-(4′-Cyclohexylbutyryl)-1-naphthol.—Freshly fused and ground zinc chloride (160 g.) was mixed with 100 g. of 4-cyclohexylbutyric acid and 85 g. of 1-naphthol.[20] The mixture was rapidly brought to 140–145°, held there for twenty minutes, cooled to 100°, and poured into water. The oily product was boiled with ethanol, collected, and recrystallized from glacial acetic acid; 72 g. (44% yield) of white needles, m. p. 103–104°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.30; H, 8.27.

2-(4′-Cyclohexylbutyryl)-4-nitro-1-naphthol.—Over a period of twelve hours a solution of 14 g. of 70% nitric acid in 50 cc. of glacial acetic acid was added to a mixture of 40 g. of 2-(4′-cyclohexylbutyryl)-1-naphthol and 150 cc. of glacial acetic acid at 15°.[20] The product that separated was washed with glacial acetic acid and dried; 32 g. (70% yield of nitro compound in the form of granules with a slight-yellow tinge), m. p. 121–122°.

Anal. Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79. Found: C, 70.66; H, 6.75.

***cis* and *trans*-2-(1′-Methylheptadecen-1-yl)-3-hydroxy-1,4-naphthoquinone (XVI and XVII).**—To a stirred mixture of 6.5 g. of magnesium turnings and 50 cc. of dry ether in an atmosphere of nitrogen, 73 g. of cetyl bromide (dissolved in 200 cc. of dry ether) was added over a period of one-half hour. When the addition was complete, the mixture was refluxed for two hours, and a mixture of 7.3 g. of the diacetate VI and 300 cc. of dry benzene was added in portions. The reaction mixture was then refluxed for four hours, cooled and poured into a mixture of ice and ammonium chloride. The two layers were well shaken, separated, and the ether–benzene layer was shaken with a 5% solution of sodium hydroxide in a 50% alcohol–water mixture for about one-half hour. The solution was then acidified with acetic acid, and the layers separated. The ether–benzene layer was washed twice with water, dried, and evaporated under reduced pressure to an oil, which was dissolved in an equal volume of dry ether, and chilled for two days. The product that separated was dissolved in a small amount of boiling glacial acetic acid, and the solution was cooled as slowly as possible; care was taken not to disturb the flask during the crystallization. After twelve hours the product was carefully collected, and spread out on a piece of white paper. There were two kinds of crystals present in the mixture, relatively large dense packets of rich-orange needles and scattered light-yellow needles. The crystals of each component were separated manually, and submitted to alternate crystallization from glacial acetic acid and ethyl ether solutions until the melting points no longer changed. In this manner 1.7 g. of rich orange needles of the *trans* isomer (XVII), m. p. 91–92°, and 1.2 g. of fine yellow needles of the *cis* isomer (XVI), m. p. 82°, were obtained.

(20) These procedures are modeled after those of Friedlaender (ref. 6) in the preparation of 2-acetyl-4-nitro-1-naphthol.

Both compounds formed a red solution with an alkaline ethanol–water mixture, and an orange solution changing through brown, green and blue to a dirty purple with concentrated sulfuric acid. A mixed melting point determination of the two substances gave 86–89°.

Anal. Calcd. for $C_{28}H_{40}O_3$: C, 79.20; H, 9.50. Found for the *cis* isomer: C, 79.14; H, 9.68. Found for the *trans* isomer: C, 79.14; H, 9.50.

Ozonolysis of *cis*- and *trans*-2-(1′-Methylheptadecen-1-yl)-3-hydroxy-1,4-naphthoquinone (XVI and XVII).—Ozone was passed into a solution of 0.3 g. of the *trans* isomer in 30 cc. of ethyl acetate till the color was discharged. The solution was then dripped into boiling water; the water was cooled and extracted twice with petroleum ether. The extracts were combined, and the solution was washed once with dilute alkali, once with water, dried, and evaporated to a volume of 10 cc. This solution was run through a small column of acid-washed alumina, and the alumina was washed well with petroleum ether. The column filtrate was evaporated to a small volume and cooled to Dry-Ice temperature. The white solid that separated was crystallized from petroleum ether; 90 mg. of palmitic aldehyde[21] (white needles), m. p. 33–34°. The *p*-nitrophenylhydrazone[21] was prepared by the usual method, m. p. 95–96°.

The *cis* isomer (100 mg.) was oxidized by the same procedure, and 25 mg. of the *p*-nitrophenylhydrazone of palmitic aldehyde was isolated, m. p. 95–96°. A mixed melting point of the two samples of this substance showed no depression.

Conversion of *trans*-2-(1′-Methylheptadecen-1-yl)-3-hydroxy-1,4-naphthoquinone (XVII) into the *cis* Isomer (XVI).—The *trans* isomer (220 mg.) was heated at 120° for one-half hour. The melt was dissolved in a small amount of glacial acetic acid, and the solution was seeded with a crystal of the *cis* isomer. The product that separated was recrystallized twice from ethyl ether to give 63 mg. of the *cis* isomer, m. p. 82°. A mixed melting point with an authentic sample of XVI gave no depression. Starting material (105 mg.) was recovered from the combined filtrates.

A similar experiment, carried out on 130 mg. of the *cis* isomer (XVI), produced 30 mg. of the *trans* isomer XVII; m. p. 91–92°, not depressed by the addition of an authentic sample.

Procedure K. Reduction of 2-Acetyl-3,4-diacetoxy-1-naphthol (VI) to 2-Acetyl-3,4-diacetoxy-5,6,7,8-tetrahydro-1-naphthol (XX) and 2-Ethyl-3-hydroxy-4-acetoxy-5,6,7,8-tetrahydro-1-naphthol (XXI).—A mixture of 5 g. of the diacetate VI, 0.1 g. of platinum oxide and 100 cc. of glacial acetic acid was shaken under a pressure of twenty-five pounds of hydrogen till all the diacetate had dissolved (two hours). The mixture was filtered, and two volumes of water were added to the filtrate. The solid that precipitated was recrystallized twice (ethanol); 2.3 g. (light brown granules), m. p. 124–125°.

This substance (XX) dissolved in dilute alkali, and gave a yellow solution that turned quickly to orange, and finally to red. (Procedure K terminates here.)

The initial filtrate from the reaction mixture was extracted with ether, and the ether layer was well washed with water, dried, and evaporated to an oil. The oil was dissolved in a small amount of ether; an equal volume of petroleum ether was added, and the solution was cooled. The product that separated was crystallized from benzene; 0.7 g. (white needles), m. p. 144–145°.

This substance (XXI), when dissolved in aqueous alkali, gives a yellow solution that changes to brown, then to amber, to red, and finally to purple.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.33; H, 7.20.

(21) A melting point of 34° for palmitic aldehyde and 95.5–96.5° for the *p*-nitrophenylhydrazone is reported in Heilbron, "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1943, p. 329.

Procedure L. 2-Acetyl-3,4-dihydroxy-5,6,7,8-tetrahydro-1-naphthol.—Diacetate XX (2.0 g.) and sodium hydroxide (20 cc. of a 5% solution) were mixed in an atmosphere of nitrogen and stirred for one-half hour. The solution was acidified, and the solid that separated was recrystallized twice from ether; 1.3 g. (canary-yellow needles), m. p. 180–182° dec. This hydroquinone gives a red solution with aqueous alkali, a yellow solution with concentrated sulfuric acid, and an orange color in an aqueous solution containing a drop of ferric chloride solution.

Procedure M. 2-Acetyl-3-hydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (XXII).—A solution of 1.0 g. of 2-acetyl-3,4-dihydroxy-5,6,7,8-tetrahydro-1-naphthol in 25 cc. of ether was treated with 1.5 g. of silver oxide and a small amount of magnesium sulfate. The mixture was stirred for two hours and filtered; the solid was warmed with glacial acetic acid and filtered. Two parts of water were added to the combined filtrates, the solution was cooled, and a crystalline solid separated. Two recrystallizations of the quinone from ether gave 0.6 g. of orange plates of quinone XXII, m. p. 87–88°. This quinone forms an orange solution in aqueous alkali that turns red upon the addition of sodium hydrosulfite, and a yellow solution in concentrated sulfuric acid.

2-Ethyl-3-hydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (XXIII).—Air was passed into a solution of 0.5 g. of XXI in 5 cc. of 1 *N* sodium hydroxide solution for ten minutes. The solution was acidified and the product that separated was crystallized twice from an ether–petroleum ether mixture; flat deep-orange rods, 0.3 g., m. p. 102–103°. This quinone (XXIII) forms a deep purple color in alkaline solution, as well as in concentrated sulfuric acid solution, and in ethanol solution containing a drop of ferric chloride solution. The alkaline solution turns colorless when sodium hydrosulfite is added.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.61; H, 6.91.

2-Ethyl-3-acetoxy-4-hydroxy-5,6,7,8-tetrahydro-1-naphthol (XXIV).—A mixture of 0.2 g. of XXIII, 1 cc. of acetic anhydride and a trace of sodium acetate was warmed on the steam-bath for one hour, cooled, and 3 cc. of water was added. After the excess acetic anhydride had decomposed, the mixture was extracted with ether, and the ether layer was washed with water. The ether solution was then shaken with a solution of sodium hydrosulfite in water, washed with water, dried, filtered through an ether-washed pad of Darco, and evaporated to an oil, which crystallized when cooled. Recrystallization of the solid from an ether–petroleum ether mixture gave 0.15 g. of white needles, m. p. 128–129°. The color reactions of this substance were similar to those of XXI.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.47; H, 7.48.

Reduction of 2-(4′-Cyclohexylbutyryl)-3,4-diacetoxy-1-naphthol (XXVII) to 2-(4′-Cyclohexylbutyl)-3,4-diacetoxy-1-naphthol (XXVIII).—Diacetate XXVII (10 g.) was dissolved in 50 cc. of purified dioxane and reduced at 150–160° for five hours under a pressure of 3900 lb. of hydrogen in the presence of 2.0 g. of copper chromite catalyst. The reaction mixture was then filtered, excess water was added to the filtrate, and the solution was extracted with ether. The ether layer was washed with water, dried, evaporated to a small volume and cooled. The product that separated was crystallized from glacial acetic acid; 3.0 g. of white prisms, m. p. 117–118°.

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.39; H, 7.73.

To the mother liquors from the original crystallization of the diacetate, 100 cc. of ethanol and 50 cc. of 1 *N* sodium hydroxide were added. Air was bubbled through this mixture for three hours, and the solution was acidified. The oily product that separated was crystallized from glacial acetic acid; 3.1 g. of quinone XXIX, m. p., alone and mixed with an authentic sample (ref. 14), 108–109°.

A small sample of the diacetate XXVIII was hydrolyzed

and oxidized by procedure I. From 500 mg. of the diacetate XXVIII, 390 mg. of the quinone was isolated; m. p., alone and mixed with an authentic sample, 108–109°.

Acknowledgment.—The author is indebted to Dr. L. F. Fieser for his many helpful suggestions concerning this study, and to Margaret M. Racich for many of the analyses reported in these papers.

Summary

1. Several new methods for the preparation of 2-acyl-3-hydroxynaphthoquinones have been developed.

2. A new boron-trifluoride-catalyzed Thiele type of reaction has been found to take place between acetic anhydride and 2-acyl-1,4-naphthoquinones; the structures of the products have been elucidated.

3. The abnormal C-alkylation of a 2-acyl-1-naphthol type of compound with diazoethane has been investigated.

4. The reaction of 2-acetyl-3,4-diacetoxy-1-naphthol with a Grignard reagent has resulted in the preparation of two *cis–trans* isomeric olefins, whose ultraviolet absorption spectra were taken, and structural assignments based on these data were made.

5. The course of reduction of 2-acyl-3,4-diacetoxy-1-naphthol type compounds was investigated.

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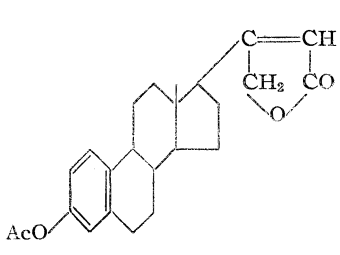
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Preparation of Two Aromatic Analogs of Desoxycorticosterone Acetate

BY CARL DJERASSI[1] AND CAESAR R. SCHOLZ

The biological testing of compounds containing both the nucleus of the estrogens and the functional side-chain of other physiologically active steroids is of considerable interest. Oettel[1a] reported on a pharmacological investigation of a cardiac aglucone derivative I, which contained an aromatic ring A, without disclosing the method of preparation, while Velluz and Muller[2] described the synthesis of an aromatic analog (II) of progesterone. The biological activity of the latter was unfortunately not indicated. The present paper summarizes our work on two independent syntheses of 3-methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III), as well as the preparation of the corresponding 1-methyl derivative XI. III and XI represent aromatic analogs of desoxycorticosterone acetate.



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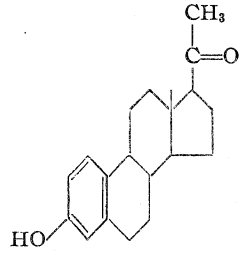

II

The starting material for the first synthesis (Flowsheet I) was 17-ethynylestradiol (IV), which has previously been converted[3] in unspecified yield by Rupe–Nickel reduction to 17-vinylestradiol (Va). The use of a palladium–calcium carbonate catalyst in pyridine solution[4] in the present instance led in 88% yield to the desired 17-vinyl derivative, which was converted into its methyl ether Vb with dimethyl sulfate. Hydroxylation of Vb with osmium tetroxide, followed by acetylation gave 50% of 3-methoxy-10-nor-1,3,5-pregnatriene-17,20,21-triol 20,21-diacetate (VI), which was subjected to a modified Serini reaction[5] in toluene solution and thus furnished directly the desired cortical hormone derivative III in 63% yield.

The aromatic analog III could also be prepared from methyl 3-ketoetiochola-1,4-dienate (VII) (Flowsheet II), which has been synthesized from cholesterol.[6] Aromatization with elimination of the angular methyl group of the dienone ester VII in tetralin solution at 650° by the general procedure of Inhoffen[7] led in 44% yield to the phenolic ester VIIIa which proved to be insoluble in 10% aqueous alkali. This methyl ester (VIIIa) as well as the 3-methyl ether 17-methyl ester (VIIIb) required drastic conditions for saponification (refluxing in 20% alcoholic potassium hydroxide solution for eighteen hours). This behavior is in marked contrast to the relative ease of saponification of the dienone ester VII or the aromatic

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(1a) Oettel, *Pharmazie*, **2**, 385 (1947).

(2) Velluz and Muller, *Compt. rend.*, **226**, 411 (1948).

(3) Inhoffen, Logemann, Hohlweg and Serini, *Ber.*, **71**, 1024 (1938).

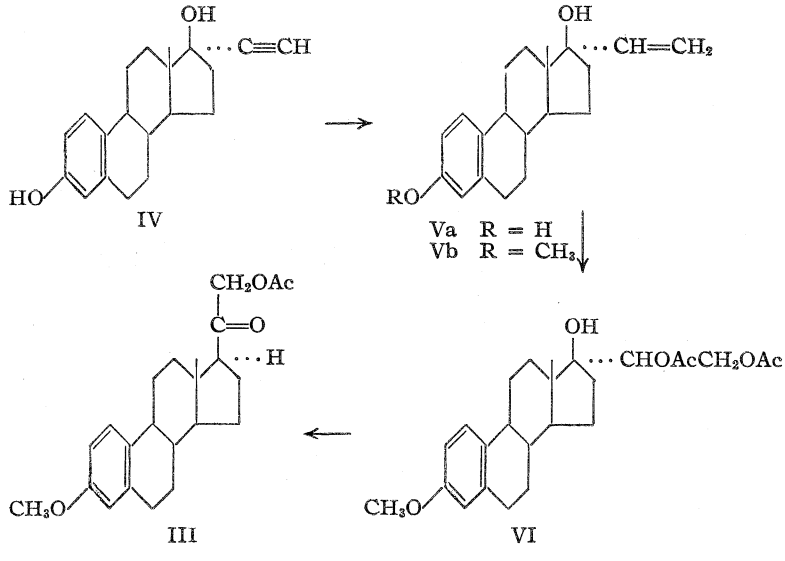
(4) Ruzicka and Müller, *Helv. chim. acta*, **22**, 755 (1939).

(5) Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corporation, New York, N. Y., 1949, pp. 440–444; see Miescher and Heer, U. S. Patent 2,372,841.

(6) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947).

(7) British Intelligence Objectives Sub-Committee F.I.A.T. Final Report No. 996, "The Commercial Development and Manufacture of Synthetic Hormones in Germany," H. M. Stationery Office, London, 1947, pp. 20 and 79; see also Inhoffen, *Angew. Chem.*, **59**, 207 (1947), and Wilds and Djerassi, THIS JOURNAL, **68**, 2125 (1946).

FLOWSHEET I

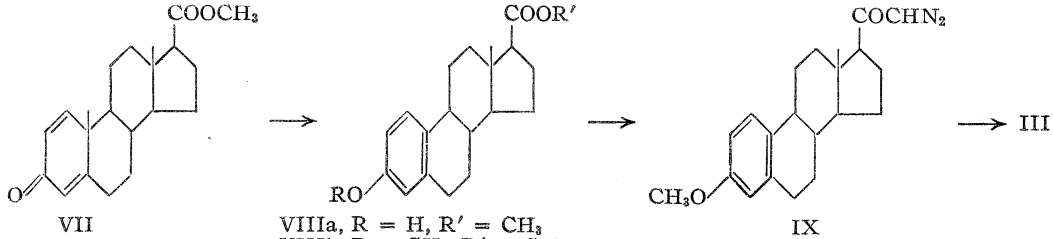


ester Xa,[6,8] which required only 5–10% alkali for *ca.* five hours. If it is assumed that the estrogens have a relatively planar all-*trans* configuration just as the other steroid hormones, then it is not possible to explain this anomalous behavior on steric grounds. An inversion at carbon atom 17 during the high temperature aromatization may be considered improbable, since the final product (III) in both syntheses proved to be the same.

Decomposition in boiling acetic acid solution gave 56% of the ketol acetate III, which was shown to be identical with the specimen synthesized by the first procedure by analysis, rotation, mixed melting point determination, ultraviolet and infrared absorption spectra. The infrared spectra were taken in carbon disulfide solution and showed maxima at 1733 and 1756 cm.$^{-1}$ characteristic of the ketol acetate grouping.[10]

The configuration of the ethynyl group in 17-ethynylestradiol (IV) is generally believed to be α by analogy to the corresponding reaction in the androstane series[11] and since the Serini reaction is known to involve inversion,[5] the final product III should have the ketol side-chain in the β-configuration as is the case with the naturally occurring cortical hormones. The satisfactory agreement in the

FLOWSHEET II



The 3-methyl ether 17-carboxylic acid (VIIIc) was converted by the Wilds–Shunk procedure[9] to the acid chloride and thence to the crystalline diazoketone IX in 61% yield (based on VIIIc).

TABLE I

EVIDENCE FOR β-CONFIGURATION OF SIDE-CHAIN BY MOLECULAR ROTATION DIFFERENCES

Compound	$[\alpha]_D$ Anhydr. ethanol	$[M]_D$[a]	$\Delta[M]_D$
3-Methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III)	+160°	592	+372
3-Methoxy-1,3,5-estratriene[b]	+ 81°	220	
Desoxycorticosterone acetate[c]	+181°	673	+382
Δ^4-Androsten-3-one[d]	+107°	291	
17-Isodesoxycorticosterone acetate[e]	− 26°	−97	−388

[a] $[M]_D$ = $[\alpha]_D$ × mol. wt./100. [b] A. Butenandt, I. Störmer and U. Westphal, *Z. physiol. Chem.*, 208, 149 (1932). [c] In 95% ethanol, $[\alpha]^{25}D$ was +188°. [d] Kindly furnished by Dr. A. F. St. André of our laboratories. [e] C. W. Shoppee, *Helv. chim. acta*, 23, 930 (1940); this rotation was determined in acetone solution.

(8) The 1-methyl-3-hydroxy-1,3,5-triene structure of the acid X and of all the other products arising from dienone-phenol rearrangements studied by us [THIS JOURNAL, **68**, 1712, 2125 (1946); **69**, 2404 (1947); **70**, 1911 (1948); *J. Org. Chem.*, **13**, 697, 848 (1948)] was assigned by analogy to an unequivocal case in the chrysene series [Wilds and Djerassi, THIS JOURNAL, **68**, 1715 (1946)] in which the structure of both the dienone and the rearrangement product was proven by total synthesis. Recent work in Prof. R. B. Woodward's laboratory at Harvard (private communication to C. D.) with simple model compounds has indicated that in the steroid series the following two structures are equally plausible: 1-methyl-4-hydroxy-1,3,5-triene or 1-hydroxy-4-methyl-1,3,5-triene. For simplicity's sake, the 1-methyl-3-hydroxy structure is used until unequivocal evidence is presented for an example in the steroid series.

(9) Wilds and Shunk, THIS JOURNAL, **70**, 2427 (1948); *cf.* also Djerassi, Scholz and Leathem, *Experientia*, **5**, 204 (1949).

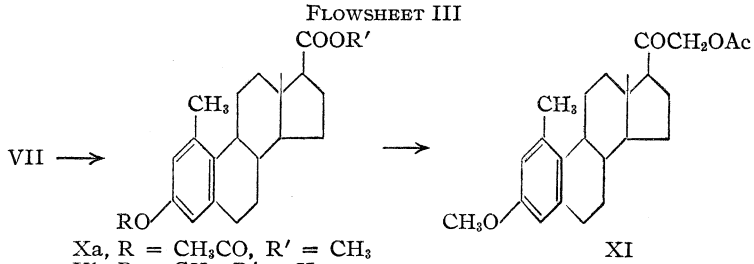
(10) Jones, Williams, Whalen and Dobriner, THIS JOURNAL, **70**, 2024 (1948).

(11) Ref. 5, p. 328.

calculation of the molecular rotation differences (Table I) lends considerable support to this statement.

The diazoketone synthesis was also employed in the preparation of the aromatic desoxycorticosterone analog XI with a methyl group at C-1[8] (Flowsheet III). Methyl 1-methyl-3-acetoxy-1,3,5-estratriene-17-carboxylate (Xa), previously obtained[6] in high yield by dienone–phenol rearrangement of VII, was converted to 1-methyl-3-methoxy-1,3,5-estratriene-17-carboxylic acid (Xb) in 76% over-all yield. Treatment of its acid chloride (prepared by the Wilds–Shunk procedure)[9] with diazomethane led to an oily diazoketone which on decomposition with acetic acid afforded the desired 1-methyl-3-methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (XI).

FLOWSHEET III



Xa, R = CH_3CO, R′ = CH_3
Xb, R = CH_3, R′ = H

XI

Preliminary results of the biological investigation by Dr. James H. Leathem of the Bureau of Biological Research, Rutgers University, indicate that the aromatic analogs III and XI of desoxycorticosterone acetate when administered in oil solution are inactive as estrogens in 1-mg. doses (uterine weight increase in rats) and do not maintain the life of adrenalectomized rats in 0.5-mg. doses (desoxycorticosterone acetate under the same conditions is effective at a 0.05-mg. level).

Acknowledgment.—The authors are indebted to the Misses Frances Hoffmann and Edwina Leathem for their capable assistance, to Miss Verda Powell for the rotations and ultraviolet absorption spectra and to Dr. A. F. St. André for furnishing the palladium catalyst and a sample of Δ^4-androsten-3-one. The infrared spectra were determined at the Sloan–Kettering Institute for Cancer Research, New York City, through the courtesy of Dr. K. Dobriner and Mrs. P. Humphries.

Experimental[12]

17-Vinylestradiol (Va).—A solution of 2.50 g. of 17-ethynylestradiol (IV)[3] in 50 ml. of C.P. pyridine was shaken at room temperature with hydrogen in the presence of 0.4 g. of 2% palladium–calcium carbonate catalyst.[1] After an initial lag of ten to thirty minutes, the hydrogen uptake proceeded smoothly and stopped after *ca.* forty minutes (one mole of hydrogen), whereupon the catalyst was filtered and solvent was removed *in vacuo*. Trituration with ether and hexane afforded 2.22 g. (88%) of colorless crystals with m. p. 142–147°, $[\alpha]^{25}D$ +59.5° (dioxane), which were satisfactory for the next step; lit.,[3] m. p. 148–150°, $[\alpha]D$ +57.3° (dioxane).

The 3-monoacetate crystallized in colorless prisms from hexane, m. p. 126–127.5°, $[\alpha]^{25}D$ +61.2° (dioxane).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.25; H, 8.19.

17-Vinylestradiol 3-Methyl Ether (Vb).—Methylation was accomplished by treating 2.22 g. of the above phenol (Va) in 50 ml. of ethanol over a period of ten minutes on the steam-bath four times alternately with 4-ml. portions each of 50% aqueous potassium hydroxide and dimethyl sulfate. The alkaline solution was heated for an additional ten minutes, then cooled and acidified with dilute acid. The precipitate (2.20 g., m. p. 90–95°) was collected and recrystallized from a mixture of hexane and acetone, whereupon it was obtained as colorless crystals with m. p. 98–100°, $[\alpha]^{25}D$ +60° (chloroform); yield 1.89 g. (82%).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.84; H, 9.37.

3-Methoxy-10-nor-1,3,5-pregnatriene-17,20,21-triol 20,21-Diacetate (VI).—A mixture of 1.85 g. of the methyl ether Vb, 2 g. of osmium tetroxide and 160 ml. of anhydrous ether was allowed to stand in a closed flask at room temperature for five days. The ether was decanted and the black residue was refluxed for three and one-half hours with 50 ml. of ethanol, 100 ml. of water and 14 g. of sodium sulfite heptahydrate. After filtration and boiling of the precipitate repeatedly with ethanol, the combined extract and filtrate were concentrated, diluted with water, extracted with ether and the washed and dried ether solution was evaporated to a small volume. The colorless crystals (1.29 g., m. p. 136–143°) of the triol were filtered and directly acetylated by heating for three and one-half hours at 65° with 15 ml. of acetic anhydride and 25 ml. of pyridine. Evaporation of the solution to dryness under reduced pressure and trituration of the residue with hexane yielded 1.28 g. (50% over-all) of diacetate with m. p. 109–113°, which was satisfactory for the Serini reaction. The analytical sample, obtained from hexane, had m. p. 111–113°, $[\alpha]^{25}D$ +19° (chloroform).

Anal. Calcd. for $C_{28}H_{34}O_6$: C, 69.74; H, 7.96; methoxyl, 7.21; acetyl, 19.99. Found: C, 69.57; H, 8.02; methoxyl, 7.67; acetyl, 19.68.

3-Methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III) from Serini Reaction on Diacetate VI.—A solution of 400 mg. of the above diacetate VI in 80 ml. of dry toluene was refluxed for forty-eight hours with 8 g. of zinc dust, then filtered while still hot and the solvent removed under reduced pressure. The residue was chromatographed on 8 g. of dil. sulfuric-acid-washed alumina (Aluminum Company of America, Grade F-20, 80–200 mesh) and the product was eluted with a mixture of hexane and benzene (60/40). Recrystallization from hexane gave 215 mg. (63%) of colorless, prismatic needles of the ketol acetate III with the following physical constants: m. p. 118–119°, $[\alpha]^{25}D$ +157 ± 0.5° (chloroform), +160° (ethanol), maximum at 278 mμ (log *E* 3.39) and minimum at 246 mμ (log *E* 2.72); the infrared spectrum showed carbonyl peaks at 1733 and 1756 cm.$^{-1}$ typical of the cortical hormone side-chain.[10]

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16; acetyl, 11.62; methoxyl, 8.38. Found: C, 74.79; H, 8.34; acetyl, 12.27; methoxyl, 8.85.

(12) All melting points are corrected unless noted otherwise. Rotations were determined on 5–10-mg. of sample in 1.2 ml. of solvent in a 1-dcm. polarimeter tube of 1-ml. capacity. All ultraviolet absorption spectra measurements were carried out in ethanol solution on a Beckman quartz photoelectric spectrophotometer, while the infrared spectra were measured in carbon disulfide solution at the Sloan–Kettering Institute on a Perkin–Elmer infrared spectrometer. The microanalyses were carried out by Mr. Joseph F. Alicino, Metuchen, N. J.

(13) Busch and Stöve, *Ber.*, **49**, 1064 (1916).

Methyl 3-Hydroxy-1,3,5-estratriene-17-carboxylate (VIIIa).[14]—A 44% yield of material of satisfactory purity (m. p. 212–216°) was realized by using the same reaction conditions for the aromatization of methyl 3-ketoetiochola-1,4-dienate (VII)[6] as were reported by Inhoffen[7] for the conversion of 1,4-androstadien-17-ol-3-one to estradiol. Recrystallization from ethanol afforded colorless crystals of the methyl ester VIIIa; m. p. 219–220°, $[\alpha]^{24}D$ +107° (acetone), which exhibited the typical ultraviolet absorption spectrum of a phenol: maximum at 280 mμ (log *E* 3.39) and minimum at 247.5 mμ (log *E* 2.63).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; methoxyl, 9.87. Found: C, 76.29; H, 8.33; methoxyl, 9.61.

The 3-acetate 17-methyl ester (VIIIe), prepared by heating the phenol VIIIa for one hour with acetic anhydride and pyridine, was obtained as colorless needles from a mixture of hexane and acetone, m. p. 146–147.5°, $[\alpha]^{24}D$ +79.7° (acetone).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; acetyl, 12.07. Found: C, 74.43; H, 7.73; acetyl, 12.37.

3-Hydroxy-1,3,5-estratriene-17-carboxylic Acid (VIIId).—The 3-hydroxy 17-methyl ester VIIIa could be saponified only with difficulty. When 150 mg. of the methyl ester was refluxed with 500 mg. of potassium hydroxide and 20 ml. of methanol for eighteen hours, less than 30% of the material was saponified. By contrast, the dienone ester VII was saponified readily under these conditions. Complete hydrolysis was accomplished by refluxing 100 mg. of the ester with either 1 g. of potassium hydroxide and 5 ml. of methanol, or 10 ml. of a hydrobromic acid–acetic acid mixture (30 ml. of glacial acetic acid, 20 ml. of 48% hydrobromic acid and 10 ml. of water)[15] for eighteen hours. The crude acid, which is readily removed from ether with sodium carbonate solution, although the sodium salt is not too soluble in water, melted at approximately 256–263° (dec., uncor.). After recrystallization from hexane–acetone, the following constants were observed: m. p. 270–274° (dec., uncor.), $[\alpha]^{25}D$ +98.4° (acetone), maximum at 280 mμ (log *E* 3.32) and minimum at 248 mμ (log *E* 2.81). A sample was dried at 120° under vacuum for twelve hours before analysis.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05; neut. equiv., 300. Found: C, 76.37; H, 8.15; neut. equiv., 304.

Methyl 3-Methoxy-1,3,5-estratriene-17-carboxylate (VIIIb).—The methylation of the phenolic methyl ester VIIIa was carried out with dimethyl sulfate exactly as described for 17-vinylestradiol (Va) and afforded 94% of material of m. p. 160–163° suitable for the saponification step. The analytical sample crystallized from ethanol as long needles, m. p. 163–164°, $[\alpha]^{26}D$ +47.6° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; methoxyl, 18.90. Found: C, 76.57; H, 8.43; methoxyl, 18.93.

3-Methoxy-1,3,5-estratriene-17-carboxylic Acid (VIIIc).—The above ester VIIIb was saponified by refluxing 2.56 g. for eighteen hours with 25 g. of potassium hydroxide and 125 ml. of methanol. Acidification with dilute acid, followed by filtration and digestion with boiling ethanol gave 2.14 g. (87%) of the desired acid VIIIc with m. p. 217–218°. Recrystallization from ethanol raised the m. p. to 219–220°, $[\alpha]^{26}D$ +102° (dioxane).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; methoxyl, 9.87. Found: C, 76.56; H, 8.28; methoxyl, 10.05.

3-Methoxy-17-(β-diazoacetyl)-1,3,5-estratriene (IX).—Six hundred milligrams of the acid VIIIc was converted into the sodium salt by dissolving in hot ethanol, adding 80 mg. of sodium hydroxide and evaporating to dryness in a current of air. The nearly colorless sodium salt was dried at 100° and 30 mm. for eighteen hours and then suspended in 15 ml. of dry benzene and 3 drops of pyridine. Oxalyl chloride (3 ml.) was added while cooling in ice and after five minutes at 10°, the yellow solution was distilled to dryness at room temperature *in vacuo*. After adding benzene twice and evaporating, the residue was stirred with benzene, filtered through sintered glass and the nearly colorless filtrate was added to an undistilled ethereal solution of diazomethane (from 7.5 g. of nitroso methylurea) kept at −10° and previously dried for two hours over solid potassium hydroxide. After one hour in ice, the solvent was removed under reduced pressure at 20° and the solid residue was recrystallized from a mixture of hexane and acetone yielding 390 mg. (61%) of the light yellow diazoketone IX with m. p. 126–128° (gas evolution complete at 135°). Extremely slow burning was necessary to obtain even fair analytical results.

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 73.87; H, 7.96; N, 8.57.

3-Methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III) from the Diazoketone IX.—The solid diazoketone (390 mg.) was dropped slowly into 20 ml. of boiling glacial acetic acid[9] and heating was continued for an additional five minutes. The yellow solution was evaporated to dryness and the residue was chromatographed as described above yielding 240 mg. (56%) of the ketol acetate III with m. p. 113–115°, $[\alpha]^{25}D$ +158° (chloroform). Further recrystallization raised the m. p. to 117–118° and no depression was observed on admixture with a specimen prepared by the first method from 17-vinylestradiol. The ultraviolet and infrared spectra of the two samples were identical.

1-Methyl-3-methoxy-1,3,5-estratriene-17-carboxylic Acid (Xb).—A solution of 1.90 g. of the 3-acetoxy 17-methyl ester Xa[6] in 80 ml. of methanol was refluxed with 8 g. of potassium hydroxide for three hours and acidified. The precipitate was collected, dried and then treated in ether solution with diazomethane.[16] The solvent was removed after a few minutes, the residue was dissolved in ethanol and methylated with dimethyl sulfate in the presence of 50% aqueous potassium hydroxide solution as described previously. The crude 3-methoxy 17-methyl ester was not purified, but was saponified directly by refluxing with 5 g. of potassium hydroxide and 60 ml. of methanol for four hours. After dilution with water and extraction with ether, the alkaline solution was acidified, and afforded 1.27 g. (76%) of the desired 3-methoxy-17-carboxylic acid (Xb) melting at 237–245°. The analytical sample crystallized from acetone; m. p. 245–246°, $[\alpha]^{23}D$ +242° (chloroform), minimum at 251 mμ (log *E* 2.77) and broad maximum at 278–284 mμ (log *E* 3.32).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; methoxyl, 9.45. Found: C, 76.41; H, 8.47; methoxyl, 9.33.

1-Methyl-3-methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (XI).—The diazoketone synthesis was carried out exactly as described above for the acid VIIIc, except that the diazoketone was obtained as an oil, and was therefore treated with acetic acid without purification. The desired ketol acetate XI was obtained in 27% yield with m. p. 152–154° after crystallization from a mixture of hexane and acetone. Further recrystallization afforded rosettes of colorless prisms with m. p. 154–156°, $[\alpha]^{24}D$ +276° (chloroform). The infrared spectrum showed the characteristic peaks[10] at 1733 and 1756 cm.$^{-1}$, while the ultraviolet absorption spectrum exhibited a broad maximum at 278–284 mμ (log *E* 3.33), already observed with the precursor Xb, and a minimum at 248 mμ (log *E* 2.34).

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.96; H, 8.39; acetyl, 11.19. Found: C, 74.72; H, 8.24; acetyl, 11.09.

Summary

Two syntheses of 3-methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III), an aromatic analog of desoxycorticosterone acetate, are described. The first procedure involved hydroxylation of 17-

(14) The identical methyl ester (mixed melting point determination) was isolated recently from strophanthidin by Ehrenstein and co-workers (*J. Org. Chem.*, in press).

(15) Johnson, Petersen and Schneider, THIS JOURNAL, **69**, 75 (1947).

(16) The intermediate methylation with diazomethane was essential for a good yield.

vinylestradiol methyl ether (Vb) with osmium tetroxide followed by acetylation and Serini reaction of the 20,21-diacetate (VI). The second method consisted of partial aromatization of ring A with the elimination of the angular methyl group of an appropriately substituted etiocholanic acid derivative (VII) and subsequent introduction of the ketol side-chain *via* the diazoketone.

The diazoketone synthesis was also employed in the preparation of an aromatic cortical hormone analog (XI) with a methyl group at C-1. Neither product showed estrogenic or life maintenance activity in rats at the dosage tested.

SUMMIT, NEW JERSEY RECEIVED JUNE 18, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF ANTIOCH COLLEGE]

Beta Acetylenic Grignard Reagents. I. Hydrolysis and Carbonation of γ-Phenylpropargylmagnesium Bromide

BY GERALD R. LAPPIN*

An earlier investigation of the reaction of β-acetylenic halides with magnesium[1] reportedly showed that no Grignard reagent was formed and only coupling occurred. It has now been found that certain of these halides do yield an organometallic derivative with magnesium, at least one, γ-phenylpropargyl bromide, giving an excellent yield under the ordinary conditions of this reaction.[2]

The structural similarity of β-acetylenic Grignard reagents to those derived from allylic halides led to the question of whether the former would undergo rearrangement similar to the well-known rearrangement of allylmagnesium halides, yielding both acetylenic and allenic products. Rearrangement of β-acetylenic compounds to allenes has been observed[3] but under conditions totally unlike those of the Grignard reaction. When it was found that these new organomagnesium compounds could be prepared it was decided to investigate this possible rearrangement. Because it required no special method and was obtained in high yield γ-phenylpropargylmagnesium bromide was chosen for this study[4] and the reactions chosen were hydrolysis and carbonation.

$$R{-}C{\equiv}C{-}CH_2MgBr + XY \longrightarrow R{-}C{\equiv}C{-}CH_2{-}X + R{-}\underset{\displaystyle X}{\underset{|}{C}}{=}C{=}CH_2 + MgBrY$$

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(1) Lai, *Bull. soc. chim.*, **53**, 1543 (1933).

(2) Since the completion of the work herein described, Newman and Wotiz, THIS JOURNAL, **71**, 1292 (1949), have briefly mentioned the preparation in 95% yield of a Grignard reagent from 1-bromo-2-heptyne using a special "high dilution technique" which was not described. Carbonation was said to yield an unidentified mixture of acids. In this Laboratory the Grignard reagent has been prepared from 1-bromo-2-octyne in about 30% yield by a method which will be described in a subsequent publication.

(3) For a summary of such rearrangements see Johnson, "Acetylenic Compounds," Edward Arnold and Company, London, 1946, Vol. I, p. 63 ff.

(4) Later results have shown this choice to be a poor one for the phenylpropadiene derivatives polymerize much more rapidly than purely aliphatic allenic compounds. Further work on these rearrangements is being carried out with octynylmagnesium bromide.

Discussion of Results

Hydrolysis.—The hydrolysis of γ-phenylpropargylmagnesium bromide (I) under oxygen and peroxide free conditions gave up to an 87% yield of monomeric hydrocarbon product. On distillation through a high efficiency fractionating column this gave phenylpropadiene (II) as well as 1-phenyl-1-propyne (III) along with a considerable amount of polymeric residue. Both products were identified by comparison with the previously reported characteristics, II being identified by its boiling point,[5,6] refractive index,[6] rapid polymerization[5,6] and rapid uptake of oxygen from the air to form a ketone, presumably methyl phenyl diketone.[5] Identification of III was made through its boiling point and refractive index.[7] Final confirmation was obtained from the oxidation of these hydrocarbons with potassium permanganate in pyridine solution,[8] II yielding only benzoic acid while III gave both benzoic and acetic acids.

An attempt was made to determine the ratio of acetylene to allene formed by oxidation followed by analysis for the ratio of benzoic to acetic acid formed.[8] Because of the rapid polymerization of II consistent results were not obtained, the amount of II present in the monomeric product ranging from 6 to 37% in various experiments. However, in those experiments which gave a low yield of monomeric II a high yield of polymer was obtained and if the polymer consisted only of phenylpropadiene this must have made up more than half of the total hydrolysis product. Since in at least one experiment practically no volatile monomer was obtained it is evident that copolymerization between II and III can occur so that any estimate of the composition of the total reaction mixture is very doubtful. It was clearly shown, nevertheless, that an allylic-like rearrangement did occur, whether during the formation of the organomagnesium bromide or during the subsequent hydrolysis it is, at present, impossible to say.

(5) Bourguel, *Compt. rend.*, **192**, 686 (1931).

(6) Ginsberg, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1029 (1938).

(7) Truchet, *Ann. chim.*, **16**, 309 (1931).

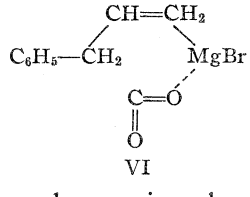
(8) Young, Ballou and Nozaki, THIS JOURNAL, **61**, 12 (1939).

Carbonation.—The carbonation of I was carried out in the usual fashion but in the absence of oxygen and peroxides. An acidic product was obtained but all attempts to isolate either of the expected products, 1-phenyl-1-propyne-3-carboxylic acid (IV) or 1-phenylpropadiene-1-carboxylic acid (V), failed because of complete polymerization of the product either on distillation or even on standing in the refrigerator for a few hours. Oxidation of a portion of the acidic product gave benzoic acid and malonic acid derived from IV but no phenylglyoxylic acid from V. However, a positive qualitative test for the presence of ketone in the oxidation product was obtained. When the unsaturated acidic product was subjected to low pressure hydrogenation over palladium catalyst before distillation, it was possible to obtain in low yield the two corresponding saturated acids, 4-phenylbutanoic acid and 2-phenylbutanoic acid, though only about 40% of the theoretical hydrogen uptake was observed indicating that extensive polymerization must have occurred. However, here again it was clearly evident that an allylic-like rearrangement had taken place.

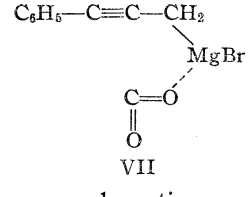
$$C_6H_5{-}C{\equiv}C{-}CH_2MgBr + CO_2 \xrightarrow{\text{hydrolysis}} C_6H_5{-}C{\equiv}C{-}CH_2COOH \quad IV$$

$$C_6H_5{-}C(=C=CH_2)(-COOH) \quad V$$

One of the possible mechanisms suggested by Young[9] for the rearrangement of allylic Grignard reagents in their reactions with carbonyl compounds involves the formation of a six-membered ring in an intermediate complex (VI). It seems structurally impossible for a β-acetylenic Grignard reagent to react through a similar mechanism (VII). Thus the rearrangement of γ-phenylpropargylmagnesium bromide on carbonation may constitute some evidence against this mechanism. However, considerably more study will be required before it can be known whether this new type of rearrangement is fundamentally or only superficially similar to that of allylic Grignard reagents.



VI



VII

Experimental[10]

Preparation and Hydrolysis of γ-Phenylpropargylmagnesium Bromide.—The reaction was carried out in a special indented flask fitted with a high speed stirrer giving extremely vigorous agitation and under the usual anhydrous conditions using an atmosphere of dry nitrogen throughout the entire experiment. To 2.88 g. (0.12 g. atom) of magnesium turnings in 150 ml. of dry ether was added dropwise over a period of four hours a solution of 24 g. (0.12 mole) of γ-phenylpropargyl bromide[11] in 200 ml. of anhydrous ether. After addition of all the bromide the solution was warmed on the water-bath for one hour. Titration of a 1-ml. aliquot with standard acid indicated a yield of 92% of RMgBr. Hydrolysis was carried out by adding to the ether solution dropwise a cold 5% sulfuric acid solution while cooling the flask in an ice–salt-bath. The ethereal layer was separated, washed with water, 5% sodium bicarbonate solution, and with water again. After drying over Drierite the ether was removed under reduced pressure at 20° and the residue was flash distilled at 1 mm. pressure and an oil-bath temperature of 65° to separate the monomeric product from polymerization products. The yield of volatile product was 12.9 g. (87% based on the product being C_9H_8). The non-volatile residue was a soft brown material resembling closely the description of phenylpropadiene polymer.[5]

Fractionation of the Volatile Product.—Still maintaining the atmosphere of dry nitrogen, 10 g. of the volatile product was distilled through a 50-plate distilling column[12] at 15 mm. pressure. Three fractions were collected. The first, b. p. 68–69°, $n^{20}D$ 1.563, 1.7 g., was colorless when first collected but rapidly turned deep yellow on exposure to air and polymerized to a soft brown solid on standing for a few hours. The freshly distilled material gave a scarlet sodium salt when warmed with sodium in dry benzene. This is a reported reaction of phenylpropadiene.[6] After short exposure to air this fraction gave a positive carbonyl test with 2,4-dinitrophenylhydrazine and alcoholic potassium hydroxide.[13] These properties and reactions agree well with those reported for phenylpropadiene.[5,6] The second fraction, b. p. 69–72°, $n^{20}D$ 1.561, 3.8 g., was colorless when collected, slowly turned pale yellow on standing for a few hours, but did not polymerize after being exposed to air for several weeks. A weak positive test for carbonyl was obtained from the yellowed fraction. This was presumed to be a mixture of II and III. The third fraction, b. p. 72–73°, $n^{20}D$ 1.560, 2.8 g., was colorless even after standing exposed to air for several hours and gave a negative ketone test after being exposed to the air for two days. Its properties agree well with those of 1-phenyl-1-propyne (III).[7] A soft polymeric residue of about 1.5 g. remained in the pot.

Oxidation of the Volatile Product and the Fractions from Distillation.—Samples (0.3–0.5 g.) of the volatile product and of each of the above-mentioned fractions were oxidized in pyridine solution with potassium permanganate by the method of Young, Ballou and Nozaki.[8] The oxidation products were analyzed for the ratio of benzoic acid to acetic acid produced as described by these authors. The volatile product analyzed for a mixture of 37% II and 63% III, but the volatile products from other similar reactions ranged from a low of 6% II to this high value. However, in those experiments which gave a low proportion of II the amount of non-volatile product was larger indicating that, while the allene was formed, it had polymerized before the flash distillation. The first fraction from the distillation analyzed for 93% II and 7% III, the second fraction for 25% II and 75% III, the third for 98% III and 2% II thus confirming the identity of these fractions.

Carbonation of γ-Phenylpropargylmagnesium Bromide.—The Grignard reagent was prepared as previously described from 24 g. (0.12 mole) of the bromide and 2.88 g.

(9) Young and Roberts, THIS JOURNAL, **68**, 649 (1946).

(10) The ether used herein was carefully freed from peroxides and stored under nitrogen. The use of ether containing 0.005% peroxide in a carbonation experiment resulted in complete polymerization of the product.

(11) This was prepared from the corresponding alcohol by reaction with phosphorus tribromide using the method of Lai [*Bull. soc. chim.*, **53**, 1533 (1933)]. However, yields of 90–95% were obtained consistently in contrast to the reported yield of about 70%.

(12) Precise Fractionation Assembly manufactured by Todd Scientific Company, Springfield, Pa.

(13) Clark and Lappin, unpublished research, Antioch College.

(0.12 g. atom) of magnesium turnings in 250 ml. of anhydrous ether using a nitrogen atmosphere. Titration of a 1-ml. aliquot indicated an 81% yield of RMgX. A large excess of air-free carbon dioxide, dried by bubbling through sulfuric acid followed by passing through anhydrous alumina, was passed into the solution of the organomagnesium bromide while cooling the reaction flask in an ice-bath. Hydrolysis was carried out immediately by adding dropwise about 50 ml. of cold 5% sulfuric acid to the cooled reaction mixture. All subsequent operations were carried out under a carbon dioxide atmosphere. The ether layer was separated and washed three times with 20-ml. portions of cold water. The acidic product was extracted with three 20-ml. portions of ice-cold 5% aqueous sodium hydroxide solution and the basic extract was washed twice with small portions of ether. The basic extract was covered with 50 ml. of ether and, while cooling in an ice-bath, acidified with cold dilute sulfuric acid. After separating the ether layer the aqueous layer was again extracted with a 25-ml. portion of ether. The combined ether extracts were dried over Drierite and the ether was removed under reduced pressure. The sirupy residue was dissolved in 100 ml. of absolute ethanol and the solution was filtered through a 1-cm. bed of decolorizing charcoal. To it was added 0.5 g. of 5% palladium-on-charcoal and hydrogenation was carried out at 60 lb. pressure and room temperature in a Parr low pressure hydrogenation apparatus. The hydrogen uptake was 6 lb. over a period of three hours, theory requiring 15.2 lb. assuming a quantitative yield of C_9H_7COOH from the organomagnesium bromide. After removal of the catalyst and distillation of the ethanol the brown sirupy residue was distilled through a small spiral-packed column at atmospheric pressure. No decomposition occurred and two main fractions were collected. The first, b. p. 268–272°, 0.8 g., was a thick yellow sirup which would not crystallize even after long standing in the refrigerator. The second, b. p. 290–294°, 3.1 g., was a thick sirup which crystallized after several weeks at 0°, m. p. 49–50° after two recrystallizations from ethanol. The reported properties of the two expected isomeric phenylbutanoic acids are: 2-phenylbutanoic acid,[14] b. p. 270–272°, m. p. 41–42°; 4-phenylbutanoic acid,[15] b. p. 290°, m. p. 51°, m. p. of amide 84–85°. Inasmuch as no solid derivative was reported for 2-phenylbutanoic acid and time did not permit the preparation of an authentic sample of this substance the neutral equivalent and molecular weight of the first fraction were determined. Calcd. for $C_{10}H_{12}O_2$: neut. equiv., 164; mol. wt., 164. Found: neut. equiv., 168; mol. wt., (cryoscopic in benzene) 170. On the basis of its boiling point, neutral equivalent and molecular weight fraction one was identified with reasonable certainty as 2-phenylbutanoic acid. Fraction two was converted to the amide in the usual manner, m. p. 83–85°, thus confirming its identity as 4-phenylbutanoic acid.

In another identical experiment an attempt was made to separate the expected acetylenic and allenic acids before hydrogenation by distillation at 0.1 mm. pressure. No distillate was obtained and the material became hard and resinous. A 3-g. sample of the unsaturated acidic product was oxidized in pyridine solution with potassium permanganate at 50° for four hours. To the mixture was added 50 ml. of water and the precipitated manganese dioxide was removed by filtration. The solution was evaporated to dryness under vacuum and the residue was redissolved in 50 ml. of water. A small portion was neutralized with dilute sulfuric acid and tested for presence of ketone,[13] a strongly positive test being obtained. However, all attempts to isolate a derivative of phenylglyoxylic acid failed. The basic solution was cooled to 5° and passed through a cation exchange resin column to convert the salts to the free acids. Evaporation of the solution to 5 ml. *in vacuo* resulted in the crystallization of 1.1 g. of benzoic acid, identified by mixture melting point with an authentic sample. The filtrate was evaporated to dryness and the residue taken up in ether. Evaporation of the ether solution to a volume of about 3 ml. *in vacuo* resulted in the crystallization of 0.3 g. of malonic acid, identified by mixture melting point with an authentic sample. No phenylglyoxylic acid was isolated.

(14) Ruber, *Ber.*, **36**, 1406 (1903).

(15) Willgerodt and Merck, *J. prakt. Chem.*, [2] **80**, 197 (1909).

Summary

1. The preparation of a Grignard reagent from a β-acetylenic halide, γ-phenylpropargyl bromide, is described for the first time.

2. Hydrolysis of γ-phenylpropargylmagnesium bromide has been shown to give not only the expected 1-phenyl-1propyne but also phenylpropadiene, indicating that an allylic-like rearrangement occurred.

3. Carbonation of this Grignard reagent gave a mixture of unsaturated acids which could not be separated because of the rapid polymerization which occurred. However, immediate hydrogenation of this mixture gave a low yield of both 4-phenylbutanoic acid and 2-phenylbutanoic acid, indicating that here, too, rearrangement of an allylic nature had occurred.

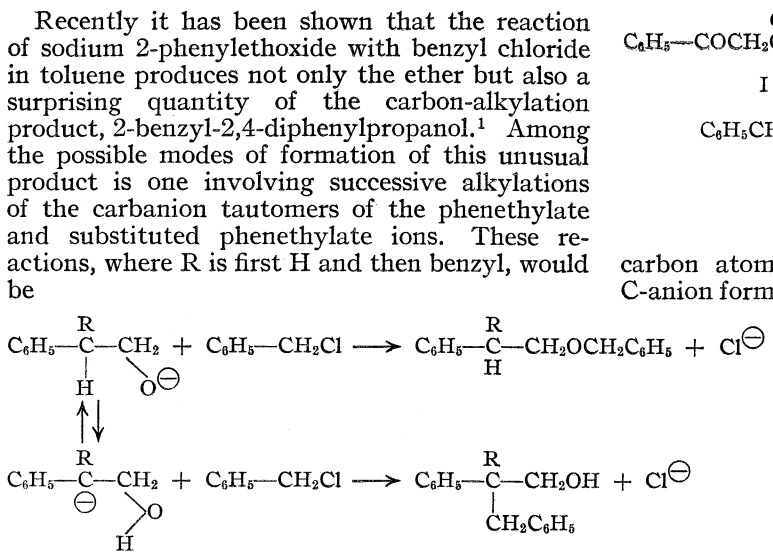
YELLOW SPRINGS, OHIO RECEIVED MAY 25, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

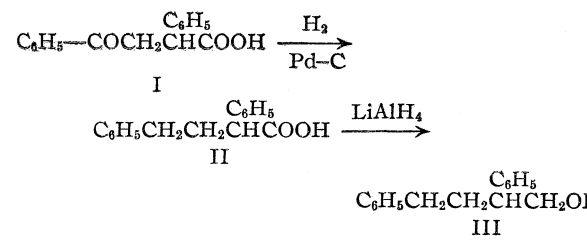
The Preparation and Attempted Racemization of Optically Active 2,4-Diphenylbutanol

BY ROBERT H. BAKER AND SIDNEY H. JENKINS, JR.

Recently it has been shown that the reaction of sodium 2-phenylethoxide with benzyl chloride in toluene produces not only the ether but also a surprising quantity of the carbon-alkylation product, 2-benzyl-2,4-diphenylpropanol.[1] Among the possible modes of formation of this unusual product is one involving successive alkylations of the carbanion tautomers of the phenethylate and substituted phenethylate ions. These reactions, where R is first H and then benzyl, would be



Although the existence of such carbanions seemed highly improbable, the possibility was easily brought to test by attempting the racemization of a suitable optically active alcohol. For this purpose the enantiomorphic forms of 2,4-diphenylbutanol were synthesized and heated at 100° with sodium in toluene. No racemization was observed and thus the possibility of the tautomeric anion is eliminated. This result might have been anticipated from those of Doering and Aschner[2] on 2-methylbutanol but it was felt that the acid-strengthening phenyl group on the 2-carbon atom would increase the probability of C-anion formation.



In a less critical test sodium 2-phenylethoxide in toluene was treated with carbon dioxide. Critical examination of the alkali-soluble hydrolysis product revealed the presence of a trace of benzoic acid, but no tropic acid could be isolated.

2,4-Diphenylbutanol was chosen for the racemization studies because it was needed in another problem and an easy synthesis was indicated. 2-Phenyl-3-benzoylpropanoic acid was resolved and the active forms were reduced catalytically to the 2,4-diphenylbutanoic acids.[3] These acids were then reduced with lithium aluminum hydride to the 2,4-diphenylbutanols, Table I. The ratios of the rotations of the (+) and (−) isomers is sufficiently constant to suggest that little or no racemization accompanies the reductions. Some attempts were made to resolve 2,4-diphenylbutanoic acid but the results were not promising.

TABLE I

REDUCTION OF ACTIVE ACIDS

2-Phenyl-3-benzoylpropanoic acid		2,4-Diphenylbutanoic acid			2,4-Diphenylbutanol				
Mmoles reduced	$[\alpha]^{27}D$	Yield, %	$[\alpha]^{27}D$	Concn. in EtOH	Mmoles reduced	Yield, %	$n^{25}D$	$[\alpha]^{27}D$	Concn. in EtOH
49	+136	84	+55	0.84	40	96	1.5673	+24	2.60
20	−111	75	−41	1.03					
30	−111	90	−43	1.13	40	77	1.5675	−15	1.74

TABLE II

α-NAPHTHYLCARBAMATES AND 3,5-DINITROBENZOATES OF 2,4-DIPHENYLBUTANOL

Cmpd. $[\alpha]^{27}D$ of alcohol	Formula	M. p., °C.	$[\alpha]^{27}D$	Conc.	Solvent	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
ANC +24	$C_{27}H_{25}NO_2$	106–107[b]	+12	0.67	EtOH	81.90	81.91	6.38	6.56
ANC −15		106–106.5	−10	.60	EtOH		81.65		6.48
DNB +24	$C_{23}H_{20}N_2O_6$	97–98.2	− 5.5	.55	EtOAc	65.71	65.67	4.81	5.04
DNB −15		97–97.5	+21[c]	.52	EtOAc		65.76		4.80

[a] Microanalyses by Margaret Hines. [b] Mr. Martin Knell of these laboratories reports the m. p. of the racemic material is 102–103°. [c] The optical purity of this compound may have been increased by its extensive crystallization preparatory to analysis.

(1) Baker, THIS JOURNAL, **70**, 3857 (1948).

(2) Doering and Aschner, *ibid.*, **71**, 838 (1949).

(3) Baker and Jenkins, *ibid.*, **68**, 2102 (1946).

in Table II. It is observed that the dinitrobenzoates have signs of rotation opposite to the alcohols from which they are derived.

Experimental

Resolution of 2-Phenyl-3-benzoylpropanoic Acid.—A solution of the acid, 50.8 g. (0.2 mole) in 1 l. of ethyl acetate was mixed with 64.8 g. (0.2 mole) of (−) quinine in 1 l. of ethyl acetate and the mixture was allowed to crystallize at 8° overnight.[4] The first crop of crystals was alternately crystallized from methanol and ethyl acetate and decomposed by sodium hydroxide to produce the acid which was crystallized from ether, $[\alpha]^{27}D$ +136° (*c*, 1.03 in ethyl acetate). This acid was 86% optically pure as judged by Hann and Lapworth's values.[4]

The ethyl acetate-soluble salt gave 13 g. (51%) of acid, $[\alpha]^{27}D$ −111° (*c*, 1.40 in ethyl acetate).

(+) and (−)2,4-Diphenylbutanoic Acids.—The keto acid, I, was reduced over palladium–charcoal in glacial acetic acid containing perchloric acid as previously described for the racemic acid.[3] The acids were crystallized once from 60–70° petroleum ether to give the results shown in Table I.

(+) and (−)2,4-Diphenylbutanols.—The active diphenylbutanoic acids were reduced in ethyl ether by lithium aluminum hydride following the directions of Nystrom and Brown.[5] After the addition of the acid the mixture was refluxed for one-half hour and then hydrolyzed with 10% hydrochloric acid. The alcohols were distilled, b. p. 178–180° (1 mm.).[6] Rotations and yields are summarized in Table I.

The α-Naphthylcarbamates and 3,5-dinitrobenzoates of the active alcohols were crystallized from petroleum ether and ethanol, respectively. Their constants are presented in Table II.

Attempted Racemizations of 2,4-Diphenylbutanols.—The procedure and essentially the apparatus which Doering and Aschner[2] had shown to be capable of excluding the effects of oxidants were used. The freshly prepared alcohols, 2 millimoles, were added to equivalent amounts of powdered sodium under toluene and allowed to react until hydrogen evolution had ceased. The suspension was then heated at 100° for a time and the alcohol recovered by washing the toluene with acid, then water, and distilling finally *in vacuo*. The specific rotations of the alcohols at comparable temperatures and concentrations before and after heating for specified times were

−15.1°	5 hr.	−14.6°
−14.6	8 hr.	−13.3
+24.3	8 hr.	+24.1

(4) These are more specific directions than those of Hann and Lapworth, *J. Chem. Soc.*, **85**, 1355 (1904).

(5) Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

(6) Marion, *Canadian J. Res.*, **16B**, 213 (1938), gives 174–180° at 1 mm. for the racemic alcohol.

EVANSTON, ILLINOIS RECEIVED JULY 5, 1949

Summary

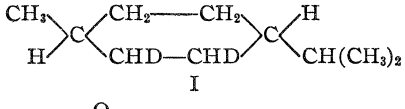
Optically active forms of 2,4-diphenylbutanoic acid and 2,4-diphenylbutanol have been prepared by convenient methods. The latter compound is not racemized by heating of its sodium derivative at 100° for eight hours.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

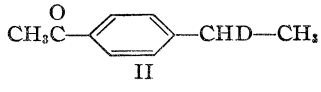
The Reduction of Optically Active Phenylmethylcarbinyl Chloride with Lithium Aluminum Deuteride[1]

BY ERNEST L. ELIEL

Recently Alexander and Pinkus[1a] showed that the reduction of optically active *trans*-2-menthene gives rise to *active* 2,3-dideutero-*trans*-menthane (I) thus demonstrating that a compound of type R_1R_2CHD is capable of rotating the plane of polarized light.



I



II

Compound I has four asymmetric centers (not all of which, however, necessarily contribute towards its rotation[1a]) and it seemed desirable to investigate again the possibility of optical activity in the case of a compound having only one carbon atom of the R_1R_2CHD-type. Such a compound is α-deuteroethylbenzene, $C_6H_5CHDCH_3$. This hydrocarbon was expected to be accessible by the reduction of phenylmethylcarbinyl chloride, $C_6H_5CHClCH_3$, with lithium aluminum deuteride–lithium deuteride according to a method recently described[2] for reductions of alkyl halides to alkanes. The fact that primary halides are reduced more easily by lithium aluminum hydride than secondary, while tertiary ones are not reduced at all,[2,3] might lead one to believe that the reaction is of the nucleophilic displacement (S_N2) type and that the reduction of optically active α-phenethyl chloride with lithium aluminum deuteride might proceed with Walden inversion and give rise to an active product. Walden inversion has been demonstrated for the reduction of epoxides with lithium aluminum hydride.[3]

The reduction of (−)-α-chloroethylbenzene with lithium aluminum deuteride–lithium deuteride in tetrahydrofuran yielded about 80% of the theoretical amount of α-deuteroethylbenzene which was free of chlorine-containing impurities

(1) Presented before the Organic Division of the American Chemical Society at Atlantic City, N. J., September 20, 1949.

(1a) Alexander and Pinkus, THIS JOURNAL, **71**, 1786 (1949). This publication reviews earlier unsuccessful attempts to synthesize optically active compounds of the R_1R_2CHD type. The present author is indebted to Dr. Elliot R. Alexander for information regarding the results of his investigation several months in advance of publication.

(2) Johnson, Blizzard and Carhart, *ibid.*, **70**, 3644 (1948).

(3) Trevoy and Brown, *ibid.*, **71**, 1675 (1949). At the time this paper appeared, the present investigation was almost complete.

and showed optical rotation far in excess of possible observational errors. Its deuterium content, calculated on the basis of density by the formula of McLean and Adams[4] appeared to be very close to the theoretical. Acetylation of the active hydrocarbon by the Friedel–Crafts procedure yielded active *p*-acetyl-α-deuteroethylbenzene (II) which, in turn, gave rise to an optically active crystalline oxime. The activity of the once-recrystallized oxime was not affected by further recrystallizations and the active ketone was regenerated by acid hydrolysis of its crystalline derivative.

It is thus established beyond doubt that α-deuteroethylbenzene is capable of rotating the plane of polarized light. The degree of optical purity and the configuration of the deuterated hydrocarbon are not known, but on the basis of the work of Trevoy and Brown[3] it seems likely that the reduction involves Walden inversion.

2,3-Diphenylbutane was obtained as a by-product in the reduction of α-chloroethylbenzene by either lithium aluminum deuteride–lithium deuteride or lithium aluminum hydride–lithium hydride. The origin of this by-product is under investigation.

Experimental

***dl*-Phenylmethylcarbinol.**[5]—Acetophenone was distilled *in vacuo* from Raney nickel. One mole (120 g.) of the distillate was reduced in the presence of about 5 g. of copper chromite[6] at a temperature of 110–120° and an initial hydrogen pressure of 2500 lb. Reduction was complete in three hours. The catalyst was separated by filtration and the liner of the bomb and catalyst were rinsed with ether. The filtrate was fractionated, *dl*-phenylmethylcarbinol being collected at 92.5–93.5° (16 mm.). The purity of the product, as established by titration of the hydroxyl group,[7] was 99%, yield 118 g. (97%).

(+) and (−)-Phenylmethylcarbinol.—*dl*-Phenylmethylcarbinol was converted to its acid phthalate by the method of Houssa and Kenyon.[8] The product precipitated as an oil when its pyridine solution was poured into dilute hydrochloric acid. It was extracted with ether and the extract was washed with water, dried over sodium sulfate and freed of solvent by distillation. The residue was crystallized from benzene and melted at 107–108° (lit.[8] 108°). The acid phthalate (300 g.) was resolved *via* its brucine salt as described in the literature.[9] Crystallization of the diasteroisomeric salts proved quite tedious until seed crystals were obtained, but once the laboratory was nucleated, crystallization proceeded with great ease and in one case part of the more soluble salt precipitated along with the less soluble. Decomposition of the salts was effected by dissolving them in methanol, pouring the solution into an excess of dilute hydrochloric acid and extracting the precipitated oily phthalate with ether. The ether was washed with water, dried over sodium sulfate and distilled and the residue was crystallized as described.[9] Basic hydrolysis[9] of the resolved phthalates yielded 33 g. of the (+)-carbinol, $[\alpha]_D$ +39.7°, and 35 g. of the (−)-carbinol b. p. 93° (14 mm.), $[\alpha]_D$ −43.6°. Since Downer and Kenyon report[9] a specific rotation of −43.5°, the (−)-carbinol obtained in this work was presumably optically pure and the (+)-carbinol about 93% pure.

(+) and (−)-Phenylmethylcarbinyl Chlorides.—The chlorides were obtained from the corresponding alcohols by treatment with purified thionyl chloride in the cold followed by fractional distillation.[10] The (−)-alcohol yielded a chloride of $[\alpha]^{25}D$ −49.2°, boiling at 74–75° (14 mm.), while the (+)-carbinol yielded a halide of $[\alpha]^{25}D$ +45.2°. Since McKenzie and Clough[10] consistently obtained material whose specific rotation was +50.6°, and Ott[11] reports a specific rotation for α-chloroethylbenzene of −50.3°, it is estimated that the (−)-chloride obtained here was 97–98% pure while the purity of the (+)-chloride was between 89 and 90%.

(−)-α-Deuteroethylbenzene.—The general method of Johnson, *et al.*,[2] was followed. To a well-stirred mixture of 75 ml. of tetrahydrofuran[12] (distilled first over potassium hydroxide, then over lithium aluminum hydride), 1 g. of lithium aluminum deuteride[13] and 3 g. of finely-ground (100 mesh) lithium deuteride,[13] 33.5 g. of phenylmethylcarbinyl chloride, $[\alpha]^{25}D$ −49.2°, was added rapidly. The reaction was not markedly exothermic. The mixture was refluxed with efficient stirring for four hours, without stirring for nine and one-half hours, and with stirring for ten more hours. It was then cooled, excess deuteride was destroyed by the addition of a solution of 20 ml. of water in 30 ml. of tetrahydrofuran, and the mixture was poured onto ice-water containing 20 ml. of sulfuric acid. The product was extracted with two portions of *ca.* 100 ml. of pentane[12] and the pentane solution was washed twice with water, four times with 85% phosphoric acid, twice with water, once with 10% sodium carbonate solution and once with water. It was dried over calcium chloride and fractionated through a Vigreux column. α-Deuteroethylbenzene was collected at 133–135° (747 mm.) and weighed 20.7 g. (79%). Its rotation was $\alpha^{25}D$ −0.51 ± 0.01° (l = 2 dm., no solvent).

When the distillation residue was taken up in acetone, the solution was found to be weakly dextrorotatory. Removal of the acetone left 0.77 g. of a semisolid material, presumably a mixture of *meso* and active 2,3-diphenylbutane. In a model experiment in which *dl*-α-chloroethylbenzene was reduced with lithium aluminum hydride–lithium hydride, the solid *meso*-form was recrystallized from 95% ethanol; it then melted at 124.5–125° and did not depress the melting point of an authentic sample of *meso*-2,3-diphenylbutane.[11]

The active α-deuteroethylbenzene was fractionated through an eight-inch helix-packed column the following fractions being obtained[14]

Fraction	Weight, g.	$n^{25}D$	$\alpha^{25}D$ deg.
1	5.5	1.4921	−0.47 ± 0.02
2	3.9	1.4925	− .48 ± .02
3	4.4	1.4923	− .53 ± .02
4	4.6	1.4922	− .52 ± .02
5	0.9	1.4922	Not observed

Fractions 1 through 4 were recombined and their rotation was found to be $\alpha^{25}D$ −0.52 ± 0.01° (l = 2 dm., no sol-

(4) McLean and Adams, *ibid.*, **58**, 804 (1936).

(5) (a) Adkins, "Reactions of Hydrogen with Organic Compounds over Copper–Chromium Oxide and Nickel Catalysts," The University of Wisconsin Press, Madison, Wis., 1937, p. 50; (b) Yamamoto and Kawata, *J. Soc. Chem. Ind. Japan*, **43**, Suppl. Binding 279–280 (1940); *C. A.*, **35**, 1893 (1941).

(6) Ref. 5a, p. 13.

(7) Siggia, "Quantitative Organic Analysis via Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 4.

(8) Houssa and Kenyon, *J. Chem. Soc.*, 2260 (1930).

(9) Downer and Kenyon, *ibid.*, 1156 (1939).

(10) McKenzie and Clough, *ibid.*, **103**, 694 (1913).

(11) Ott, *Ber.*, **61**, 2124 (1928).

(12) All solvents used in this work were checked for optical rotation which in no case was found to exceed 0.01° in a 2-dm. tube.

(13) Metal Hydrides, Inc., Beverly, Mass., isotopic purity 99+%.

(14) Rotations observed in a 2-dm. capillary tube of 2-ml. capacity. All other rotations were observed in a wide-bore 2-dm. tube of 13-ml. capacity.

vent) whence, taking $d = 0.87$,[15] $[\alpha]^{25}D$ $-0.30°$. The compound gave negative halogen tests both by the Beilstein method and with alcoholic silver nitrate.[16]

The reduction of 9 g. of (+)-α-phenethyl chloride by means of 0.35 g. of lithium aluminum hydride and 1.0 g. of lithium hydride in 30 ml. of tetrahydrofuran gave rise to 3.9 g. of ethylbenzene boiling at 132.5–134.5° (742 mm.) whose rotation was αD $-0.03 \pm 0.02°$ ($l = 2$ dm., no solvent).[14]

(−)-α-Deuteroethyl-*p*-acetylbenzene (II).—The method of Klages[17] was followed. To a solution of 14.5 g. of (−)-α-deuteroethylbenzene and 18 g. of acetyl chloride in 60 ml. of petroleum ether[12] (b. p. 30–60°), 19 g. of aluminum chloride was added gradually with efficient stirring. The mixture was refluxed for one-half hour and poured onto ice and hydrochloric acid. The layers were separated and the aqueous layer was extracted once with ether.[12] The petroleum ether and ether layers were successively washed with dilute hydrochloric acid, water, 10% sodium carbonate solution and water and then dried over sodium sulfate. Fractionation of the solvents followed by distillation *in vacuo* yielded 1.3 g. of unchanged α-deuteroethylbenzene,[18] b. p. 37–38° (17 mm.), and 14.5 g. (72%) of the desired ketone collected at 123–126.5° (18 mm.). The ketone had $n^{25}D$ 1.5260[19] and $\alpha^{23}D$ $-0.54 \pm 0.01°$ ($l = 2$ dm., no solvent), whence, assuming a density of 0.99 (see below), $[\alpha]^{23}D$ $-0.27°$.

Oxime of II.—Sodium acetate trihydrate (29 g.) and hydroxylamine hydrochloride (14.5 g.) were ground together in a mortar and the resultant slurry was extracted three times with 50-ml. portions of ethanol.[12] The filtered ethanol solution was added to a solution of 14 g. of II in 15 ml. of ethanol and refluxed for twelve hours. Part of the ethanol was then distilled and crystallization induced by the addition of water to the cloud point and cooling. The crystalline oxime was collected, washed with dilute ethanol and dried; it weighed 13.2 g. (85% and melted in 82.5–84°. The optical rotation of a solution of 5 g. of oxime in benzene[12] (total volume 15 ml.) was $-0.16 \pm 0.01°$ ($l = 2$ dm., $t = 23°$).[20] Recrystallization of the oxime from dilute ethanol raised the melting point to 83–84°[21] and changed $\alpha^{27}D$ to $-0.11 \pm 0.01°$ ($l = 2$ cm., in benzene). Further recrystallization from the same solvent did not change the melting point; $\alpha^{28}D$ $-0.12 \pm 0.01°$ ($l = 2$ dm., in benzene). Recrystallization from benzene–petroleum ether left the melting point unchanged, $\alpha^{29}D$ $-0.11 \pm 0.01°$ ($l = 2$ dm., in benzene), whence $[\alpha]^{28}D$ $-0.17°$ in benzene.

Recovery of the Ketone II from its Oxime.—A suspension of 7 g. of the oxime of II in 100 ml. of *ca.* 1 *N* hydrochloric acid was steam distilled. The distillate was extracted twice with ether and the ether layers were washed with 5% sodium carbonate solution and then three times with water. Drying over sodium sulfate followed by concentration and distillation *in vacuo* yielded 5.5 g. (86%) of the recovered ketone (II) collected at 127–129° (25 mm.). Its physical constants were as follows: $n^{25}D$ 1.5261, d^{25}_4 0.9915[22]; $\alpha^{30}D$ $-0.50 \pm 0.02°$[14] ($l = 2$ dm., no solvent). The rotation of the ketone was unaffected by eleven hours of refluxing with 1 *N* aqueous hydrochloric acid.

Acknowledgments.—The author wishes to express his appreciation to Dr. Charles C. Price for helpful advice, to Mr. Erwin Kohn for carrying out the high-pressure hydrogenation of acetophenone and to the Electrochemicals Department of the du Pont Company for a generous supply of tetrahydrofuran.

Summary

1. The reduction of (−)-phenylmethylcarbinyl chloride of $[\alpha]^{25}D$ $-49.2°$ with lithium deuteride–lithium aluminum deuteride yields active α-deuteroethylbenzene of $[\alpha]^{25}D$ $-0.30°$.

2. The active α-deuteroethylbenzene has been converted into optically active *p*-acetyl-α-deuteroethylbenzene whose crystalline oxime retained its activity through several recrystallizations and regenerated the active ketone upon hydrolysis.

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(15) The values for d^{25}_4 found were 0.8628 for ethylbenzene and 0.8712 for deuteroethylbenzene. Application of the formula of McLean and Adams (ref. 4) to the ethylbenzene value gives an expected density of 0.8710 for the deuterium compound.

(16) The silver nitrate test was shown to be sensitive to a solution containing one part of α-phenethyl chloride in 700 of ethylbenzene.

(17) Klages, *Ber.*, **32**, 1558 (1899).

(18) The rotation of the recovered hydrocarbon was determined by diluting 0.8 ml. with 2.4 ml. of ordinary ethylbenzene and taking readings in a 2-dm. capillary tube (*cf.* ref. 14). The observed rotation was $-0.13 \pm 0.01°$, corresponding to a rotation of $-0.52°$ for the undiluted material.

(19) The data reported by Klages, ref. 16, for the hydrogen compound are: b. p. 130° (23 mm.), $n^{20}D$ 1.5310, d^{20}_4 0.991. Here observed: b. p. 114–116° (13 mm.), $n^{25}D$ 1.5269, d^{25}_4 0.9851.

(20) This reading may have been affected by a systematic error; the field was very much distorted.

(21) Klages, *Ber.*, **35**, 2245 (1902), reports a melting point of 82–83° for the hydrogen compound while the present author observed 83–84°.

(22) The expected density on the basis of the corresponding value for the hydrogen compound (ref. 19) and the formula of McLean and Adams (ref. 4) is 0.9917.

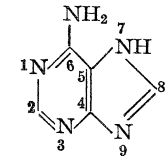
[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH, NEW YORK]

Degradations in the Purine Series Studied with Isotopes of Nitrogen and Carbon[1]

BY LIEBE F. CAVALIERI, JOHN F. TINKER AND GEORGE BOSWORTH BROWN

Tracer studies concerned with the metabolism of purines have evoked the need for methods suitable for determining the location of isotopes in purines isolated from tissue constituents. Oxidative and hydrolytic degradations of the purines adenine,[2,3,4] guanine,[5,6] xanthine,[7] hypoxanthine[2] and uric acid have been reported but only in the case of guanine[6] has the mechanism been clarified by the degradation of samples labeled with isotopes in known positions. The availability in this laboratory of several synthetic purines variously labeled with the isotopes of nitrogen (N^{15}) and carbon (C^{13} or C^{14}) has permitted the study of a number of such degradations.

The action of concentrated hydrochloric acid on the purines, adenine, guanine, xanthine, hypoxanthine and uric acid leads to the formation of glycine, ammonia, carbon monoxide and carbon dioxide. By analogy to the results with 7-methyl uric acid, which yields sarcosine under these conditions,[8] it has been assumed for both uric acid[9,10] and guanine[11] that the glycine arises from the 4- and 5-carbon atoms and the 7-nitrogen. However, no direct proof of this assumption has been presented.



I

tained excess C^{13}. Decarboxylation of a sample of *p*-tosylglycine revealed that the C^{13} was present only in the carboxyl group of the glycine (Table I). Further, since the isotope concentration in the carbon dioxide was equal to that originally present in either the 4- or 6-carbons, dilution had not occurred. That no excess N^{15} was found in the glycine indicates that the amino group must have arisen from the 7- or 9-nitrogens or the 6-amino group of adenine, but not from the 1- or 3-nitrogens. Origin of the amino group of glycine from the 6- or 9-nitrogens would require the carboxyl group to come from the 5-carbon, but since it was the carboxyl carbon of the isolated glycine which contained the excess C^{13}, it follows that the amino group of the glycine originated from the 7-nitrogen.

In the case of guanine a sample was hydrolyzed which contained C^{13} in the 4-position only.[12]

TABLE I

HYDROCHLORIC ACID HYDROLYSIS

Starting compound						Degradation product				
			Nitrogen, %		Isotope		Nitrogen, %		Isotope analysis[a]	
Name	Label	Formula	Calcd.	Found	analysis[a]	Formula	Calcd.	Found	Expected	Found
Adenine	N^{15} in 1, 3	$(C_5H_5N_5)_2 \cdot H_2SO_4 \cdot 2H_2O$	34.9	35.2	N^{15}, 0.36	$C_9H_{11}O_4NS$[b]	6.1	6.3	N^{15}, 0.00	0.01[c]
Adenine	C^{13} in 4, 6		8.1[d]	7.9[d]	C^{13}, 0.14	CO_2[e]			C^{13}, 0.33	0.35
Guanine	N^{15} in 1, 3	$(C_5H_5ON_5)_2 \cdot H_2SO_4 \cdot 2H_2O$	32.1	31.9	N^{15}, 0.60	$C_9H_{11}O_4NS$	6.1	6.3	N^{15}, 0.00	0.01[c]
Guanine	C^{13} in 4		32.1	32.2	C^{13}, 0.09	CO_2[e]			C^{13}, 0.45	0.43
Xanthine	N^{15} in 1, 3	$C_5H_4O_2N_4$	36.9	36.2	N^{15}, 0.50	$C_9H_{11}O_4NS$	6.1	6.4	N^{15}, 0.00	0.02[c]
Uric acid	N^{15} in 1, 3	$C_5H_4O_3N_4$	33.3	33.7	N^{15}, 0.50	$C_9H_{11}O_4NS$	6.1	6.2	N^{15}, 0.00	0.02[c]

[a] Atom % excess. [b] In all cases glycine was isolated as the *p*-tosyl derivative. [c] These values represent about 1% of the N^{15} present in either the 1- or 3-positions. This N^{15} probably arises from *p*-toluenesulfonamide which is formed from traces of ammonia remaining in the residue of the reaction mixture. [d] Sulfur analysis. [e] This carbon dioxide was obtained by the decarboxylation of the *p*-tosylglycine.

Adenine (I), labeled with C^{13} in the 4- and 6-positions and with N^{15} in the 1- and 3-positions, was hydrolyzed with concentrated hydrochloric acid and the glycine which was isolated con-

(1) This work was supported by grants from the National Cancer Institute of the United States Public Health Service, the Office of Naval Research, United States Navy and the James Foundation of New York, Inc.

(2) Krüger, *Z. physiol. Chem.*, **16**, 160 (1892).
(3) Kossel, *ibid.*, **12**, 241 (1888).
(4) Jolles, *J. prakt. Chem.*, [2] **62**, 61 (1900).
(5) Wulff, *Z. physiol. Chem.*, **17**, 468 (1893).
(6) Plentl and Schoenheimer, *J. Biol. Chem.*, **153**, 203 (1944).
(7) Schmidt, *Ann.*, **217**, 308 (1883).
(8) Fischer, *Ber.*, **32**, 435 (1899).
(9) Shemin and Rittenberg, *J. Biol. Chem.*, **167**, 875 (1947).
(10) Sonne, Buchanan and Delluva, *J. Biol. Chem.*, **173**, 69 (1948).
(11) Abrams, Hammarsten and Shemin, *J. Biol. Chem.*, **173**, 429 (1948).

This led to the formation of glycine with the C^{13} in the carboxyl group and this decisively confirms the origin of the carboxyl carbon of glycine from this purine.

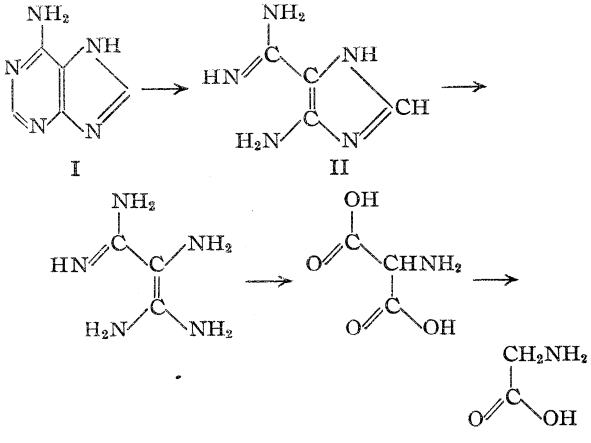
The acid hydrolysis of guanine, labeled with N^{15} in the 1- and 3-positions and in the 2-amino group, and of xanthine and uric acid, each labeled in the 1- and 3-positions, yielded glycine with no excess N^{15}. This is in conformity with the origin of the glycine from the 4, 5 and 7 atoms.

Under milder conditions, the acid hydrolysis of adenine led to the formation of 4(5)-amino-5(4)-imidazolecarboxamidine (II). Since II exhibits a distribution constant (0.12 *n*-butanol phosphate, *p*H 6.5) different from that of adenine

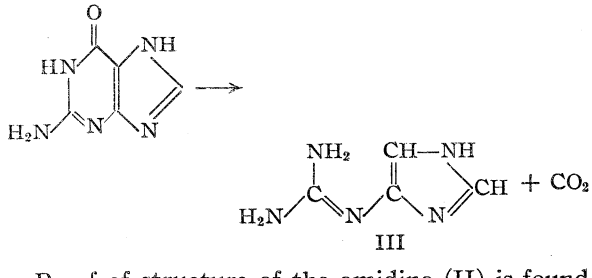
(12) Lowy, unpublished.

(2.2) reaction mixtures were readily analyzed and optimum conditions for the formation of II from adenine were thus easily found. The production of this carboxamidine is consistent with the observed production of formic acid in the hydrolysis of adenine or of nucleic acids.[13] This degradation permits a differentiation between the 2- and 8-carbons of adenine.

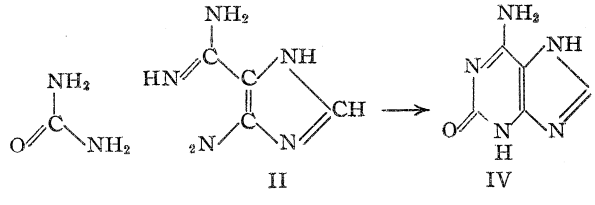
On the basis that the amidine (II) is an intermediate, it can be postulated that the formation of glycine from adenine proceeds according to the scheme shown.



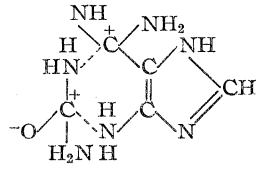
The sequence of steps involving the degradation of II may not necessarily be the one shown, but the over-all mechanism is consistent with the data. It is of interest to note that 4(5)-guanidinoimidazole (III) has been isolated by Hunter[14] after subjecting guanine to very nearly the same hydrolytic conditions.



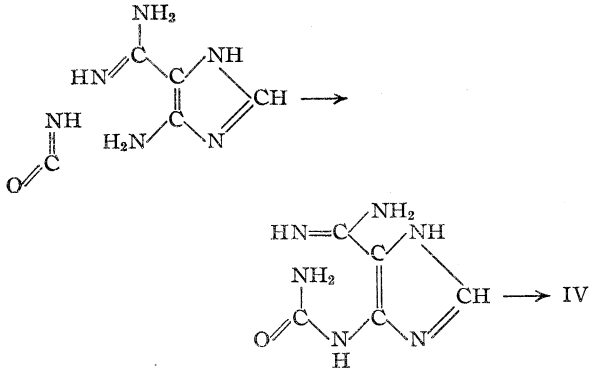
Proof of structure of the amidine (II) is found in the conversion to isoguanine (IV) by the



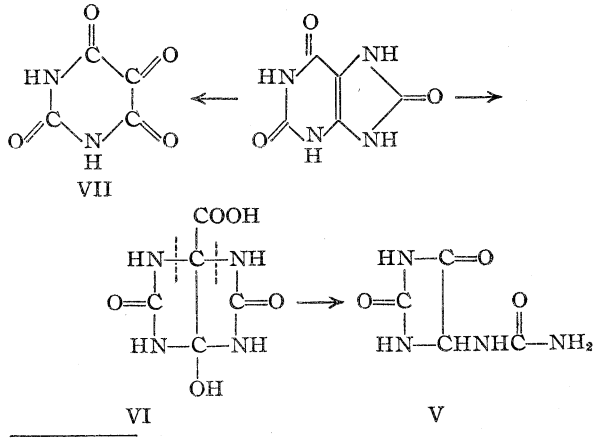
action of either urea or phosgene. When the fusion with urea was carried out on a sample of II containing N^{15} in both the amino and amidine groups (prepared from 1,3 labeled adenine), the N^{15} of the resulting isoguanine (III)[15] was 88% of that originally present in the II. Since it is likely that the 4(5)-amino group is a nucleophilic center attacking the electrophilic carbon of the urea, it is reasonable to assume that the N^{15}



was not eliminated from the amino substituent, but rather from the amidine grouping which can act both as a nucleophilic and electrophilic entity. Indeed, the 12% loss of N^{15} may be taken as a measure of the electrophilic character of the amidine unit in this molecule. An alternative but similar mechanism involves the addition of cyanic acid which is present in the reaction mixture.



Oxidative degradations of the purines have been carried out employing acid and alkaline permanganate, perchlorate,[6] nitric acid,[16,17] and various other oxidizing agents. The oxidation of uric acid with alkaline permanganate yields allantoin (V) via a symmetrical intermediate (VI), while



(13) Stevens, *J. Biol. Chem.*, **120**, 751 (1937).

(14) Hunter, *Biochem. J.*, **30**, 1183 (1936)

(15) Bendich, Tinker and Brown, THIS JOURNAL, **70**, 3109 (1948).

(16) Wöhler and Liebig, *Ann.*, **26**, 256 (1838).

(17) Biltz and Heyn, *ibid.*, **413**, 60 (1917).

TABLE II

OXIDATION OF ADENINE

Position of tracer	Adenine: Elementary analyses, % Calcd.	Found	Isotope analysis[a]	Dixanthydrol urea: Elementary analysis, % Calcd.	Found	Isotope analysis[a]	NH_3 Isotope analysis[a]	CO_2 Isotope analysis[a]
1,3-N^{15}	S, 8.3	8.2	0.43	N, 6.7	6.7	0.50	0.42	
4,6-C^{13}	S, 8.3	7.9	0.14					0.14
8-C^{13}	N, 28.9	28.7						
	S, 13.2[b]	13.7	0.54	N, 6.7	6.9	0.01		
4,6-C^{14}	N, 51.8	52.2	126 cpm/mg.[c]	N, 6.7	6.1 cpm/mg.[d]			

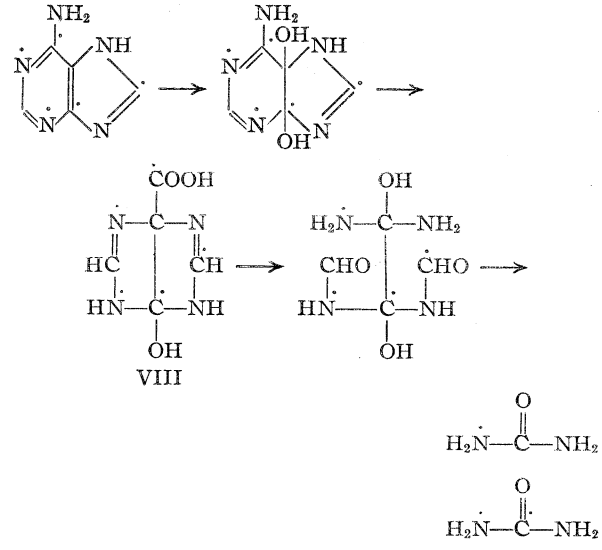
[a] The C^{13} and N^{15} values are expressed as atom % excess over the normal abundance. [b] Adenine may be obtained as the mono sulfate depending upon the rate of crystallization. [c] Sufficient adenine was burned to give a value of 4500 c. p. m. over background. [d] Sufficient dixanthydrol urea was burned to give a value of 150 c. p. m. over background.

with nitric acid the imidazolone ring is cleaved to produce alloxan (VII).[18]

The oxidation of adenine with permanganate in acid solution has been reported[3,4] to yield one mole of glycine, two moles of urea, and one mole of carbon dioxide. In our hands, this reaction did not result in the formation of glycine. The mechanism of this reaction was studied employing adenine which was labeled with N^{15} in the 1- and 3-positions, C^{14} in the 4- and 6-positions and C^{13} in the 8-position.[19] The oxidation was carried out by the use of potassium permanganate in sulfuric acid solution. Urea was isolated as dixanthydrol urea, and the ammonia and carbon dioxide collected. Since the isotope values of the ammonia and carbon dioxide evolved were essentially equal to those of the parent adenine, it is clear that complete degradation of a large portion of the sample occurred.

The isotope analyses (Table II) reveal that the N^{15} content of the urea isolated was appreciably higher than the average N^{15} content of the adenine and was one-half (47%) of that contained in either the 1 or 3 nitrogens. Since only 0.01 atom % of C^{13} was found in the urea, the 7-, 8- and 9-atom unit contributed but to a small extent to the urea found. The ratio of C^{14}:C^{12} in the urea was 0.6:1.0 and it was constant upon repeated recrystallization of the dixanthydrol urea.

Upon examination of the adenine molecule it is evident that, if no rearrangement occurs, the urea can arise in four ways, *viz.*, from the (1,3), (1,6), (3,9) or (7,9) positions. No one of these four possibilities or any combination of them is consistent with the isotope analyses. On this basis it appears necessary to postulate a rearrangement similar to that occurring in the permanganate oxidation of uric acid in alkaline solution. In this case, however, it is required that preponderant cleavage of the proposed intermediate (VIII) takes place as shown, although the C^{13} value, together with the low C^{14}:C^{12} ratio, indicates some cleavage similar to that of VI to V. Since a sample of urea under the conditions of the experiment was oxidized to the extent of only 5 to 10%, it can be assumed that once the urea is formed in the reaction it remains for the most part intact. Thus each molecule of the urea



VIII

contained one atom of N^{15} originally present in the 1- or 3-position and one normal nitrogen from the 7- or 9-position. Appreciably less than half of the urea molecules must have contained C^{14}, arising chiefly from the 4-carbon.

Experimental

Isotope Analyses.—All N^{15} and C^{13} determinations were carried out with a Consolidated–Nier mass spectrometer, Model 21-201. The average error in the N^{15} determinations was ±0.002; in the C^{13} determinations ±0.005. For the C^{14} measurements the samples were converted to barium carbonate and the analyses were carried out on carbon dioxide.[20]

Materials.—Adenine containing N^{15} in the 1- and 3-positions and C^{13} (or C^{14}) in the 4- and 6-positions was synthesized according to Cavalieri, Tinker and Bendich[21] and adenine labeled with C^{13} in the 8-position was prepared according to Cavalieri and Brown.[19] Guanine, xanthine[2,22] and uric acid[23] with N^{15} in the 1- and 3-positions were prepared as in previous communications. C^{13} was introduced into the 4-position of guanine by employing methyl cyanoacetate ($C^{13}NCH_2COOCH_3$) obtained by a previous procedure.[21]

(18) Cavalieri and Brown, THIS JOURNAL, **70**, 1242 (1948).

(19) Cavalieri and Brown, *ibid.*, **71**, 2246 (1949).

(20) Eidinoff, *Science*, **108**, 535 (1948).

(21) Cavalieri, Tinker and Bendich, THIS JOURNAL, **71**, 533 (1949).

(22) Getler, Roll, Tinker and Brown, *J. Biol. Chem.*, **178**, 259 (1949).

(23) Cavalieri, Blair and Brown, THIS JOURNAL, **70**, 1240 (1948).

4(5)-Amino-5(4)-imidazolecarboxamidine Hydrochloride (II).—Adenine sulfate (2 g.) was heated in a sealed tube containing 30 cc. of 6 *N* hydrochloric acid at 150 ± 2° for two hours. The solution was evaporated to dryness and extracted with two 10-cc. portions of warm concentrated hydrochloric acid. To this filtrate was added 30 cc. of ethanol and the solution cooled to induce crystallization. The crystalline deposit was recrystallized three times by dissolving it in warm concentrated hydrochloric acid (*ca.* 2 cc.) and adding alcohol (15 cc.). The yield of pure material was 200 mg. (10%); distribution constant, 0.12 (*n*-butanol–phosphate buffer, *p*H 6.5); ultraviolet absorption spectrum: λ_{max} 287 mμ, log ε 4.03.

Anal. Calcd. for $C_5H_7N_5 \cdot 2HCl$: N, 35.3. Found: N, 35.3.

Conversion of II to Isoguanine. (a) Phosgene Method.—Fifty milligrams of II was dissolved in 5 cc. of *N* sodium hydroxide and phosgene passed through the solution for one hour, during which time three 4-cc. portions of 40% sodium hydroxide were added. The mixture was then aerated for one hour. One cubic centimeter of 2 *N* sulfuric acid was added and the solution heated, decolorized and filtered. On cooling 14 mg. (26%) of material was obtained which was recrystallized from 2 *N* sulfuric acid. The ultraviolet absorption spectrum[24] at various *p*H values was identical with that of isoguanine prepared by another synthesis.[15]

Anal. Calcd. for $(C_5H_5ON_5)_2 \cdot H_2SO_4 \cdot H_2O$: S, 7.6. Found: S, 7.7.

(b) Urea Fusion Method.—Seventy-five milligrams of II (containing 0.97 atom % excess N^{15}) was fused with 410 mg. of urea at 180° for one hour. The cooled melt was extracted with 5 cc. of boiling water and the extract discarded. The residue was recrystallized twice from 2 *N* sulfuric acid; yield 37 mg. (47%). The N^{15} content of this isoguanine sulfate was 0.85 or 88% of that present in II.

Anal. Calcd. for $(C_5H_5ON_5)_2 \cdot H_2SO_4 \cdot H_2O$: S, 7.6. Found: 7.8.

Hydrolytic Degradation.—The hydrolyses of adenine, guanine, xanthine and uric acid were carried out by heating about 1 g. of the purine in 15 cc. of concentrated hydrochloric acid at 180° in a sealed tube for eighteen hours (Table I).

Isolation of Glycine.—The mixture from the above hydrolysis was evaporated to dryness and to the residue was added 10 cc. of 5% sodium hydroxide. The ammonia was removed by aeration, while warming the mixture. One gram of *p*-toluenesulfonyl chloride was added to the alkaline solution and the mixture stirred for six hours at room temperature. The solution was filtered and acidified. The precipitation of *p*-tosylglycine was complete in two hours and the product was collected by filtration. Two recrystallizations from ethyl acetate–petroleum ether gave 30–50 mg. of pure *p*-tosylglycine (Table I).

Decarboxylation of *p*-Tosylglycine.—*p*-Tosylglycine (20 mg.) was mixed intimately with copper powder and heated to 200 ± 5° for one-half hour in a stream of nitrogen. The carbon dioxide was collected in saturated barium hydroxide; yield $BaCO_3$, 14–16 mg. (81–92%).

Oxidation of Adenine (Table II).—Adenine sulfate (400 mg.) was dissolved in 80 cc. of water containing 4 cc. of concentrated sulfuric acid. To the boiling solution was added dropwise over a period of five minutes 2.6 g. of potassium permanganate in 35 cc. of water. Carbon dioxide was collected in saturated barium hydroxide during this time. After the outlet tube had been disconnected the excess permanganate was destroyed with oxalic acid. The solution was filtered, and 160 cc. of glacial acetic acid was added followed by 2 g. of xanthydrol (in 20 cc. methanol). Precipitation of dixanthydrol urea began after one-half hour and was complete after standing overnight. The product was recrystallized three times from glacial acetic acid; yield 120 mg. A sample of ammonia was obtained from the original oxidation mixture (after treatment with oxalic acid) by adding excess alkali and collecting the ammonia in boric acid.

Acknowledgment.—The authors wish to thank Dr. Maxwell Leigh Eidinoff for performing the C^{14} determinations, Roscoe C. Funk, Jr., and John Deonarine for the microanalyses and the N^{15} and C^{13} determinations.

Summary

The acid hydrolysis of purines has been studied by means of tracer elements, and it has been confirmed that glycine arises from the 4,5- and 7-atoms. The oxidation of adenine with potassium permanganate produces urea which is postulated to arise from the 1,7- and 3,9-nitrogen atoms.

The preparation and characterization of 4(5)-amino-5(4)-imidazolecarboximidine are described.

A new synthesis of isoguanine is described.

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
NEW YORK, N. Y. RECEIVED JUNE 6, 1949

(24) Cavalieri, Bendich, Tinker and Brown, THIS JOURNAL, **70**, 3875 (1948).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF GALAT CHEMICAL DEVELOPMENT, INC.]

A New Method for the Isolation of Histamine

BY ALEXANDER GALAT AND HARRIS L. FRIEDMAN

Histamine is usually prepared by the bacterial decarboxylation of histidine in solution, and it is isolated in the form of its dipicrate. The decarboxylation of histidine proceeds readily and in good yield but the isolation of pure histamine by the picrate method offers a number of disadvantages. The purification of the dipicrate by recrystallization from water or dilute alcohol requires large volumes of solvent since the compound is sparingly soluble even at the boiling point. The conversion of the dipicrate into histamine salts, such as the dihydrochloride, involves the treatment of the dipicrate with an excess of hydrochloric acid, removal of the bulk of picric acid by filtration and extraction with an organic solvent to free the product from the last traces of this reagent. Because of the low solubility of the dipicrate these operations must be conducted in hot, dilute solutions which finally must be evaporated to dryness. This method is quite inconvenient for the preparation of relatively large amounts of histamine.

Recently, Vickery described a method for the isolation of histidine involving the precipitation of

this amino acid with *o*-dichlorobenzenesulfonic acid.[1] It seemed of interest to investigate the use of the same reagent for the isolation of histamine. We have found that when an excess of *o*-dichlorobenzenesulfonic acid is added to solutions containing histamine, the disulfonate of this base precipitates in the form of white, well-formed crystals. A nearly quantitative yield was obtained when *o*-dichlorobenzenesulfonic acid was added to solutions of histidine fermented by the method of Ackermann.[2] The new compound is readily soluble in hot water and very sparingly in cold, so that purification was effected conveniently and in good yield. The conversion of the disulfonate into histamine base and its salts was effected with equal ease, as described in the experimental part.

Experimental

Histamine Bis-*o*-dichlorobenzenesulfonate.—Twenty grams of histidine monohydrochloride monohydrate was fermented with *B. coli* organisms according to the method of Ackermann.[2] To the mixture there was added 120 g. of *o*-dichlorobenzenesulfonic acid, prepared by the method of Vickery,[1] and the precipitation completed by allowing the mixture to stand overnight. The crystals of histamine bis-*o*-dichlorobenzenesulfonate were filtered off, washed with water and recrystallized from 400 ml. of boiling water with the addition of activated charcoal. The product, dried at 100°, weighed 47 g. (87%) and melted at 225–227° (cor.).

Anal. Calcd. for $C_{17}H_{17}O_6Cl_4N_3S_2$: C, 36.10; H, 3.00; N, 7.43. Found: C, 36.35; H, 3.05; N, 7.35.

(1) Vickery, *J. Biol. Chem.*, **143**, 77 (1942).

(2) Ackermann, *Z. physiol. Chem.*, **65**, 505 (1910).

Histamine Di-hydrochloride.—A solution of 11.3 g. (0.02 mole) of histamine bis-*o*-dichlorobenzenesulfonate in 100 ml. of boiling *n*-butanol was saturated with hydrogen chloride and cooled to room temperature. The precipitate of histamine dihydrochloride was filtered off, washed with *n*-butanol followed by benzene and finally dried *in vacuo;* yield 3.4 g. (92%), m. p. 242–246° (cor.).

Histamine Diphosphate.—A hot solution of 11.3 g. (0.02 mole) of histamine bis-*o*-dichlorobenzenesulfonate in 50 ml. of water was treated with a hot solution of 6.3 g. (0.01 mole) of barium hydroxide octahydrate in 25 ml. of water. The mixture was cooled and the precipitate of barium *o*-dichlorobenzenesulfonate filtered off and washed with water. To the filtrate was added 6.0 g. of 85% phosphoric acid diluted with 10 ml. of water. The solution was then concentrated *in vacuo* to a small volume and histamine diphosphate precipitated by the gradual addition of methanol; yield 5.5 g. (90%), m. p. 130°.

Histamine Base.—A hot solution of 11.3 g. (0.02 mole) of histamine bis-*o*-dichlorobenzenesulfonate in 50 ml. of water was mixed with a hot solution of 6.3 g. (0.01 mole) of barium hydroxide octahydrate in 25 ml. of water, the mixture cooled and the precipitate filtered off and washed with cold water. The filtrate was concentrated to a small volume, cooled and a small additional amount of the barium salt removed by filtration. The filtrate was evaporated to dryness *in vacuo*, the sirup dissolved in 50 ml. of absolute isopropyl alcohol, treated with charcoal, filtered and evaporated *in vacuo* to dryness. The residue crystallized on cooling and seeding; yield: 1.90–1.95 g. (85–87%), m. p. 82–85° (sealed tube).

Summary

A new method for the isolation of histamine is described. Histamine is precipitated as bis-*o*-dichlorobenzenesulfonate which is readily converted in good yield into the histamine base or its salts.

YONKERS, N. Y. RECEIVED JULY 9, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN CO.]

Studies in Pterine Chemistry. I. 2-Amino-4-hydroxy-6-polyhydroxyalkylpterines

BY H. G. PETERING AND J. A. SCHMITT

Karrer, Schwyzer, Erden and Siegwart[1] reported that aldoses (IIa) and ketoses (IIb) may be condensed with 2,4,5-triamino-6-hydroxypyrimidine (I) to form 7- and/or 6-polyhydroxyalkylpterines (IV). These authors did not clearly indicate which of the isomers was obtained in any case, but they did appear to accept the hypothesis that aldoses formed 7-isomers and ketoses formed 6-isomers. The fact that D-glucose forms a 7-isomer with I was confirmed by Petering and Weisblat,[2] but neither the latter authors nor Karrer, *et al.*,[1] offered proof which could gainsay the claim of Weygand, *et al.*,[3] that the product of D-fructose (IIb) and (I) is 2-amino-4-hydroxy-7-(2′, 3′, 4′)-trihydroxybutylpterine (V) and not 2-amino-4-hydroxy-7-tetrahydroxybutyl-(D-arabo)-pterine. Thus the method of Karrer, *et al.*,[1] and that of Petering and Weisblat[2] yields 7-isomers rather than the 6-isomer, and the nature of the condensation product of D-glucose or D-fructose and I is still in doubt.

Forrest and Walker[4] have reported the synthesis of 2-amino-4-hydroxy-6-tetrahydroxybutyl-(D-arabo)-pterine from D-glucose or D-fructose and I in the presence of hydrazine (III) and boric acid by the application of the method of Ohle and Hielscher[5] for the preparation of 2-tetrahydroxybutylquinoxaline. We also have studied this method and wish to present our findings which extend the reports of Forrest and Walker in a number of ways and which are in disagreement with the latter in some respects. The data presented here depend on the fact that the authors have found that the absorption spectra of 6- and 7-alkyl-

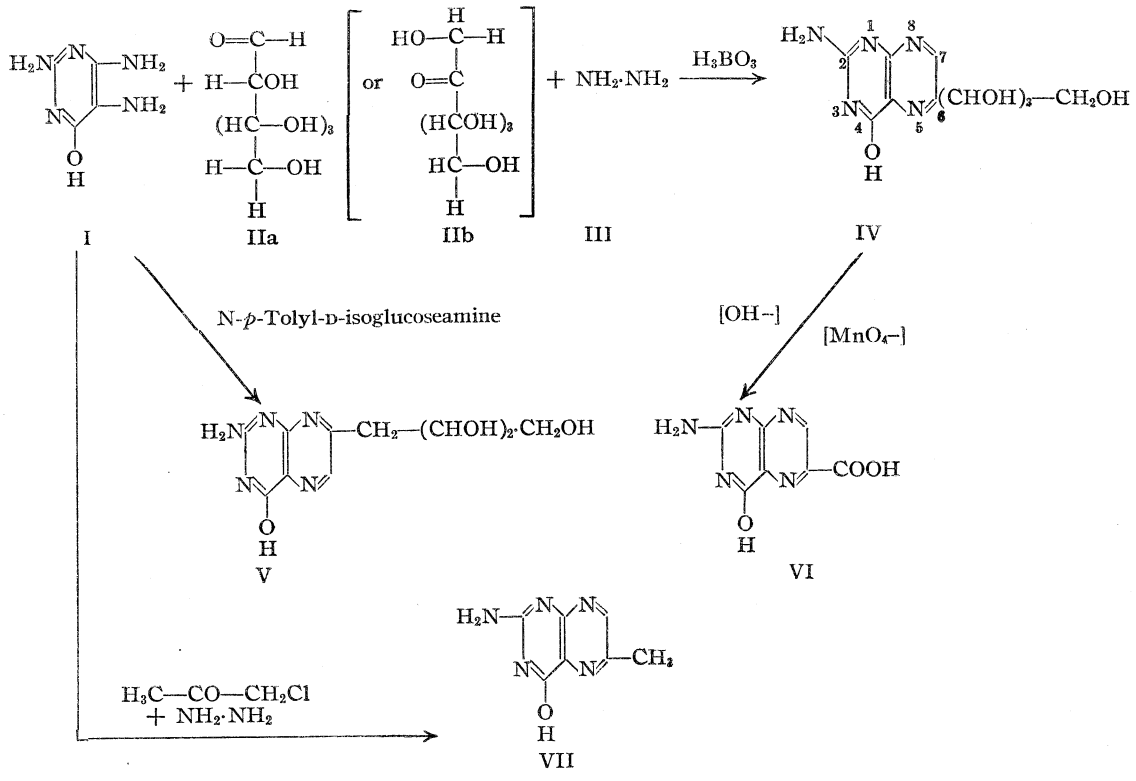
(1) Karrer, Schwyzer, Erden and Siegwart, *Helv. Chim. Acta*, **30**, 1031 (1947).

(2) Petering and Weisblat, THIS JOURNAL, **69**, 2566 (1947).

(3) Weygand, Wacker, and Schmied-Kowarzik, *Experientia*, **IV**, 427 (1948).

(4) Forrest and Walker, *Nature*, **161**, 308 (1948); *J. Chem. Soc.*, 79 (1949).

(5) Ohle and Hielscher, *Ber.*, **74**, 13 (1941).



pterines differ both qualitatively and quantitatively to such a marked extent that crude isomer mixtures can be directly analyzed, and the conditions governing the course of the synthesis can be readily determined. Some of the conditions necessary for the preparation of the 6-isomer in high purity have been defined.

Experimental

Materials.—2,4,5-Triamino-6-hydroxypyrimidine (I) was prepared according to the method of Traube[6] with the modification that the reduction of 2,4-diamino-5-nitroso-6-hydroxypyrimidine was carried out with zinc in hydrochloric acid solution, with the result that I-dihydrochloride was obtained. I-hydrosulfate was prepared from a solution of I or I-dihydrochloride by the addition of dilute sulfuric acid. Hydrazine hydrate (85%) was obtained from Eastman Kodak Co. and used without further purification. D-Glucose was used as the commercial hydrate Cerelose. D-Fructose was obtained from Eastman Kodak Co. L-Sorbose was prepared by the oxidation of sorbitol with *Acetobacter suboxydans* according to the method of Wells, *et al.*[7]

Ultraviolet Absorption Spectra.—Ultraviolet spectra were obtained with a Beckman spectrophotometer. Solvents were 0.1 *N* sodium hydroxide, and 0.08 *N* hydrochloric acid. The latter solvent was chosen because it was found easier to dissolve the materials in acidic media if the 0.1 *N* sodium hydroxide solution was diluted 1:10 with 0.1 *N* hydrochloric acid than to make a solution directly in 0.1 *N* hydrochloric acid. The ratio of the maxima was used as an intrinsic property of the molecule and in the case of crude products it was valuable as an analytical tool regardless of the content of inorganic or other non-absorbing impurities. It was found to be characteristic of the 7- or 6-isomer. *E* 252 mμ/*E* 360 mμ for 7-polyhydroxyalkylpterines in 0.1 *N* sodium hydroxide has been found to be 2.2, and *E* 255 mμ/*E* 365 mμ for 6-polyhydroxyalkylpterines in the same solvent has been found to be 3.2.

In studying the condensation of sugars with I in the presence of an oxidizing agent such as hydrazine three general types of conditions were suggested, based primarily on the observations of Ohle and Hielscher[5]: namely, (a) the condensation in the presence of boric acid, (b) the condensation in the absence of boric acid, and (c) the condensation in the presence of oxidizing agents other than hydrazine. The results with other oxidizing agents—*i. e.*, (c)—can be summarized very briefly in the statement that no good substitute was found, although hydrogen peroxide, benzoyl peroxide, hydroxylamine, methylhydrazine, phenylhydrazine and semicarbazide were tried. Pterines were only obtained with hydroxylamine and the hydrazine derivatives, but the yields were no better than if no oxidizing agent had been used. Hydroxylamine seemed to be useful in directing the synthesis to the 6-form, but it did not affect the

(6) Traube, *Ber.*, **33**, 1371 (1900).

(7) Wells, Stubbs, Lockwood and Roe, *Ind. Eng. Chem.*, **29**, 1385 (1937); **31**, 1518 (1939).

yield over the condensation without any oxidizing agent.

Condensation of 2,4,5-Triamino-6-hydroxypyrimidine with Hexoses in the Presence of Boric Acid and Hydrazine.—Since hydrazine is a reducing agent in alkaline solution, there seemed no reason to study its action above *p*H 7. Therefore the *p*H range was kept at 4.5–7.0, since it was found that strongly acidic solution caused the formation of unreactive salts of I. Three moles of boric acid were always used for one mole of hexose and two moles for one mole of pentose. Its role was not studied in any detail when it was found that it could be eliminated. The volume and type of solvent, the concentration of reactants, and the molar ratio of sugar and hydrazine to pyrimidine were studied. After the identity of the products was proved by careful analysis and alkaline permanganate degradation studies the absorption spectra of the polyhydroxyalkylpterines themselves were relied upon to determine the purity of the products and the isomer composition of the mixture.

It was found that maximum yield was only obtained at *p*H less than 7.0. The reaction at *p*H 5.0 was complete in less than two hours, and was adversely affected by dilution. Using a molar ratio of pyrimidine:sugar:hydrazine of 1:1:1 the yield of product with D-glucose was 38% and with D-fructose and D-sorbose 55–60%. The aqueous ethanol condensation method improved the purity of the 6-isomer obtained from D-glucose, but did not affect the yield of product in the case of any of the hexoses used.

Condensation of 2,4,5-Triaminopyrimidine with Hexoses in the Absence of Boric Acid and Presence of Hydrazine.—The same conditions of study as described above apply to this phase of the work. Figure 1 shows graphically the relationship of the molar ratio of sugar × hydrazine/(pyrimidine)^2 *vs.* yield for D-glucose and L-sorbose. In most cases the reactants were mixed in water at a definite *p*H and then heated at 95°. However in the case where the solvent was aqueous alcohol, the procedure used was to dissolve the reactant in the boiling alcoholic solution and then to carry out the reaction by distillation of the solvent at atmospheric pressure until the volume had been brought to a very small amount, at which time a voluminous precipitate appeared. Since this procedure did not increase the yield, but in the case of the hexose aldoses it did increase the purity of the 6-isomer obtained, it is thought that the condensation reaction was slowed up to the point where the aldose could be converted into a ketose or some common intermediate rapidly enough to prevent the formation of appreciable 7-isomer. This seems to be a logical basis for explaining why ketoses were not appreciably affected by this latter method. Something like an Amadori rearrangement appeared to change the aldose to a ketose.

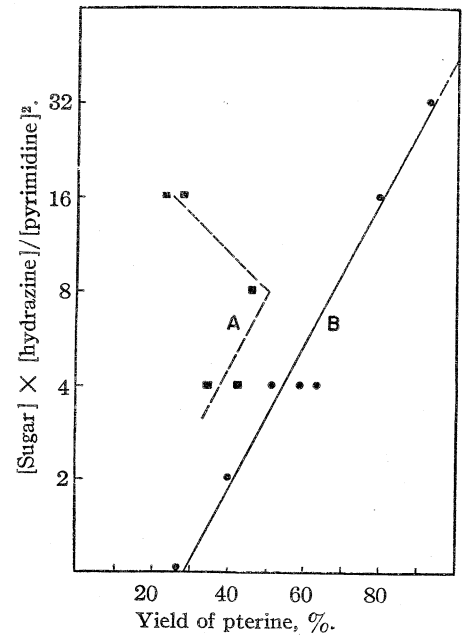


Fig. 1.—Relationship of reactants to yield in reaction without boric acid, time forty-five minutes, temp. 95°: (A), D(+)glucose; (B), L(−)sorbose.

D-Fructose was found to behave in the same manner as L-sorbose, and D-galactose similar to D-glucose in respect to the effect of the conditions described on yield and purity of 6-isomer. Pentose aldoses yielded mixtures of 6- and 7-isomer by the methods described.

The data shown in Fig. 1 were obtained at *p*H 4.5–5.5 and at a reaction time of forty-five minutes. It was found that at 95° the reaction without boric acid required thirty to forty-five minutes for completion. Analytical data together with specific illustration of the methods of preparation and purification of the compounds are given below.

2-Amino-4-hydroxy-6-tetrahydroxybutyl-(D-arabo)-pterine.—2.13 grams of I-dihydrochloride, 1.7 g. of sodium bicarbonate and 4.0 g. of D-glucose monohydrate were mixed with 17 ml. of water; 2.5 ml. of glacial acetic acid and 1.3 ml. of hydrazine hydrate (85%) in 8 ml. of water were added to this solution. The solution in a small erlenmeyer flask was allowed to react on a steam-bath at 90–95° for forty-five minutes. (After twelve minutes of heating a precipitate began to form.) The mixture was cooled and centrifuged, and the precipitate was washed with cold water, hot ethanol and ether (*p*H of mother liquor, 4.9); yield was 1.17 g. Ultraviolet ratio of 0.1 *N* sodium hydroxide solution was 2.99 indicating a product of high 6-isomer content.

One gram of this product was added to 100 ml. of water at 90° and enough ammonia was added dropwise to effect solution; 0.20 g. of Darco G60 was added and the mixture heated fifteen minutes, after which the charcoal was removed by filtration through filter-aid. The filtrate was brought to *p*H 5.0 with acetic acid and cooled to 15°. The precipitate was collected and washed with hot ethanol and ether. The product was dried *in vacuo;* yield 880 mg. *Anal.* Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.4; H, 4.59; N, 24.75. Found: C, 41.2; H, 4.86; N, 24.39. $[\alpha]_D$ −97.26 (0.323% in 0.1 *N* NaOH; *E* 255 mμ/*E* 365 mμ (0.1 *N* NaOH), 2.9.

The ratios of these preparations varied from 2.9 to 3.1 and $E^{g/l.}_{1\,cm.}$ (0.1 *N* NaOH) for similar preparations varied from 71.1–76.7 at 254 mμ and 24.3–24.7 at 365 mμ.

2-Amino-4-hydroxy-6-tetrahydroxybutyl-(L-xylo)-pterine.—2.13 grams of I-dihydrochloride, 1.7 g. of sodium bicarbonate and 3.6 g. of L-sorbose were dissolved in 25 ml. of water. To this solution 2.5 ml. of acetic acid and 1.3 ml. of hydrazine hydrate (85%) were added. The mixture was heated on the steam-bath at 90° for forty-five minutes, after which it was cooled and the precipitate was collected. It was washed well with water and hot ethanol and dried; yield 1.78 g.; ultraviolet ratio in 0.1 *N* sodium hydroxide was 3.0.

One gram of this product was extracted in a Bailey–Walker extraction unit with 110 ml. of water for three and one-half hours. The extract was made alkaline with ammonia to *p*H 11 and the resulting solution was decolorized with 0.2 g. of Darco G60.

The filtrate was brought to *p*H 5.0 with acetic acid and cooled. The precipitate was collected and washed with hot ethanol and ether. The precipitate was dried *in vacuo;* yield 640 mg.; ultraviolet ratio in 0.1 *N* sodium hydroxide = 3.0. *Anal.* Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.4; H, 4.59; N, 24.75. Found: C, 41.3; H, 5.10; N, 23.08. $[\alpha]_D$, −69.0 (0.393% in 0.1 *N* sodsum hydroxide; *E* 354 mμ/*E* 365 mμ (0.1 *N* sodium hydroxide), 3.0. In general this ratio has been found to vary from 2.9–3.2 and the $E^{g/l.}_{1\,cm.}$ in a manner similar to those found for 6-tetrahydroxybutyl-(D-arabo)-pterine preparations.

Oxidation with Alkaline Permanganate

To indicate the basis of the analysis of the ultraviolet absorption spectra for isomer composition the following data obtained by oxidative degradation to the corresponding 6-(or 7)- carboxypterine are presented.

a. 6.1 mg. of 2-amino-4-hydroxy-7-tetrahydroxybutyl-(D-arabo)-pterine was dissolved in 50.0 ml. of 0.1 *N* sodium hydroxide and the solution heated to 70°. A concentrated solution of barium permanganate was added dropwise until a permanent purple color remained after one hour of heating at 70°. The solution was cooled and to it formaldehyde was added dropwise to discharge the purple color. The mixture was filtered through filter-aid and the filter-cake was washed with a small amount of 0.1 *N* sodium hydroxide. The volume was made to 60.0 ml. and the ultraviolet absorption spectrum of a 1:10 dilution was analyzed. The original compound had an ultraviolet ratio of 2.4.

b. In a similar way 6.05 mg. of a preparation with ultraviolet ratio of 3.2 was oxidized and the ultraviolet absorption spectrum of the oxidized product analyzed.

The ultraviolet curves for the carboxypterines described above are given in Fig. 3, and show the variations in the spectra between the 7-isomer and the 6-isomer. These curves check very well with those reported for 7-carboxypterine and 6-carboxypterine by Mowat, *et al.*,[8] and Wittle, *et al.*[9] The oxidation product of a mixture of 6- and 7-tetrahydroxybutylpterines gives ultraviolet curves intermediate between **a** and **b**.

2-Amino-4-hydroxy-6-methylpterine.—Two and four-tenths grams of I-hydrosulfate and 1.06 g. of sodium carbonate were mixed in 25 ml. of water. To this solution were added 1.0 ml. of glacial acetic acid and 1.2 ml. of hydrazine hydrate (85%). The mixture was cooled in an ice-bath. To this cool mixture was added 2.0 g. of monochloroacetone in 5 ml. of alcohol. The mixture was kept cool (25°) during the ensuing reaction, and the *p*H was kept at 6.0 with small additions of solid sodium bicarbonate. A rapid reaction continued and the mixture was kept cool until a red-colored precipitate began to form. It was then heated on a steam-bath for forty-five minutes and cooled. An equal volume of ethanol was added and the mixture centrifuged. The precipitate was washed well with methanol and finally dissolved in 45 ml. of 10% ammonia water. The solution was warmed to 75° and the dark residue was removed by centrifugation. The solution was decolorized with 0.2 g. of Darco G60, and the filtrate brought to *p*H 5.0 with acetic acid. The cooled mixture was centrifuged and the precipitate washed with warm methanol. It was dried with acetone and ether and *in vacuo;* yield 700 mg.

Anal. Calcd. for $C_7H_7N_5O$: N, 39.6. Found: N, 39.3. *E* 252 mμ/*E* 360 mμ (0.1 *N* sodium hydroxide), 3.2.

Discussion

In view of the fact that the $[\alpha]_D$ of the pterine obtained by the condensation of I and D-glucose in the presence of hydrazine is identical with that obtained by the condensation of I and D-glucosone,[6] there seems little doubt that the side-chain is 1′,2′,3′,4′-tetrahydroxybutyl. This means that hydrazine must act as an oxidizing agent and there is no chance for the formation of CH_2 at C_1′.

It has been found that the reaction of I and IIa or IIb in the presence of hydrazine does not require boric acid as an assisting agent. The data obtained also suggest that the reaction requires equimolar quantities of the sugar and hydrazine, and that the action of hydrazine is more rapid and complete with ketoses than with aldoses. The fact that the reaction can be made to go to the 6-isomers with aldoses indicates a possible Amadori rearrangement. In fact it has been found that D-xylose if first treated with aniline or toluidine to give D-arylaminoxyloketose the reaction proceeds smoothly to a 6-isomer, whereas D-xylose or any other pentose yields only a mixture of isomers by any of the methods which were satisfactory for D-glucose. Similarly the preparation of 2-amino-4-hydroxy-6-methylpterine indicates that simple 6-alkylpterines may be readily prepared by the condensation of a suitable ketone and pyrimidine in the presence of hydrazine.

If the data for the aldoses and ketoses are analyzed in such a way that the expression log [sugar × hydrazine/(pyrimidine)^2] is plotted against % yield, the striking difference in behavior of the ketoses and aldoses is shown (Fig. 1).

Increasing either sugar or hydrazine increases the percentage yield based on the pyrimidine for L-sorbose or D-fructose, but for D-glucose this is not true. In the latter case an excess of either component beyond the value where sugar × hydrazine/(pyrimidine)^2 is greater than 8 results in a lowering of the yield.

The conditions for directing the synthesis to the 6-isomer for ketose are broad. In general the *p*H should be kept at 4–7, and the temperature above 90° for rapid reaction. Small volume of aqueous medium is desirable, for it facilitates isolation since the 6-isomer is more soluble than the 7-isomer. Boric acid is of no value.

The conditions for the synthesis of 6-isomer from I and aldose hexoses in the presence of hydrazine include low volume of aqueous medium—*i. e.*, high concentration of reactants—and a slight excess of hydrazine and/or sugar; the molar ra-

(8) Mowat, Boothe, Hutchings, Stokstad, Waller, Angier, Semb and SubbaRow, THIS JOURNAL, **70**, 16 (1948).

(9) Wittle, O'Dell, Vandenbelt and Pfiffner, *ibid.*, **69**, 1786 (1947).

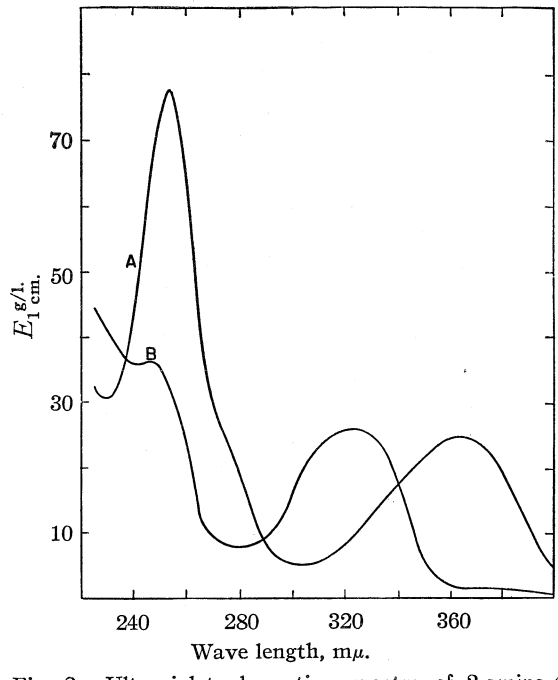


Fig. 2.—Ultraviolet absorption spectra of 2-amino-4-hydroxy-6-tetrahydroxybutyl-(D-arabo)-pterine: (A) in 0.1 *N* sodium hydroxide; (B) in 0.08 *N* hydrochloric acid.

tio of sugar × hydrazine/(pyrimidine)[2] should not exceed 8. The *p*H should be kept at 4–7 as in the case of ketoses. An alternate method of preparing 6-isomers of high purity involves the use of aqueous ethanolic medium, the reaction being carried out during the distillation of the solvent at atmospheric pressure.

Under any condition it seems that hydrazine acts as an oxidizing agent with the probable formation of ammonia in the reaction. We have found that all hexoses studied react normally, while all pentose aldoses do not. If, however, the pentoses are converted to ketoses, then the directed synthesis to 6-isomer proceeds smoothly.

The value of the absorption spectra of the polyhydroxyalkylpterines in elucidating the isomer problem can readily be seen from the data of Figs. 2 and 3. More details of the physical properties of pterines will be published later.

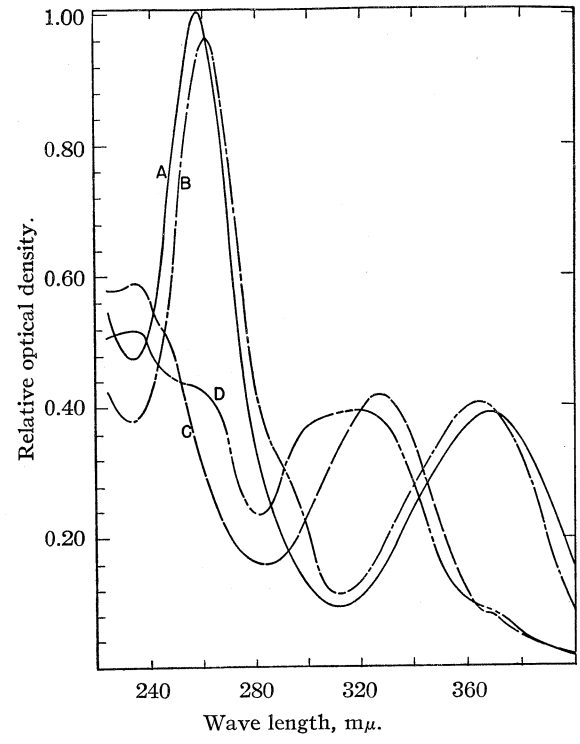


Fig. 3.—Ultraviolet absorption spectra of permanganate oxidation products from polyhydroxyalkylpterine: 2-amino-4-hydroxy-7-tetrahydroxybutylpterine (A) in 0.1 *N* sodium hydroxide, (C) in 0.08 *N* hydrochloric acid: 2-amino-4-hydroxy-6-tetrahydroxybutylpterine, (B) in 0.1 *N* sodium hydroxide and (D) in 0.08 *N* hydrochloric acid.

Summary

Methods for the direct synthesis of 2-amino-4-hydroxy-6-tetrahydroxyalkylpterines from the corresponding aldo- and ketohexoses are described and discussed.

Evidence is presented to show that the ratio E 255 mμ/E 365 mμ in 0.1 *N* sodium hydroxide of 6-tetrahydroxybutylpterines is 3.2 and is characteristic of these compounds. This fact is used in studying conditions affecting the isomer composition of the products obtained.

KALAMAZOO, MICH. RECEIVED MAY 2, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Condensation of 2-Pyrrolealdehyde with Hippuric Acid: Isolation of *cis* and *trans* Isomers

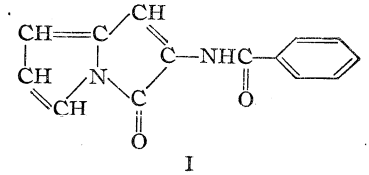
BY WERNER HERZ[1]

In the course of work which had as its objective the synthesis of β-2-pyrrolealanine,[2] the condensation of 2-pyrrolealdehyde with several compounds containing active methylene groups was investigated.[3] Complications were encountered when attempts were made to repeat earlier work[4] dealing with the reaction of pyrrolealdehyde and hippuric acid. It has now been found that these difficulties may be attributed to the formation of geometric isomers of the expected azlactone.

Erlenmeyer[5] first suggested the possibility of *cis–trans* isomerism in the azlactone series when condensing cinnamaldehyde with hippuric acid, although he was unable to isolate the two forms. Carter and co-workers[6] obtained *cis* and *trans* isomers of α-benzoylaminocrotonic azlactone and of α-benzoylaminocinnamic azlactone on heating the α-benzoylamino-β-methoxy acids with acetic anhydride. It is interesting to note that the condensation of 2-indolealdehyde with hippuric acid[7] is not reported to result in the formation of a mixture, nor were two products obtained from the few substituted pyrrolealdehydes subjected to the azlactone synthesis.[8]

Asahina and Mitsunaga[4] reported that 2-pyrrolealdehyde condenses with hippuric acid to give a product which sinters at 155° and melts at 163°. Hydrolysis with 1% sodium hydroxide resulted in two distinct acids, m. p. 173° and m. p. 235°. The only empirical formula given, that of the higher-melting acid, corresponds to the composition of the expected α-benzoylamino-β-(2-pyrrole)-acrylic acid.

The data reported in this article differ markedly from the results reported by these authors. Recrystallization of the crude product from most solvents yielded crystals melting in the range 145–163° which indicated the presence of a mixture. Crystals obtained by recrystallization from benzene melted sharply at 173°; in the following this compound will be referred to as azlactone II. From the mother liquors, fractions with considerably lower melting points were obtained. All fractions gave analyses correct for the predicted azlactone. The existence of *cis* and *trans* isomers of 2-phenyl-4-pyrrolal-5-oxazolone was therefore suspected. Another possibility, the formation of a lactam (I) in a manner similar to the formation of a coumarin from salicylaldehyde and hippuric acid,[9] was ruled out by the deep color of all fractions and by the fact that the infrared spectra



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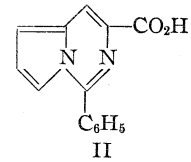
which would be expected to differ widely if the lactam were present showed only minor variations.

Hydrolysis of the low-melting mixture with 0.4 *N* sodium hydroxide yielded two isomeric acids of the composition expected for α-benzoylamino-β-(2-pyrrole)-acrylic acid. Acid I, dec. 192°, precipitated immediately and gave a methyl ester of m. p. 153°. Acid II, dec. 239–240°, separated on standing and was characterized by a methyl ester of m. p. 179°. Undoubtedly it is identical with the high-melting acid of Asahina and Mitsunaga.[4]

Dehydration of acid I with acetic anhydride yielded an azlactone, 2-phenyl-4-pyrrolal-5-oxazolone I, different from azlactone II. Acid II on treatment with acetic anhydride regenerated azlactone II. The infrared spectra of the pure azlactones were similar, but not identical. In the double-bond region, azlactone I exhibited two strong bands at 1740 cm.$^{-1}$ (lactone frequency) and at 1637 cm.$^{-1}$ (C=N frequency); in azlactone II these bands occur at 1751 and 1649 cm.$^{-1}$,[10]

The alkaline hydrolysis of the azlactones was further complicated by the formation of a third product arising from the reaction of acid II with alkali. This compound, an acid of formula $C_{14}H_{10}N_2O_2$, could be obtained from acid II or directly from azlactone II by hydrolysis with 1% sodium hydroxide; it frequently contaminated preparations of acids I or II when base was in excess. The absence of NH frequencies from the infrared



II

(1) American Cyanamid Company Postdoctorate Fellow, 1947-1949. Present address: Department of Chemistry, The Florida State University, Tallahassee, Florida.

(2) Herz, Dittmer and Cristol, THIS JOURNAL, **69**, 1698 (1947); **70**, 504 (1948).

(3) Dittmer and Herz, *ibid.*, **70**, 503 (1948).

(4) Asahina and Mitsunaga, *J. Pharm. Soc. Japan*, 986 (1917).

(5) Erlenmeyer and Matter, *Ann.*, **337**, 271 (1904).

(6) Carter and Stevens, *J. Biol. Chem.*, **133**, 117 (1940); Carter and Risser, *ibid.*, **139**, 255 (1941).

(7) Restelli, *Añales asoc. quím. argentina*, **23**, 58 (1935).

(8) Fischer and Hofmann, *Z. physiol. Chem.*, **245**, 139 (1936–1937); Fischer and Wasenegger, *Ann.*, **461**, 277 (1928).

(9) Erlenmeyer and Stadlin, *Ann.*, **337**, 283 (1904).

(10) These frequencies are in the range given for the lactone and C=N bands of azlactones containing a 4-exocyclic double bond.[11]

(11) Thompson, Brattain, Randall and Rasmussen, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 387.

spectrum of the acid and its methyl ester as well as the solubility of both compounds in dilute acid suggests the formula of 4-phenyl-pyrrolo[1,2-*C*]-pyrimidine-2-carboxylic acid (II), the product of an intramolecular condensation between the benzoyl radical and the pyrrole nitrogen. If this interpretation is correct, configurations may be assigned to azlactones I and II and the acids resulting from their hydrolysis. Because the pyrrolopyrimidine could not be obtained from acid I or azlactone I, the pyrrole nitrogen and the benzoyl group in these compounds must be *trans* to each other, whereas the *cis* configuration of acid II permits ring closure to occur. It is intended to investigate the applicability of this reaction to other compounds of this type.

Experimental

2-Phenyl-4-pyrrolal-5-oxazolone, II.—An intimate mixture of 9 g. of 2-pyrrolealdehyde,[12] 18 g. of hippuric acid and 18 g. of anhydrous sodium acetate was heated on the steam-bath with 45 ml. of acetic anhydride. After one hour, the mixture was cooled, broken up with a stirring rod, triturated with water, filtered, washed with water and dried. The yield of dark-brown material was 16.5 g. Eleven grams of the crude product was extracted with 200 ml. of boiling benzene. The benzene solution was treated with charcoal and deposited 1.5 g. of orange plates, m. p. 173°. The melting point was not raised by further recrystallizations from benzene. This fraction had the analysis given below. On evaporation of the benzene mother liquor to 125 ml. and cooling, 1.1 g. of material, m. p. 172°, precipitated. Further evaporation and cooling yielded 3.5 g. of material melting in the range 135–145°.

Anal.[13] Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 71.10; H, 4.49; N, 11.76.

Five grams of the crude condensation product was extracted with two 50-ml. portions of boiling ethanol. The combined extracts were treated with charcoal and on cooling deposited 1.5 g. of yellow crystals, m. p. 148–163°. On evaporation of the filtrate to smaller volume, 0.6 g. of material melting in the same range was obtained. Dilution of the mother liquor with water yielded 1.6 g. of lower-melting material. Hydrolysis experiments showed that the first two fractions consisted almost exclusively of azlactone II in spite of the melting point range. Reprecipitation from pyridine solution with water raised the m. p. to 173°.

α-Benzoylamino-β-(2-pyrrole)-acrylic Acids I and II.—The crude product resulting from the condensation of 9 g. of 2-pyrrolealdehyde and 18 g. of hippuric acid was stirred with one portion of 50 ml. and one portion of 25 ml. of cold ethanol. This removed a considerable portion of azlactone II. The undissolved material was recrystallized from acetone–water and weighed 4.5 g., m. p. 155–160°. Four grams was heated on the steam-bath with 200 ml. of 0.4 *N* sodium hydroxide. After three hours, the solution was acidified with concd. hydrochloric acid. A light-yellow precipitate which appeared to decompose rapidly was filtered immediately and washed with water. The filtrate deposited 1.4 g. of grey-blue needles on standing. Five recrystallizations of the first precipitate from dilute ethanol, accompanied each time by treatment with charcoal, gave 0.23 g. of slightly-colored crystals (acid I) which decomposed at 192° when the capillary was immersed at a bath temperature of 185°.

(12) Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 152.

(13) Analyses by Miss Emily Davis, Miss Rachel Kopel and Mr. Maurice Dare. Infrared measurements were carried out by Miss Elizabeth Peterson.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.61; H, 4.72; N, 10.94. Found: C, 65.74; H, 4.94; N, 10.80.

The second product was dissolved in dilute sodium hydroxide and filtered from insoluble material. The precipitate obtained on acidification was recrystallized three times from dilute ethanol, each recrystallization being accompanied by treatment with charcoal. The almost white needles weighed 0.25 g. and decomposed at 239–240° when the capillary was immersed at 230° and the bath was heated up rapidly.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.61; H, 4.72; N, 10.94. Found: C, 65.86; H, 4.90; N, 10.96.

Hydrolysis of 2 g. of the low-melting material obtained from the benzene mother liquors of azlactone II, using 80 ml. of 0.5 *N* sodium hydroxide, yielded 0.85 g. of crude acid I, contaminated by acid II.

Methyl Ester of Acid I.—A solution of 95 mg. of acid I in 5 ml. of methanol was treated with an ethereal solution of diazomethane. After removal of the ether, the solution was diluted with water and deposited 79 mg. of ester. Recrystallization from dilute methanol gave needles melting at 153°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.85; H, 5.44; N, 10.46.

Methyl Ester of Acid II.—In the same way, 93 mg. of acid II gave 87 mg. of light-yellow crystals melting at 179°. The ester was also obtained in 70% yield when azlactone II was treated with sodium methoxide in methanol, following the procedure of Fischer and Hofmann.[3]

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.88; H, 5.41; N, 10.11.

2-Phenyl-4-pyrrolal-5-oxazolone I.—A mixture of 27 mg. of pure acid I and 1 ml. of acetic anhydride was warmed on the steam-bath for ten minutes. Dilution with water caused the separation of a light-brown precipitate weighing 24 mg. Repeated slow crystallization from ethanol yielded golden needles, m. p. 186°, mixed m. p. with azlactone II 145–155°.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.41; H, 4.16; N, 11.63.

Treatment of 38 mg. of acid II with acetic anhydride gave 33 mg. of orange crystals, m. p. 173°, showing no depression on admixture of azlactone II.

Hydrolysis of Azlactone II with 1% Sodium Hydroxide.—A mixture of 300 mg. of azlactone II and 15 ml. of 1% sodium hydroxide solution was warmed on the steam-bath for one hour until the azlactone was dissolved completely. The red solution was cooled and made barely acid to congo-red paper. A light-green precipitate separated. It was filtered and washed rapidly to prevent decomposition. The mother liquor on chilling deposited a small amount of acid II. The precipitate was recrystallized three times from 10 ml. of ethanol, using charcoal. The light-green needles were soluble in dilute base and acid, insoluble in water, m. p. 182–183° with decomposition. The infrared spectrum showed the complete absence of any —NH and C=O frequencies other than those ascribed to conjugated carboxyl at 1680 cm.$^{-1}$ and acid —OH. In ethanol solution the compound gave a carmine-red color with ferric chloride.

Anal. Calcd. for $C_{14}H_{10}O_2N_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.59; H, 4.25; N, 11.71.

This acid was also obtained by warming acid II with 1% sodium hydroxide solution on the steam-bath.

The methyl ester was prepared by dissolving 150 mg. of the acid in methanol and adding an ether solution of diazomethane. Removal of the ether followed by dilution with water yielded a yellow oil which solidified on standing. Three recrystallizations from methanol–water gave yellow needles, m. p. 107°, soluble in dilute acid, insoluble in base. The infrared spectrum contained a strong band at 1718 cm.$^{-1}$ which can be ascribed to a conjugated ester group.

Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.44; H, 4.84; N, 11.11. Found: C, 71.35; H, 5.06; N, 11.13.

Summary

The condensation of 2-pyrrolealdehyde with hippuric acid and acetic anhydride gives rise to two isomeric azlactones. Configurations have been tentatively assigned to these isomers on the basis of an intramolecular condensation which only one of them appears to undergo.

URBANA, ILLINOIS RECEIVED JUNE 27, 1949

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Comparative Properties of Some Methyl Substituted 8-Quinolinols

BY JOHN P. PHILLIPS[1] AND LYNNE L. MERRITT, JR.

As part of an investigation in this Laboratory of some new analytical reagents of the 8-quinolinol series, the 2- and 4-methyl derivatives were studied.[2,3] Because these derivatives showed some rather interesting differences from each other and from 8-quinolinol, the properties here described were determined and the results compared.

Experimental

Purification of Materials.—The substituted 8-quinolinols were prepared and purified as previously described.[3,4] A further check on the purity of the 8-quinolinol and 2-methyl-8-quinolinol used was obtained through their quantitative bromination[5] with standard potassium bromate, both analyzing better than 99.7%.

Infrared Spectra.—All spectra were obtained with a Beckman IR-2 instrument with automatic recording. The intensity curves for solvent and solution were recorded on the same graph and the ratios of the two curves calculated at corresponding wave lengths in order to get per cent. transmission. The assignment of wave lengths was calculated from the known absorption bands of carbon tetrachloride, carbon dioxide and water vapor with an estimated accuracy of $\pm 0.05\mu$ over most of the range studied.

Approximately saturated solutions in carbon tetrachloride in 0.1 mm. thick salt cells were used throughout.

Ultraviolet Spectra.—Curves were recorded with a Beckman Model DU Quartz Spectrophotometer using 1.00 cm. cells and slit widths from 0.1–2.0 mm. as required. Readings were made every one millimicron in the vicinity of an absorption maximum and at somewhat wider intervals elsewhere. All compounds obeyed Beer's law satisfactorily in the concentration range studied. Molecular extinctions are considered accurate to two significant figures.

Powder Diffraction Lines.—The finely powdered samples, mounted on a rotating hard glass fiber coated with vaseline, were exposed for five hours to filtered copper X-ray radiation. The "*d*" values, calculated in the usual way, are the average values from two or more photographs for each compound. Relative intensities were estimated visually.

Quantitative Precipitations of Metals.—The procedure was the same as previously described[2] except that, owing to coprecipitation of the excess substituted quinolinol, it was usually necessary to ignite the precipitates to the oxides for weighing.

The standard solutions of Cu^{++}, Zn^{++}, Mg^{++}, Co^{++}, Mn^{++}, Fe^{+++} and Al^{+++} were prepared by standard methods from weighed quantities of reagent grade chemicals and further analyzed by precipitation with 8-quinolinol. Determinations were made at 0.2 *p*H unit intervals to obtain the *p*H values at which precipitation begins and is complete.

Reactions with Diazomethane.—A 100–200% excess of an ether solution of diazomethane was added to an ether solution of the substituted 8-quinolinol. Red precipitates formed with 8-quinolinol, 4-methyl-8-quinolinol and 5,7-dibromo-8-quinolinol but did not form with 2-methyl- or 2,4-dimethyl-8-quinolinol. The red products were filtered and recrystallized from benzene; they had indefinite decomposition points and were, therefore, characterized by their ultraviolet and visible absorption spectra. Nitrogen analyses on the product from 8-quinolinol (7.20%) do not conform to that calculated (8.80%) from the structure proposed by Schenkel-Rudin.[6]

Results and Discussion

The infrared absorption spectra (Figs. 1–4) from 2–11μ of these four quinolinols in approximately saturated solutions show several bands that can be correlated with known structural features of all the compounds, but few characteristics capable of distinguishing the compounds from each other. (It is evident from the graphs that 4-methyl-8-quinolinol has a low solubility in carbon tetrachloride compared to its 2-methyl isomer.)

The absorption band at 2.8μ is evidently the O–H stretching band; it is completely absent in the 8-methoxy derivatives of these compounds.[7] The bands at approximately 3.2–3.3μ are due to C–H stretching and vary somewhat in wave length and structure probably because of the different kinds of C–H linkages in the different compounds. (The absence of these bands in 4-methyl-8-quinolinol can be attributed to the low concentration of the solution.) The strong absorption maxima at about 6.35, 6.65 and 6.8μ are fundamental frequencies of the aromatic ring system. The bands at 7.1, 7.3 and 7.5μ are probably due to C–H bending, the one at 7.5μ perhaps being caused by the C–H bond in the active 2-methyl group since it is lacking in 8-quinolinol and 4-methyl-8-quinolinol. Maxima at 7.9–8.1μ are perhaps associated with C–O or C–N stretching vibrations.

No maxima identifiable with a C=O linkage could be found in any of these compounds, although the existence of a considerable proportion of the keto tautomer of 8-quinolinol in non-

(1) Abstracted from a thesis by John P. Phillips in partial fulfillment of the requirements for the degree Doctor of Philosophy at Indiana University, 1949. Du Pont Fellow for 1948–1949.

(2) L. L. Merritt and J. Walker, *Ind. Eng. Chem., Anal. Ed.*, **16**, 387 (1944).

(3) J. P. Phillips and L. L. Merritt, THIS JOURNAL, **70**, 410 (1948).

(4) J. P. Phillips, R. L. Elbinger and L. L. Merritt, THIS JOURNAL, **71**, 3986 (1949).

(5) M. V. Tsypkin, *Farmatsiya i Farmakol.*, 1937, No. 2, 43.

(6) Schenkel-Rudin, *Helv. Chim. Acta*, **27**, 1456 (1944).

(7) Unpublished observations in this Laboratory.

TABLE I

ABSORPTION MAXIMA IN ULTRAVIOLET SPECTRA OF 8-QUINOLINOLS (WITH MOLECULAR EXTINCTION COEFFICIENTS)

Substituent	Neutral solvent mμ	mμ	Hydrochloric acid mμ	mμ	mμ	Sodium hydroxide mμ	mμ
None[e]	242(42000)	320(2400)[a]	250(40000)	318–9(1700)	358 (1700)	253(32000)	345[d](2700)
CH_2N_2 addn. prod.	260, 280	354, 480[c]	255	323	365–6	238–9, 273	333, 346, 441
4-CH_3–	242(48000)	319(3300)[a]	250(44000)	315–8(1700)	350–3(2400)	253(28000)	343[d](3900)
2-CH_3–[f]	246(53000)	309(2900)[a]	255(44000)	320 (3100)	345 (1700)	255(30000)	335(3000)
2,4-$(CH_3)_2$–	246(50000)	309(3300)[a]	252(48000)	318 (3100)	342 (2400)	255(31000)	337(4200)

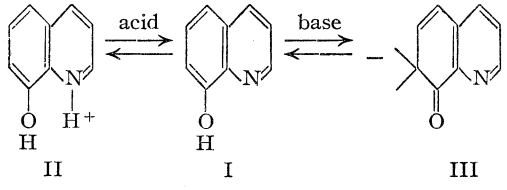
[a] In cyclohexane. [b] In chloroform. [c] In 95% alcohol. [d] Center of a broad band. [e] Copper chelate (in neutral solvent) 262–3(45000), 405–11(4400).[b] [f] Copper chelate (in neutral solvent) 268–9(45000), 392–6(4200).[b]

polar solvents appears probable from other considerations.[8]

The above conclusions should be viewed with caution, however, since overlapping can obscure many absorption maxima and lead to erroneous correlation of structural features with observed spectra.

The maxima in the ultraviolet absorption spectra of these compounds from 225–400 mμ (Table I) furnish additional information about their structure. (It was not considered necessary to graph these spectra since they are all very similar in shape to the curves for 8-quinolinol already recorded in the literature.[9])

The considerable change in the spectra in acidic and basic solvents is probably caused by structure changes of the following sort[10]



The spectra of the copper chelates is of interest because of the complete similarity, except for a large bathochromic shift, of their spectra to those of the parent compounds, which suggests that the role of the copper in the chelate is the same as that of the acidic hydrogen in 8-quinolinol. Similar spectra were observed with the chelates of other divalent metals.

For characterization purposes, the X-ray powder diffraction lines of these compounds and a few derivatives were measured (Table II).

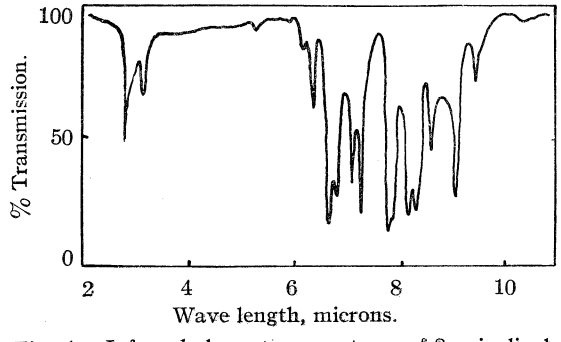


Fig. 1.—Infrared absorption spectrum of 8-quinolinol.

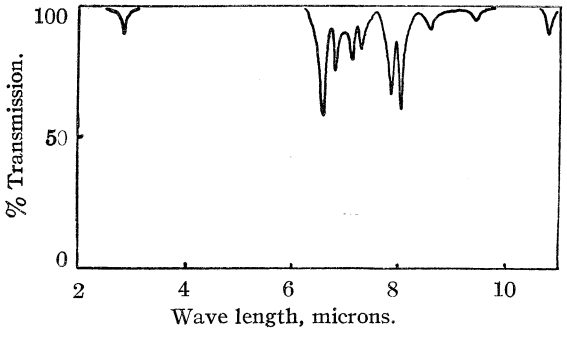


Fig. 2.—Infrared absorption spectrum of 4-methyl-8-quinolinol.

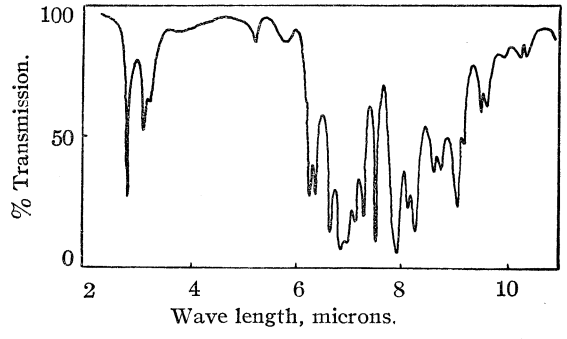


Fig. 3.—Infrared absorption spectrum of 2-methyl-8-quinolinol.

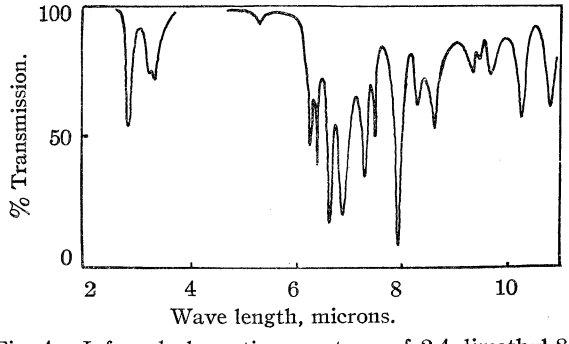


Fig. 4.—Infrared absorption spectrum of 2,4-dimethyl-8-quinolinol.

The analytical behavior of 8-quinolinol is well known; the 2- and 4-methyl derivatives show the

(8) P. Seguin, *Bull. Soc. Chim.*, **13**, 566 (1946).
(9) Ewing and Steck, THIS JOURNAL, **68**, 2181 (1946).
(10) Stone and Friedman, THIS JOURNAL, **69**, 209 (1947).

TABLE II

"*d*" VALUES OF SUBSTITUTED 8-QUINOLINOLS (IN ORDER OF DECREASING INTENSITY)

Substituent								
None	6.27	3.18	3.82	3.50				
5,7-Br_2–	3.52	3.89	4.06	4.26	3.09	3.20	3.36	6.81
2-CH_3–	3.92	3.67	3.13	5.45	5.93	2.07	5.00	7.94
5,7-Br_2-2-CH_3–	3.52	4.64	3.78	3.10				
4-CH_3–	3.30	6.01	7.29					
2,4-$(CH_3)_2$–	7.14	3.55	3.98	4.50	3.24			
5,7-Br_2-2,4-$(CH_3)_2$–	4.03	3.42	4.31					

same properties with the important exception that 2-methyl- and 2,4-dimethyl-8-quinolinol will not form insoluble chelate compounds with aluminum, the smallest ion of the group tested. Since 4-methyl-8-quinolinol will precipitate aluminum, it seems probable that the 2-methyl group prevents reaction with aluminum by steric hindrance. Further evidence of steric effects by the 2-methyl group is the observation that 2-methyl- and 2,4-dimethyl-8-quinolinol do not give the red addition products with diazomethane that are obtained from 8-quinolinol and 4-methyl-8-quinolinol under comparable conditions.

Quantitative data on the precipitation behavior of these compounds with metals are presented in Table III; the similar results for 8-quinolinol as determined by Goto[11] are included for comparison.

TABLE III

THE *p*H OF PRECIPITATION OF METAL CHELATES OF SUBSTITUTED 8-QUINOLINOLS

Substituent ion	None[d]		4-CH_3		2-CH_3		2,4-$(CH_3)_2$	
	Start[a]	End[b]	Start	End	Start	End	Start	End
Al^{+3}	2.8	4.2	3.5	...	None	None	None	None
Fe^{+3}	2.4	2.8	2.4	3.6	3.1[c]	5.7[c]	3.0	5.4
Mg^{+2}	6.7	8.2	6.8	8.4	7.6[c]	8.9[c]	8.2	>9.5
Mn^{+2}	4.3	5.9	4.6	6.0	5.0	6.6	5.2	7.0
Co^{+2}	2.8	4.2	3.4	4.6	3.8	5.2	4.2	5.8
Zn^{+2}	2.8	4.4	3.2	5.2	3.4[c]	5.3[c]	3.2	5.2
Cd^{+2}	2.2	2.7	...	3.4	2.9[c]	4.5[c]	2.4	4.8

[a] The highest *p*H without any precipitation. [b] The lowest *p*H at which the metal is wholly precipitated. [c] Previously determined.[2] [d] Previously determined.[11]

It is interesting that the order of increasing *p*H at which a given metal ion is precipitated by these four compounds is roughly the order of decreasing acidity of the substituted 8-quinolinols (the ionization constants have been previously reported[3]).

8-Quinolinol — increasing K_a ↓
4-Methyl-8-quinolinol
2-Methyl-8-quinolinol
2,4-Dimethyl-8-quinolinol — increasing *p*H ↑

This is explained by noting that, although the weaker acids should form more stable complexes with metallic ions[12] and should, therefore, form precipitates in more acid solutions, it is necessary to go to more basic solutions in order to obtain comparable amounts of the active chelating ion. The latter effect is apparently the predominant one.

Summary

1. The ultraviolet and infrared absorption spectra of the 2- and 4-methyl derivatives of 8-quinolinol have been measured and their correlation with structure discussed.

2. The precipitation behavior of these compounds with metal ions has been determined and evidence for steric hindrance by the 2-methyl group in such reactions presented.

3. The possible relation of the function of the acidic hydrogen in 8-quinolinol to that of the metal ion in the corresponding chelate, as shown by the relation of K_a to *p*H of precipitation, has been pointed out.

(11) H. Goto, *J. Chem. Soc. Japan*, **54**, 725 (1933), and later references.

(12) Calvin and Wilson, THIS JOURNAL, **67**, 2003 (1945).

BLOOMINGTON, IND. RECEIVED APRIL 25, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

Preparation of Some Substituted 8-Hydroxy- and 8-Methoxyquinolines

BY JOHN P. PHILLIPS,[1] REBECCA LEASH ELBINGER[1,2] AND LYNNE L. MERRITT, JR.

As a result of the discovery[3] that 8-hydroxyquinaldine differed in its analytical behavior from 8-hydroxyquinoline, the compounds here described were synthesized with the hope of obtaining more selective analytical reagents of the 8-hydroxyquinoline series.

The steric nature of the failure of 8-hydroxyquinaldine to react with aluminum was demonstrated by the observation that all the 8-quinolinols studied having alkyl groups in the 2-position would not react with aluminum while the isomeric compounds with substituents in the 3- and 4-positions would react. With the expectation that larger groups in the 2-position would create greater steric hindrance, perhaps enough to prevent reaction with other metal ions besides aluminum, a series of 2-aryl- and 2-styryl 8-quinolinols was prepared, but qualitative tests with several representative metal ions indicated no improvement in selectivity.

All alkyl substituted 8-hydroxy- and 8-methoxyquinolines (Table I) were made by the Doebner–

(1) Abstracted in part from theses submitted by Rebecca Leash Elbinger and John P. Phillips in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University.

(2) Present address: University of Illinois Extension, Navy Pier, Chicago, Illinois.

(3) L. L. Merritt and J. Walker, *Ind. Eng. Chem., Anal. Ed.*, **16**, 387 (1944).

von Miller reaction[4] between α,β-unsaturated carbonyl compounds and *o*-aminophenol or *o*-anisidine. No effective oxidizing agent for these reactions was found. (Nitrobenzene, *o*-nitrophenol and picric acid were tried.) This probably accounts, in part, for the very low yields obtained.

The 2-aryl-8-quinolinols (Table I) were prepared by the reaction of an excess of the proper lithium aryl with 8-quinolinol according to the method of Gilman.[5] The preparation of the corresponding 8-methoxy derivatives from 8-methoxyquinoline could be effected with greater economy of the lithium aryl, but it was not found possible to cleave the resulting ethers by the usual procedures at ordinary pressures using hydriodic acid, hydrobromic acid or potassium hydroxide and ethylene glycol.

2-Styryl-8-quinolinol and some related compounds (Table I) were made by the condensation, by heating, of 8-hydroxyquinaldine with benzaldehydes.

TABLE I

SUBSTITUTED 8-QUINOLINOLS AND 8-METHOXYQUINOLINES

Substituent	M. p. (uncor.), °C.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found	Procedure
8-Quinolinols					
4-CH_3– [a]	141	20	8.80	9.01	A
2,4-$(CH_3)_2$– [b]	64	32	..	..	A
2,4-$(CH_3)_2$-5,7-Br_2–	108	100	.. [c]	..	.. [d]
3,4-$(CH_3)_2$–	123–124	5	8.14	8.51	A
2,3,4-$(CH_3)_3$–	89–91	5	6.96	6.83	A
2-C_2H_5-3-CH_3–	46–47	5	.. [e]	..	A
2-C_2H_5-3-CH_3-5,7-Br_2–	150	100	4.06	4.29	.. [d]
2-C_6H_5– [f]	59	44	6.34	6.27	B
2-*m*-$CH_3C_6H_4$–	58–59	30	5.96	5.83	B
2-*p*-$CH_3C_6H_4$–	83–83.5	32	5.96	6.10	B
2-*p*-$C_6H_5C_6H_4$–	170–171	30	4.71	4.71	B
2-*p*-$CH_3OC_6H_4$–	101–102	30	5.58	5.52	B
2-*p*-$C_2H_5OC_6H_4$–	84–85	30	5.29	5.15	B
2-*p*-$(CH_3)_2NC_6H_4$– [g]	151–152	30	10.6	10.7	B
2-*p*-$(C_2H_5)_2NC_6H_4$–	94–95	34	9.60	9.98	B
2-C_6H_5CH=CH–	104–105	50	5.66	5.47	C
2-*m*-$CH_3C_6H_4CH$=CH–	60–61	36	5.36	5.47	C
2-*p*-$CH_3OC_6H_4CH$=CH–	110–111	30	5.05	5.10	C
2-(2,3-$(CH_3O)_2$)-C_6H_3CH=CH–	102–103	30	4.56	4.43	C
8-Methoxyquinolines					
2,4-$(CH_3)_2$–	99–100	...	7.48	7.72	A
2,3,4-$(CH_3)_3$–	99–102	...	7.00	6.68	A
2-C_6H_5–	69.5–70.5	70	5.96	6.04	B
2-*o*-$CH_3C_6H_4$–	171	28	5.62	5.62	B
2-*m*-$CH_3C_6H_4$–	86–87	40	5.62	5.18	B
2-*p*-$CH_3C_6H_4$–	94–94.5	53	5.62	5.76	B

[a] This compound previously prepared by a different method.[6] [b] Previously prepared in unspecified yield by this reaction, recorded m. p. 64°.[7] [c] Analysis for Br: Calcd.: 48.28; found: 47.98. [d] Prepared by quantitative bromination of the parent compound with std. potassium bromate. [e] Analysis of copper salt for Cu: Calcd.: 14.7; found: 14.5. [f] Previously prepared by a different method.[8] [g] Previously made in unspecified yield by this reaction.[4]

(4) O. Doebner and W. von Miller, *Ber.*, **16**, 1665, 2465 (1883).

(5) H. Gilman, J. Towle and S. Spatz, THIS JOURNAL, **68**, 2017 (1946).

(6) Busch and Koenigs, *Ber.*, **23**, 2686 (1890).

(7) Bauer and Engler, *ibid.*, **22**, 210 (1889).

(8) O. Doebner and Fettback, *Ann.*, **281**, 9 (1894).

Most of the 8-quinolinols prepared showed little or no fluorescence under ultraviolet light, while the corresponding 8-methoxy compounds generally had a strong blue-white fluorescence.

Data on the ultraviolet and infrared absorption spectra, X-ray powder diffraction patterns and quantitative reactions with metal ions of these compounds will be reported later.

Experimental

A. The general procedure used to make the alkyl substituted 8-quinolinols was as follows:

One-quarter of a mole (27.3 g.) of *o*-aminophenol was added to 100 ml. of concentrated hydrochloric acid in a flask fitted with condenser, stirrer and dropping funnel. The flask was heated to about 100° and a 30–100% excess of the appropriate α,β-unsaturated carbonyl compound added dropwise over a period of thirty to forty-five minutes. After stirring for six hours at 100–120°, the mixture was allowed to stand overnight and then steam distilled briefly to remove volatile impurities. It was then made slightly alkaline to litmus and steam distilled until all the product had come over. The products were recrystallized from alcohol–water mixtures.

The procedure used to make the 8-methoxyquinolines from *o*-anisidine differed from the above in that, after making the solution alkaline to litmus with sodium hydroxide, a gummy solid separated which was distilled under reduced pressure to obtain the product. The 8-methoxyquinolines were recrystallized from petroleum ether or cyclohexane.

In several cases it was possible to prepare the equivalent of the α,β-unsaturated carbonyl compounds by saturating a mixture of the aldehyde and ketone which were to be condensed with dry hydrogen chloride and using the resulting chloroketone without isolation, as suggested by Bauer and Engler.[7] This procedure naturally gave lower yields than when the intermediate unsaturated carbonyl compounds were isolated before use, as was usually done. Aldol condensation type reactions recorded in the literature were used to make these compounds.

B. The general method for making the 2-aryl-8-quinolinols was the following:

In a three-necked flask fitted with stirrer, dropping funnel, and condenser protected from moisture, the whole system being swept with dry nitrogen, were placed 300 ml. of dry ether and 3.5 g. (0.5 mole) of lithium metal cut into thin shavings. One quarter of a mole of the required aryl bromide was added dropwise, a vigorous reaction occurring. After the reaction was over, 0.05 mole (7.3 g.) of 8-quinolinol dissolved in ether was added over five to ten minutes. Stirring was continued for forty-five minutes and the mixture was then poured over ice and the ether layer separated. After removal of the ether by distillation, the residue was dissolved in hot dilute hydrochloric acid and then neutralized with sodium carbonate. An oil (or sometimes a solid) separated which was distilled under reduced pressure. The products generally boiled between 240 and 320° at approximately 25 mm. They were recrystallized from 95% alcohol.

The corresponding 8-methoxy compounds were prepared similarly from 8-methoxyquinoline except that, after removing the ether, vacuum distillation gave the desired products directly. These were recrystallized from petroleum ether.

The use of nitrogen was later found to be an unnecessary precaution since refluxing ether served to keep air out of the reaction flask.

C. The condensation of 8-hydroxyquinaldine or 8-methoxyquinaldine with aromatic aldehydes was effected by this general procedure:

One-tenth of a mole (15.9 g.) of 8-hydroxyquinaldine was refluxed with 30–40 g. of the required aldehyde if it boiled below 180° or heated at 150–175° if the aldehyde was high boiling, for five hours. The mixture was then

vacuum distilled to obtain the products, which were all light yellow solids. These compounds were recrystallized from 95% alcohol.

Acknowledgment.—One of the authors (J. P. P.) wishes to acknowledge the help of a du Pont Fellowship in Chemistry for the year 1948–1949. The authors also wish to acknowledge the assistance of Mrs. B. Jarvis who performed the microanalyses.

Summary

Several new 8-quinolinols substituted in the pyridine ring have been prepared. Several new substituted 8-methoxyquinolines have also been prepared. The steric hindrance of substitution of 8-quinolinol in the 2-position on the reaction with aluminum ion is shown by the fact that shifting the substituent to the 3- or 4-position permits reaction.

BLOOMINGTON, IND. RECEIVED APRIL 26, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. II. Tertiary Aminoalkane Thiol Esters of Disubstituted Acetic Acids

BY H. G. KOLLOFF, JAMES H. HUNTER, E. H. WOODRUFF AND ROBERT BRUCE MOFFETT

Studies of synthetic spasmolytic agents of the type described in a recent report from this Laboratory[1] have been extended to the preparation of a series of analogous thiol esters for the purpose of comparative evaluation of their antispasmodic activity. This investigation appeared desirable since data on such thiol esters are relatively limited.[2,3]

In the synthesis of the thiol esters whose salts are listed in Table II, disubstituted acetic acid chlorides were condensed with 2-diethylaminoethanethiol[4] and various pyrrolidylalkanethiols. The latter were prepared from the corresponding alcohols,[5] via the intermediate pyrrolidylalkane chloride hydrochlorides and isothiouronium chloride hydrochlorides recorded in Table I, by the general procedure of Albertson and Clinton.[4] In order to suppress spontaneous oxidation of these thiols, the ethereal extract from the alkaline decomposition of the pyrrolidylalkane isothiouronium salts was dried and treated with the appropriate acid chloride immediately.

Preliminary pharmacological assays by Dr. Milton J. Vander Brook of our Department of Pharmacology indicate that these thiol esters have less activity against acetylcholine chloride induced spasms than the corresponding oxygen esters.

Experimental[6,7]

The examples below illustrate the procedures used for the preparation of the various intermediates and thiol ester salts.

2-(2-Methyl-1-pyrrolidyl)-ethyl Chloride Hydrochloride.—Hydrogen chloride gas was passed into a cooled solution of 51.8 g. (0.4 mole) of 2-(2-methyl-1-pyrrolidyl)-ethanol[5] in 200 ml. of dry benzene until strongly acid. Then 36.3 ml. (0.5 mole) of thionyl chloride was added slowly with cooling in an ice–water-bath. When the addition was complete the solution was heated on a steam-bath for two hours during which time hydrogen chloride and sulfur dioxide were evolved. The chloride hydrochloride crystallized and, after cooling, was collected and washed first with benzene, then with absolute ether, and dried giving a quantitative yield of nearly white crystals, m. p. 183.5–185°. This was used without further purification for the preparation of the isothiouronium salt. An analytical specimen was prepared by recrystallization from isopropyl alcohol using decolorizing charcoal; m. p. 184–185.5°.

2-(2-Methyl-1-pyrrolidyl)-ethyl-isothiouronium Chloride Hydrochloride.—A solution of 46.0 g. (0.25 mole) of the above chloride hydrochloride and 19.0 g. (0.25 mole) of thiourea in 50 ml. of 95% ethanol was refluxed on a steam-bath for twenty hours. The product which separated after cooling was collected, washed successively with ethanol and acetone, and recrystallized from about 250 ml. of 95% ethanol giving 43.3 g. of nearly white crystals, m. p. 216–218°. Dilution of the filtrate with acetone gave an additional 7.9 g., m. p. 215–217°.

2-(2-Methyl-1-pyrrolidyl)-ethyl Phenyl-Δ^2-cyclopentenylthiolacetate Hydrochloride.—In an apparatus designed for continuous extraction[8] of an aqueous solution by ether was placed a solution of 16.9 g. (0.065 mole) of the above isothiouronium salt in 30 ml. of water and the air in the apparatus displaced with nitrogen. A solution of 5.3 g. of sodium hydroxide in 20 ml. of water was added and the mixture extracted continuously with peroxide-free ether for six hours. The ether extract was dried over Drierite, filtered and added to a solution of 13.3 g. (0.06 mole) of phenyl-Δ^2-cyclopentenylacetyl chloride[9] in 50 ml. of dry benzene. The mixture became warm and an oil separated. After refluxing for two hours, the mixture was shaken with ice-water containing a small amount of hydrochloric acid. The ether layer was extracted again with water and the combined aqueous solution washed with ether and made basic with sodium hydroxide. The oily ester which separated was taken up in ether, washed well with water and dried first over sodium sulfate and then over Drierite. The solution was filtered and hydrogen chloride gas introduced until strongly acidic. The hydrochloride separated as a viscous oil which crystallized partly on standing. After decanting the ether, the crude hydrochloride was dissolved in warm ethyl acetate. On cooling it crystallized and was collected, washed with ethyl acetate and dried. It was recrystallized from ethyl acetate giving 7.0 g. of white crystals, m. p. 111–115°.

2-(2-Methyl-1-pyrrolidyl)-ethyl-Δ^2-cyclopentenyl-*n*-propylthiolacetate Acid Citrate.—The hydrochloride cor-

(1) Kolloff, Hunter, Woodruff and Moffett, THIS JOURNAL, **70**, 3862 (1948).

(2) Richardson, U. S. Patent 2,390,555.

(3) Clinton and Salvador, THIS JOURNAL, **68**, 2076 (1946).

(4) Albertson and Clinton, *ibid.*, **67**, 1222 (1945).

(5) Moffett, *J. Org. Chem.*, **14**, 862 (1949).

(6) Melting points and boiling points are uncorrected.

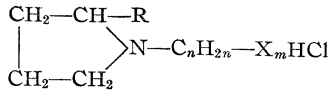
(7) Analyses by Mr. Harold Emerson and staff of our Microanalytical Laboratory.

(8) This apparatus is a modification of that described in "Organic Syntheses," **23**, 49 (1943).

(9) Horclois, *Chemie and industrie*, Special No. 357 (April, 1934).

TABLE I

PYRROLIDYLALKANE CHLORIDE AND ISOTHIOURONIUM CHLORIDE HYDROCHLORIDES

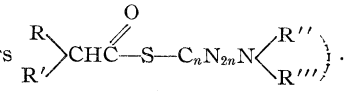


R	C_nN_{2n}	m	X	Yield, %	M. p., [6] °C.	Formula	Analyses, % Chlorine Calcd.	Chlorine Found[7]	Nitrogen Calcd.	Nitrogen Found[7]	Sulfur Calcd.	Sulfur Found[7]
H	$-CH_2CH_2-$	2	$-S-CN_2H_4$ [a]	77.7	174–175	$C_7H_{17}Cl_2N_3S$	...	...	17.07	17.11	13.02	13.18
CH_3	$-CH_2CH_2-$	1	Cl	100	184–185.5	$C_7H_{15}Cl_2N$	38.52	38.72	...	...	...	...
CH_3	$-CH_2CH_2-$	2	$-SCN_2H_3$	78.7	216–218	$C_8H_{19}Cl_2N_3S$	...	...	16.15	16.07	12.32	12.47
H	$-CH(CH_3)CH_2-$	1	Cl	65.3 [b]	150–163	$C_7H_{15}Cl_2N$	38.52	38.48	...	...	...	...
H	$-CH(CH_3)CH_2-$	2	$-SCN_2H_3$	50.0 [c]	184.5–186	$C_8H_{19}Cl_2N_3S$	...	...	16.15	16.15	12.32	12.60
H	$-(CH_2)_4-$	1	Cl	66.3 [d]	111–113	$C_8H_{17}Cl_2N$	35.79	35.68	...	...	...	...
H	$-(CH_2)_4-$	2	SCN_2H_3	86.2	168–169.5 [e]	$C_9H_{21}Cl_2N_3S$	...	...	15.32	15.43	11.69	11.61
H	$-CH_2CH(CH_3)CH_2-$	1	Cl	100 [f]	164.5–165.5	$C_8H_{17}Cl_2N$	35.79	35.13	...	...	...	...
H	$-CH_2CH(CH_3)CH_2-$	2	SCN_2H_3	71.7 [g]	215–216.5	$C_9H_{21}Cl_2N_3S$	...	...	15.32	15.42	11.69	11.34

[a] This compound was prepared by Dr. William Bradley Reid, Jr., in this Laboratory. [b] Yield after recrystallization from methyl ethyl ketone. [c] This yield represents the first crop of pure crystals. An additional yield of 32% of material melting at 170–175° was obtained from the filtrate. [d] Yield after recrystallization from a mixture of methyl ethyl ketone and ethyl acetate. [e] Crystallized from ethanol with the aid of decolorizing charcoal. [f] The yield reported was obtained by diluting the reaction mixture with absolute ether. It was nicely crystalline material melting at 156–161° and was used without further purification. A small sample for melting point and analysis was recrystallized from a mixture of methyl ethyl ketone and a little ethyl acetate. [g] Yield of material, m. p. 214–217°, obtained directly from the reaction mixture. A small sample was recrystallized from ethanol for melting point and analysis.

TABLE II

TERTIARY AMINOALKANE THIOL ESTER SALTS



· HCl (OR ACID CITRATE)

R	Acid used R′	Amino thiol	Yield, % [a]	Crystn. solvent	M. p., [6] °C.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found[7]	Sulfur Calcd.	Sulfur Found[7]	Chlorine Calcd.	Chlorine Found[7]
C_6H_5-	C_6H_5	$(CH_2)_4-N-(CH_2)_2-$	...	MeEtCO	140–141 [b]	$C_{20}H_{24}ClNOS$	3.87	4.09	8.86	9.02	9.80	9.63
$(CH_2)_4CH-$	$CH_3(CH_2)_2-$ [c]	$(CH_2)_4-N-(CH_2)_2-$	[d]	EtOAc	146–148	$C_{16}H_{30}ClNOS$	..	..	10.02	9.89	11.08	11.09
C_6H_5	A [p,q]	$(CH_2)_3CH(CH_3)-N-(CH_2)_2-$	50 [l]	EtOAc	111–115	$C_{20}H_{28}ClNOS$	3.83	3.61	8.76	8.83	9.69	9.64
A [p]	$CH_3(CH_2)_2-$ [q]	$(CH_2)_3CH(CH_3)-N-(CH_2)_2-$	45 [m]	EtOAc-MeEtCO	100–102	$C_{23}H_{37}NO_6S$	2.87	2.90	6.58	6.79	...	...
C_6H_5	$(CH_3)_2CHCH_2-$	$(CH_2)_4-N-CH(CH_3)CH_2-$	66 [e]	H_2O	158–158.5	$C_{26}H_{37}NO_6S$	2.74	2.91	6.27	6.31	...	...
C_6H_5	B [q,r]	$(CH_2)_4-N-(CH_2)_4-$	31 [n]	MeEtCO	133–134	$C_{22}H_{32}ClNOS$	3.56	3.69	8.14	8.14	9.00	9.13
C_6H_5	$(CH_2)_4CH-$ [r]	$(CH_2)_4-N-CH_2CH(CH_3)CH_2-$	52 [f]	EtOAc	121–124	$C_{21}H_{32}ClNOS$	3.67	3.77	8.39	8.36	9.28	9.46
C_6H_5	$(CH_2)_4CH-$ [r]	$(CH_3CH_2)_2N-(CH_2)_2-$ [s]	30 [g,h]	PhH-Et_2O	106–108	$C_{19}H_{30}ClNOS$	3.94	3.79	9.00	8.79	9.96	10.21
C_6H_5	A [p,q]	$(CH_3CH_2)_2N-(CH_2)_2-$ [s]	20 [h,i]	PhH-Et_2O	102–105	$C_{19}H_{28}ClNOS$	..	..	...	..	10.00	9.93
C_6H_5	C_6H_5-O-i	$(CH_3CH_2)_2N-(CH_2)_2-$ [s]	30 [h,k]	EtOAc	97–98 [l]	$C_{20}H_{26}ClNO_2S$	..	..	8.44	8.83	9.33	9.39

[a] The yield is reported for recrystallized material and is based on the isothiouronium chloride hydrochloride. [b] Some sintering at 132–134°. [c] Moffett, Hart and Hoehn, THIS JOURNAL, 69, 1849 (1947). [d] The free base was distilled, b. p. 107° (0.025 mm.) but did not seem to be pure. [e] This is the yield of acid citrate crystallized from the reaction mixture, m. p. 154–156°. A sample for analysis was recrystallized from ethanol and then from water. [f] The free base was distilled, b. p. 160–170° (0.05 mm.), but did not seem to be pure. [g] The free base was distilled, b. p. 133° (0.042 mm.). [h] The yield reported for recrystallized hydrochloride is based on the acid used. [i] The free base was distilled, b. p. 145° (0.09 mm.). [j] Meyer and Boner, *Ann.*, **220**, 51 (1883). [k] The free base was distilled, b. p. 180° (0.14 mm.). [l] Started to sinter at 94.5°. [m] Acid citrate salt. [n] With methyl ethyl ketone. [p] A = $(CH_2)_2CH=CH-CH-$. [q] B = $(CH_2)_3-CH=CH-CH-$. [r] $(CH_2)_4CH-$ = $CH_3(CH_2)_2-CH(C_2H_5)-$. [s] $(CH_3CH_2)_2N-(CH_2)_2-$ = $(C_2H_5)_2N-CH_2CH_2-$.

responding to this compound, prepared by a method similar to that described above, was an intractable oil. It was reconverted to the free base, and a solution of 10.7 g. (0.036 mole) of this basic ester in 50 ml. of ethyl acetate was treated with 7.66 g. (0.04 mole) of citric acid in 10 ml. of absolute ethanol. The product which separated was recrystallized from a mixture of methyl ethyl ketone and ethyl acetate giving 14.2 g. of white crystalline powder with the properties listed in Table II.

Phenylisobutylacetyl Chloride.—Crude phenylisobutylacetic acid[10] was prepared by alkylation of diethyl phenylmalonate with isobutyl bromide, followed by hydrolysis and decarboxylation. Although the crude product was contaminated with phenylacetic acid, it was converted to

(10) This acid has been prepared by Bodroux and Taboury [*Bull. soc. chim.*, **7**, 668 (1910)] by the alkylation of benzyl cyanide, followed by hydrolysis.

the acid chloride with thionyl chloride, and the resulting mixture of acid chlorides separated by distillation through a 12-in. column packed with 1/8-in. glass helices. After removing the phenylacetyl chloride, a sharp cut of the desired acid chloride was obtained; b. p. 115° (14 mm.), $n^{25}D$ 1.5071.

Anal. Calcd. for $C_{12}H_{15}ClO$: Cl, 16.83. Found: Cl, 16.50.

Phenyl-Δ²-cyclohexenylacetyl Chloride.—A solution of 125.7 g. (0.615 mole) of phenyl-Δ²-cyclohexenylacetic acid[1] in 100 ml. of dry benzene and 73 ml. of thionyl chloride was heated on a steam-bath for one hour. After removal of the solvent the product was distilled through a short column giving 111 g. (77%) of yellow product, b. p. 97° (0.04 mm.), $n^{25}D$ 1.5478.

Anal. Calcd. for $C_{14}H_{15}ClO$: Cl, 15.11. Found: Cl, 15.24.

Summary

Ten new pyrrolidylalkyl and diethylaminoethyl thiol esters of disubstituted acetic acids have been prepared.

Several new intermediate pyrrolidylalkyl chloride hydrochlorides and isothiouronium salts are reported.

KALAMAZOO, MICHIGAN RECEIVED MARCH 28, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS COLLEGE OF PHARMACY]

Methoxysubstituted Benzamidines as Local Anesthetics[1]

BY N. J. SINTOV,[2a] J. S. RODIA, J. A. TURSICH,[2b] H. L. DAVIS AND G. L. WEBSTER

The hydrochlorides of certain amidines, derived from both aliphatic and aromatic acids, have been shown to exhibit local anesthetic activity.

Most, if not all, of the fatty acid amidines fall into three categories: (1) homologs of Holocaine, $CH_3 \cdot C(NC_6H_4OC_2H_5)(NHC_6H_4OC_2H_5)$, (2) Holocaine or its homologs in which different substituents appear on the N-substituted phenyl groups, and (3) compounds of the type of Holocaine or its homologs in which one or both of the substituents on the nitrogen atoms are varied.

Taube[3] prepared a number of amidines of the Holocaine type in which the two phenyl groups were substituted with methoxy or ethoxy groups, ortho (or para) in one phenyl group and para (or ortho) in the other.

Goldschmidt[4] prepared a series of similarly substituted formamidines which showed local anesthetic activity. He also prepared formamidines in which the two N-substituted phenyl groups were substituted in the para-position with either carbethoxy or carbomethoxy groups.

Hill and Rabinowitz[5] attempted to overcome the undesirable characteristics of Holocaine by substituting for the methyl group the ethyl, propyl, butyl, isobutyl and benzyl radicals. In the amidines containing the two latter radicals one of the phenetidyl groups was replaced by an amino group and one phenetidyl radical in Holocaine was replaced by a diethylamino group. Hill and Cox[6] modified the lower homologs of Holocaine by substituting for one or both of the phenetidyl groups the *p*-carbethoxyphenyl group.

The substituted and unsubstituted benzamidines have not generally exhibited local anesthetic activity. Easson and Pyman[7] prepared and tested meta and para aminobenzamidine and 3,4-dimethoxybenzamidine, none of which showed local anesthetic properties, but they found slight anesthetic activity in both *p*-carbethoxybenzamidine and *p*-carbethoxyphenylguanidine. These authors, reasoning from the structure and properties of Holocaine, prepared and tested N-veratrylbenzamidine and found that it "had well-marked" local anesthetic character.

With the results of this previous work in mind, the purpose of these experiments was to prepare and test pharmacologically N,N'-diphenylbenzamidines in which one or more of the three phenyl groups were substituted with one or more methoxy groups.

These amidines, listed in Table I, were prepared by a modification of the method of Hill and Cox[6] in yields ranging from 32 to 62%.

In the preparation of these compounds it made no difference in the yield or purity of the product if the imidyl chloride was formed first and then it reacted with the appropriate amine or if the anilide and amine were at once added to the benzene solution of phosphorus pentachloride and the reaction completed in one operation.

The hydrochlorides of amidines numbered 1, 2, 5, 6, 8, 9 and 10 in Table I precipitated as a cream-colored powder during refluxing and no yield of hydrochloride was obtained from the benzene filtrates.

Since the disubstituted amidines are tautomeric[8] those having two different substituents on

(1) From theses presented by the first three authors in partial fulfillment of the requirements for the M.S. degree. This work was supported in part by a grant from the Lederle Laboratories, Pearl River, N. Y.

(2) Present addresses: (a) Searn Laboratories, Inc., Franklin Park, Ill.; (b) Riley Tar and Chemical Corporation, Indianapolis, Ind.

(3) "Chemische Technologie" (Wagner) **41**, 620, 621 (1895).

(4) Goldschmidt, *J. Chem. Soc.*, 785 (1902).

(5) Hill and Rabinowitz, THIS JOURNAL, **48**, 732 (1926).

(6) Hill and Cox, THIS JOURNAL, **48**, 3215 (1926).

(7) Easson and Pyman, *J. Chem. Soc.*, 2991 (1931).

(8) Burtles and Pyman, *J. Chem. Soc.*, 361 (1923).

TABLE I

	Derivative	Amidines M. p., °C.	Formula	Nitrogen, % Calcd.	Found	Amidine hydrochlorides M. p., °C.	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found	Anesthesia[a,b] Corneal[c] 2%	1%	Local[d,e,f] 1/2%	1/10%	1/20%	1/40%
	Benzamidines															
1	N-*p*-Anisyl-N′-phenyl	114	$C_{20}H_{18}ON_2$	9.27	9.15	205	8.27	8.02	10.48	10.32	10	28	35	65	69	26
2	N,N′-Di-*p*-anisyl	125	$C_{21}H_{20}O_2N_2$	8.49	8.30	227–228	7.64	7.53	9.68	9.58	60	26	35	51	81	34
3	N-Veratryl-N′-phenyl	125	$C_{21}H_{20}O_2N_2$	8.43	8.13	202	7.60	7.28	9.61	9.45	30	10	None	19	22	80
4	N-Veratryl-N′-phenetyl	147	$C_{23}H_{24}O_2N_2$	7.44	7.38	Could not be obtained pure										
	Anisamidines															
5	N-*p*-Anisyl-N′-phenyl	124	$C_{21}H_{20}O_2N_2$	8.43	8.12	227	7.51	7.24	9.61	9.72		35	None	16	82	60
6	N,N′-Di-*p*-anisyl	105	$C_{22}H_{22}O_3N_2$	7.73	7.50	248 dec.	7.02	6.87	8.89	8.79			38	47	28	70
7	N-Veratryl-N′-phenyl	126	$C_{22}H_{22}O_3N_2$	7.73	7.57	196					50	50				
8	N,N′-Di-veratryl	143	$C_{24}H_{26}O_5N_2$	6.63	6.47	106	6.12	5.82	7.74	7.49	61	15	5	17	24	27
	Veratramidines															
9	N-*p*-Anisyl-N′-phenyl	145	$C_{22}H_{22}O_3N_2$	7.73	7.70	238	7.03	6.86	8.90	8.72		29	15	25	34	27
10	N,N′-Di-*p*-anisyl	140	$C_{23}H_{24}O_4N_2$	7.14	7.17	234	6.44	6.54	8.28	8.04	35	24	25	38	31	15
	Cocaine hydrochloride											36	32			
	Nupercaine															62

[a] Duration in minutes. [b] The pharmacological tests were made by Mr. Rodia under the direction of Dr. C. C. Peiffer Head of the Department of Pharmacology, University of Illinois College of Medicine. [c] All solutions were in contact with the rabbit cornea for thirty seconds. [d] 0.2 ml. aqueous solution was used, at least two effective intradermal wheals were produced on the back of a guinea pig. [e] The LD. 50 dose for mice of compounds 2, 9, 6 and 10 was, respectively, in mg./kg., 153, 328, 105 and 123. [f] Compounds 1, 3, 5 and 8. produced sloughing of the skin.

the two nitrogen atoms may be made by starting with an anilide prepared from either amine. N,N′-Veratrylphenylbenzamidine was prepared from benzanilide and veratrylamine and from benzoylveratryl amide and aniline to learn if the hydrochloride of the amidine would precipitate during formation. It did not precipitate in either case. N,N′-*p*-Anisylphenylbenzamidine was prepared by starting with benzoyl-*p*-anisidide and also with benzanilide. The melting point of veratroyl anilide was found by us to be 166° but is given by Shriner and Fuson[9] to be 154°. The analysis of our anilide and of the amidine prepared from it, using *p*-anisidine, prove the composition of this anilide. The proof of the structure of this amidine was shown by the fact that the identical amidine was prepared from veratroyl-*p*-anisidide and aniline.

Preliminary experiments to determine which amine should be converted into the anilide for best results in the preparation of the amidine showed that better yields were obtained from anilides prepared from the amines which have the most substituents. It was also observed that when the more highly substituted free amine was added to the imidyl chloride a greater amount of undesirable side-reaction occurred and a considerable amount of unreacted anilide was recovered. Comparative yields are illustrated by the preparation of N,N′-veratrylphenetylbenzamidine. When prepared from benzoylveratryl anilide and phenetidine the yield of amidine was 42%, while the combination of benzoyl-*p*-phenetidide and veratrylamine yielded only 17% of theoretical.

Intradermal wheals produced by injection of 0.1 ml. of 0.025% solutions of compounds 2, 6, 9 and 10 into the human arm gave immediate anesthesia that lasted for 39, 26, 34 and twenty-eight minutes, respectively. Each of these injections produced sloughing of the skin.

Experimental

4-Aminoveratrole.—It is very important that this amine be as pure as possible. The best product was obtained in the best yields by using the directions given in "Organic Syntheses."[10]

Preparation of Monosubstituted Amides.—The procedure of Kuehn and McElvain[11] was modified for the preparation of these amides. In the preparation of the acid chlorides 5 molecular proportions of thionyl chloride were mixed with one molecular proportion of acid, the solution was refluxed for four hours and the excess thionyl chloride removed by vacuum distillation. The acid chloride was used immediately.

Veratroyl-*p*-anisidide.—Prepared by the above method in 75% yield, m. p. 173°.

Anal. Calcd. for $C_{16}H_{17}O_4N$: N, 4.88. Found: N, 4.85.

Veratroyl Anilide.[9]—Prepared by the above method in 65% yield, m. p. 166°.

Anal. Calcd. for $C_{15}H_{15}O_3N$: N, 5.45. Found: N, 5.45.

Preparation of the Amidines.—This procedure was a modification of that used by Hill and Cox.[6] Ten per cent. more than one molecular proportion (6.9 g.) of phosphorus pentachloride in 50 ml. of sodium-dried benzene was heated on a water-bath under reflux until the evolution of hydrogen chloride had ceased. The solution was then cooled. At this point the procedure was varied in two different ways with the same final result. (1) One molecular proportion of the anilide was added and the imidyl chloride formed by refluxing the mixture until no more hydrogen chloride was evolved (about thirty minutes). The solution was cooled and one molecular proportion of the amine was added. (2) One molecular proportion each of the anilide and amine were added, in this order. Following either procedure (1) or (2) the mixture was heated for six hours, or, if the amidine hydrochloride precipitated during the reaction, until no more precipitation occurred.

If the amidine hydrochloride precipitated during the re-

(9) Shriner and Fuson, "The Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd edition, 1940, p. 184.

(10) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. II, 1943, pp. 619–623.

(11) Kuehn and McElvain, THIS JOURNAL, **53**, 1173 (1931).

action the reaction mixture was worked up by cooling it and filtering off the amidine hydrochloride. The filtrates did not yield more product. The dried crude hydrochloride was stirred for fifteen minutes with 200 ml. of water, the mixture filtered and the amidine precipitated by the addition of concentrated ammonia water or solid potassium carbonate to complete precipitation. The undissolved residue from the crude hydrochloride was repeatedly extracted with water until the extracts yielded no more amidine.

The amidines numbered 3, 4 and 7 in Table I did not precipitate as the hydrochloride during refluxing, although the time of refluxing was extended to ten hours. After refluxing, the solution in each case was distilled under reduced pressure until the benzene and phosphorus oxychloride were removed. The brown, viscous residue was thoroughly stirred with 10–15 ml. of 5% hydrochloric acid and the latter decanted. The viscous paste solidified after this treatment to a soft solid. This mass was extracted, at room temperature, with 60 ml. of 5% hydrochloric acid and the amidine precipitated from the filtered extract with concentrated ammonia water. Repeated extractions were required to remove all the amidine from the residue. The first extracts yielded a brown product which became a pale ivory in color when reprecipitated from 5% hydrochloric acid. The crude amidine crystallized from 75% alcohol as a white or slightly ivory-colored, finely-divided solid.

Preparation of Amidine Hydrochlorides.—Five grams of amidine was dissolved in the least amount of ether (because of the solubility of their hydrochlorides benzene was used with the amidines numbered 3, 8, 9 and 10 in Table I) and dry hydrogen chloride gas was passed into the solution until complete precipitation of the hydrochloride, when the solution was immediately filtered by suction. The crude hydrochlorides crystallized in white needles from an alcohol–ether mixture.

Summary

Ten new amidines have been prepared and their hydrochlorides have been tested for local anesthetic activity.

All of the amidine hydrochlorides produced local anesthesia. Their solution produced sloughing of tissue at the site of injection.

CHICAGO, ILLINOIS RECEIVED MAY 28, 1949

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

N,N-Disubstituted Amidines. II. Benzamidines. The Effect of Substitution on Basicity[1]

BY EMIL LORZ AND RICHARD BALTZLY

By means of the synthetic method recently reported from these laboratories[2] a series of N,N-disubstituted benzamidines has been prepared. The primary object herein was to determine on relatively accessible compounds the effect of substitutions in the ring on the local anesthetic potency. Taken together with the benzamidines previously reported (Compounds I–VII, XIII and XXI–XXIV in our first paper)[2] the series suffices for the prediction with reasonable accuracy of the influence of convenient substitutions on the physiological properties of amidines of this type. While none of the substances reported in this paper and none of the benzamidines described earlier are of exceptional merit, the regularities observed have been found transferable to other series of greater inherent potency.

The new amidines prepared are shown together with analytical data in Table I, the numbering being consecutive with that of our earlier paper.[2] N,N-Di-*n*-butylbenzamidine (I) has a toxicity about four times that of cocaine (LD_{50} = 26.5 mg./kg. administered intraperitoneally) in mice and a potency as a surface anesthetic about one-half that of cocaine (by the method of application to the cornea of a guinea pig). Substitution of the ring by methyl, methoxyl or dimethylamino groups or by chlorine increased the potency; substitution by hydroxyl eliminated it. The most pronounced effect here was that of *p*-chlorine substitution: *p*-chloro-N,N-di-*n*-butylbenzamidine having 7.4 times the potency of cocaine. In general, the potencies run from two to five times that of cocaine.

Chlorine substitution tends to increase toxicity though not very markedly and with little selective action in respect to position. Methoxyl substitution, on the other hand, diminishes toxicity considerably in the meta and para positions and increases it markedly in the ortho: the LD_{50} for the *o*-, *m*- and *p*-methoxy-N,N-di-*n*-butylbenzamidines are 9, 30 and 36 mg./kg., respectively. This phenomenon is quite consistent, the 2,5-dimethoxy and 2,6-dimethoxy compounds (XXXI and XXXII) having LD_{50} = 13.5 and 7, respectively, while the 3,4-dimethoxy and 3,4,5-trimethoxy analogs (XXXIII and XXXV) have LD_{50} = 38 and 52.

The presence of an aromatic radical on the amidine nitrogen confers lower toxicity but increases the potency only a little.

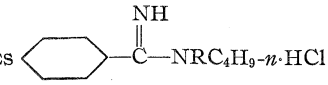
There was a distinct possibility that these variations might be correlated with the basicity of the amidines. Since amidines have not been studied very extensively from this standpoint and amidines of the present type were formerly rather rare, a number of the hydrochlorides sufficient to indicate the effect of substitutions on basicity, were titrated in 50% methanol. Use of a partly organic solvent is necessary to prevent serious error due to precipitation of base; Hall and Sprinkle[3] showed that this device gives satis-

(1) The work here reported is part of a joint research carried out in collaboration with a Pharmacological group in these laboratories.

(2) Lorz and Baltzly, THIS JOURNAL, **70**, 1904 (1948).

(3) Hall and Sprinkle, *ibid.*, **54**, 3469 (1932).

TABLE I

N,N-DIALKYLBENZAMIDINE HYDROCHLORIDES 

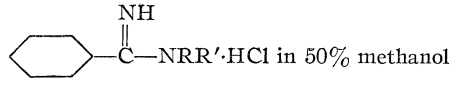
Compound no.	Ring substituents	R	Method of isolation[a] yield, %	M. p., °C.[b]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
XXV	None	4-MeOC$_6$H$_4$	A 67[c]	211	$C_{18}H_{23}ClN_2O$	67.80	68.09	7.27	7.17
XXVI	3-MeO	n-C$_4$H$_9$	B 70	138	$C_{16}H_{27}ClN_2O$	64.30	64.53	9.11	8.89
XXVII	3-MeO	2-CH$_3$C$_6$H$_4$	B′ 51	201–202	$C_{19}H_{25}ClN_2O$	68.55	68.55	7.57	7.43
XXVIII	4-MeO	n-C$_4$H$_9$	B 77	185	$C_{16}H_{27}ClN_2O$	64.30	64.55	9.11	9.21
XXIX	4-BzO	n-C$_4$H$_9$	C 36[d]	201	$C_{22}H_{31}ClN_2O$	70.47	70.80	8.33	8.39
XXX	4-OH	n-C$_4$H$_9$	[e]	166	$C_{15}H_{25}ClN_2O$	63.25	63.32	8.85	8.81
XXXI	2,5-(MeO)$_2$	n-C$_4$H$_9$	A′ 65	171–172	$C_{17}H_{29}ClN_2O_2$	62.08	61.79	8.89	8.80
XXXII	2,6-(MeO)$_2$	n-C$_4$H$_9$	A′ 81	196	$C_{17}H_{29}ClN_2O_2$	62.08	62.38	8.89	8.78
XXXIII	3,4-(MeO)$_2$	n-C$_4$H$_9$	B 70	194	$C_{17}H_{29}ClN_2O_2$	62.08	62.25	8.89	8.85
XXXIV	3,4-OCH$_2$O	n-C$_4$H$_9$	A′ 50	146	$C_{16}H_{25}ClN_2O_2$	61.43	61.50	8.06	7.76
XXXV	3,4,5-(MeO)$_3$	n-C$_4$H$_9$	A′ 54	167	$C_{18}H_{31}ClN_2O_3$	60.24	60.11	8.71	8.37

[a] Yield based on quantity of solid hydrochloride before recrystallization, except as otherwise noted. [b] All melting points are corrected. [c] Yield calculated on weight of distilled base, b. p. (1 mm.), 175–180°. [d] Based on analytically pure hydrochloride. [e] The purification was difficult and the yield hard to estimate.

factorily comparable results which vary in a consistent fashion from values obtainable in water. The dissociation constants so obtained, expressed as pK_a, are presented in Table II.

TABLE II

ACID DISSOCIATION CONSTANTS OF BENZAMIDINE HYDROCHLORIDES



Ring substituents	R	R′	pK_a[c]	Compound no.
None	n-C$_4$H$_9$	n-C$_4$H$_9$	11.27	I
None	C$_6$H$_5$	n-C$_4$H$_9$	10.40	XXII
None	C$_6$H$_5$CH$_2$	C$_6$H$_5$CH$_2$	9.98	XIII
None	4-MeOC$_6$H$_4$	n-C$_4$H$_9$	10.52	XXV
None	N-RR′ = N-tetrahydroquinolyl		9.79	XXIII
None	N-RR′ = N′-benzylpiperazino		10.54[a]	XXIV
2-Cl	n-C$_4$H$_9$	n-C$_4$H$_9$	10.70	IV
2-MeO	n-C$_4$H$_9$	n-C$_4$H$_9$	11.51	III
3-Cl	n-C$_4$H$_9$	n-C$_4$H$_9$	10.68	V
3-MeO	n-C$_4$H$_9$	n-C$_4$H$_9$	11.20	XXVI
3-MeO	2-CH$_3$C$_6$H$_4$	n-C$_4$H$_9$	10.28	XXVII
4-Cl	n-C$_4$H$_9$	n-C$_4$H$_9$	10.90	VI
4-MeO	n-C$_4$H$_9$	n-C$_4$H$_9$	11.50	XXVIII
4-OH	n-C$_4$H$_9$	n-C$_4$H$_9$	12.05[b]	XXX
4-NMe$_2$	n-C$_4$H$_9$	n-C$_4$H$_9$	11.65	VII
3,4-(MeO)$_2$	n-C$_4$H$_9$	n-C$_4$H$_9$	11.30	XXXIII
3,4,5-(MeO)$_3$	n-C$_4$H$_9$	n-C$_4$H$_9$	11.14	XXXV
2,4,6-Me$_3$	n-C$_4$H$_9$	n-C$_4$H$_9$	11.74	XXI

[a] Two pK_a values observed, at 4.46 and 10.54. The former must be that of the tertiary benzylamino nitrogen. [b] Two pK_a values observed, at 8.80 and 12.05. The former is obviously that of the hydroxyl group whose acidity should be increased by the presence of the cationic amidinium portion. [c] pK_a values were calculated according to the formula given in Clark, ref. 6, Chapter I, p. 16.

At first sight it appears surprising that an aromatic group on the amidine nitrogen diminishes the basicity so little (compare I with XXII and XXV also XXVI with XXVII), less than one unit in the pK scale. Actually, this corresponds very closely with the observations in the guanidine series[3,4] it having been shown that pK_a diminishes in the series: guanidine > phenylguanidine > N,N′-diphenylguanidine from 13.65 to 10.77 to 10.12. It would seem that the resonance possibilities in the benzamidinium ion are very close to those in the phenylguanidinium ion while compound XXII is comparable to *sym*-diphenylguanidine.

The influence of ring substitution on the basicity is in general consistent with theoretical expectations. The very high basicity observed with the 4-hydroxy derivative is obviously correlated with the fact that the hydroxyl group has been titrated first and the oxygen is anionic in the pH range involved in the titration of the amidinium moiety. It is to be noted that the three coöperative methyl groups of the mesityl derivative (XXI) exercise an influence greater than that of a para methoxyl or dimethylamino group. This may be partly due to steric inhibition of resonance between the amidine moiety and the ring which probably has an over-all tendency to diminish the basicity of the amidine. Schwarzenbach and Lutz[5] report pK_a for acetamidine hydrochloride as 12.40 (in water) which is significantly above the value for any of these aromatic amidines.

Experimental

Compound XXX, 4-hydroxy-N,N-di-n-butylbenzamidine hydrochloride was prepared by hydrogenolysis of its benzyl ether (XXIX) with palladized charcoal. With this exception all the amidines here reported were obtained by the addition of the appropriate bromomagnesium amide to a benzonitrile.[2] The nitriles employed are all described in the older literature. Most of the significant information is presented in Table I, the method of isolation being indicated by the letters A, A′, B, B′ and C, in the column

(4) Davis and Elderfield, THIS JOURNAL, **54**, 1499 (1932).

(5) Schwarzenbach and Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940).

headed "Method of isolation." Methods A, B and C have been described previously.[2]

Method B′ is a modification of B in which steam distillation of the basic material is omitted and the amidine is separated from secondary amine by extraction from ethereal solution by successive portions of dilute hydrochloric acid. This is to be preferred with N-arylamidines since the secondary amine is feebly basic and the amidine base may undergo some decomposition during a prolonged steam distillation.

Method A′ differs from A only in that the amidine base is not itself distilled. The secondary amine is volatilized by heating *in vacuo* to a temperature preferably not over 160°. In some cases more drastic heating (up to 200° at 1 mm.) was employed with no apparent decomposition but it is believed that the yield of pure amidine hydrochloride suffered from such treatment.

The amidine hydrochlorides were purified by crystallization from ethanol–ether mixtures.

Electrometric Titrations.—These were performed at 0.02 molar initial concentration of amidine hydrochloride in 50% methanol, adding 0.1 *N* sodium hydroxide solution. The apparatus was a Beckman *p*H meter, Model G. Determinations of the *p*H range 6–9 were accomplished with a glass electrode 960 standardized at *p*H 4 and *p*H 7 with potassium acid phthalate and phosphate buffers, respectively. Above *p*H 9 a high *p*H glass electrode 960 E standardized at *p*H 9 and *p*H 12 with sodium chloride–glycine[6] buffers was employed.

Direct comparison of titrations in water and in 50% methanol is not possible with most of these amidines. The most accurate but laborious procedure is to perform a series of titrations in diminishing concentrations of methanol so as to permit extrapolation to zero per cent.—as was done by Hall and Sprinkle.[3] From observations on certain quinoline amidines we believe that in the range 9.5–11, the pK_a observed in 50% methanol runs about 0.3 unit above that in water. Compound XXX was titrated both in 50% methanol and in water. The two curves were roughly parallel, that for methanol being above that for water except at high *p*H (at 11.9 the curves cross). The first two pK_a values, at 8.65 in water and 8.80 in 50% methanol, presumably are due to the phenolic hydroxyl group. The higher pK_a values, relating to the amidine portion were at 12.05 in 50% methanol and 12.15 in water.

Summary

1. A number of N,N-disubstituted benzamidines have been prepared.

2. The effect of substitutions upon the basicity of unsymmetrically disubstituted benzamidines is discussed.

(6) Clark, "The Determination of Hydrogen Ions," 3rd Edition, Williams and Wilkins Co., Baltimore, Md., 1928, Chapter IX.

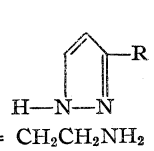
TUCKAHOE 7, N. Y. RECEIVED JUNE 11, 1949

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Synthesis of Some Amines and Amino Acids Containing the Pyrazole Nucleus

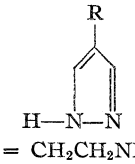
BY REUBEN G. JONES

As part of a study concerned with the biological activity of certain amines and amino acids[1] the two isomeric β-aminoethylpyrazoles, I and II, and the two corresponding pyrazolealanines, III and IV, were prepared.



I, R = $CH_2CH_2NH_2$

III, R = $CH_2CHNH_2CO_2H$

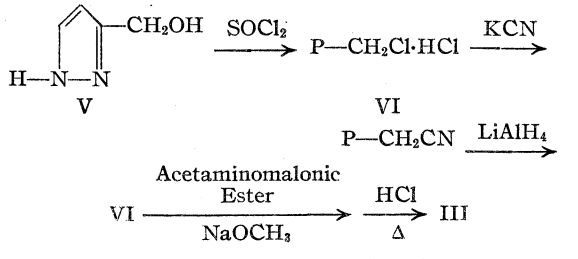


II, R = $CH_2CH_2NH_2$

IV, R = $CH_2CHNH_2CO_2H$

These pyrazole compounds were of particular interest because of their apparently close structural resemblance to the imidazole derivatives, histamine and histidine.

Compounds I and III were synthesized by straightforward procedures as indicated in the accompanying reactions.



Two methods were developed for the preparation of the starting material, 3-hydroxymethylpyrazole, V. Reduction of ethyl 3-pyrazolecarboxylate[2] with lithium aluminum hydride in ether gave V in 84% yield. Compound V was also prepared by the condensation of diazomethane with propargyl alcohol. It has been observed that substituted acetylenes of the type R—C≡CH undergo reaction with diazomethane to yield predominately 3-substituted pyrazoles,[3]

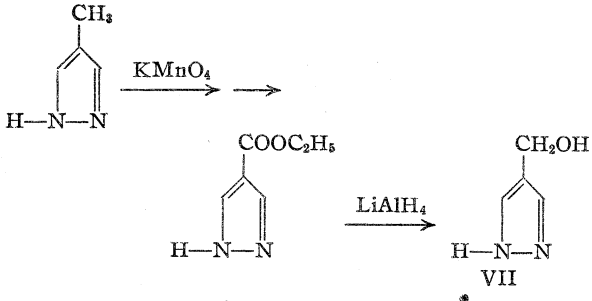
(1) (a) Jones, THIS JOURNAL, **71**, 383 (1949); (b) Jones, *ibid.*, **71**, 644 (1949).

(2) Knorr, *Ber.*, **37**, 3522 (1904).

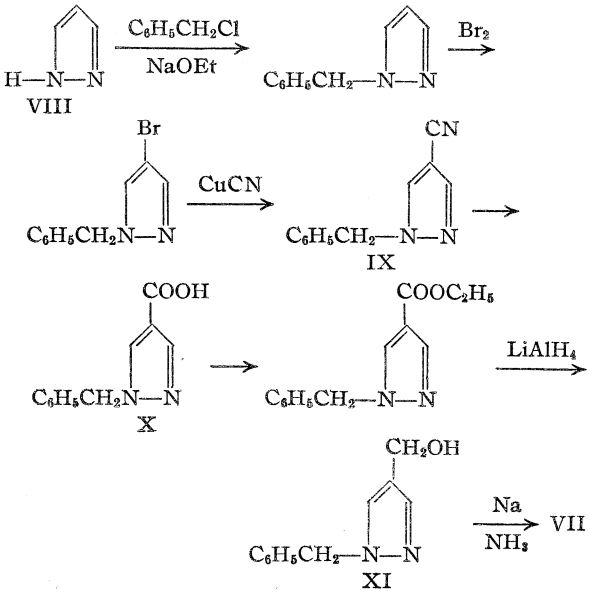
(3) (a) Kuhn and Henkel, *Ann.*, **549**, 279 (1941); (b) Huttel, *Ber.*, **74**, 1680 (1941).

and only insignificant amounts of the alternative 4-substituted isomers. In the present case the yield of 3-hydroxymethylpyrazole was about 50% and that of 4-hydroxymethylpyrazole about 2%.

A number of unforseen difficulties were encountered in the preparation of the 4-substituted pyrazole compounds, II and IV. It was at first supposed that these could be synthesized readily from 4-hydroxymethylpyrazole by the same methods as outlined above for the corresponding 3-isomers. Consequently the preparation of 4-hydroxymethylpyrazole, VII, was undertaken. One series of reactions by which VII was obtained consisted of the permanganate oxidation of 4-methylpyrazole[4] to yield 4-pyrazolecarboxylic acid,[5] which was esterified, and the resulting ester was then reduced with lithium aluminum hydride.



An alternative method of preparing VII is outlined in the following series of reactions.



Pyrazole VIII, the starting material for these latter reactions, was conveniently obtained by the condensation of hydrazine hydrochloride with the recently available 1,1,3,3-tetraethoxypropane.[6]

(4) Auwers and Cauer, *J. prakt. Chem.*, **126**, 146 (1930).

(5) (a) Büchner and Fritsch, *Ann.*, **273**, 253 (1893); (b) Behaghel and Büchner, *Ber.*, **35**, 34 (1902).

(6) Obtained from Carbide and Carbon Chemicals Corporation; see Hultquist, U. S. Patent 2,459,076.

The reaction of 1-benzyl-4-bromopyrazole with cuprous cyanide required a very careful control of experimental conditions in order to obtain satisfactory yields of IX. Several attempts to carry out a similar reaction between 4-bromopyrazole and cuprous cyanide resulted in failure to obtain any of the desired 4-cyanopyrazole. Sodium in liquid ammonia smoothly cleaved the benzyl group from XI to yield VII. Likewise, the acid X underwent facile cleavage to yield 4-pyrazolecarboxylic acid. Thus the 1-benzylpyrazoles behave in the same way as the 1-benzylimidazoles toward sodium in liquid ammonia.[1a]

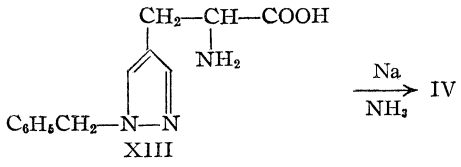
4-Hydroxymethylpyrazole reacted vigorously with thionyl chloride but the resulting 4-chloromethylpyrazole hydrochloride, unlike the isomeric 3-chloromethyl compound, was completely insoluble in thionyl chloride. Furthermore, 4-chloromethylpyrazole proved to be a highly reactive and unstable substance, and no analytically pure sample was isolated. It appeared to react rapidly with ice-water to form 4-hydroxymethylpyrazole. From the reaction of a cold absolute alcohol solution of 4-chloromethylpyrazole hydrochloride with excess potassium cyanide there was obtained a small yield of 4-cyanomethylpyrazole. This was treated with lithium aluminum hydride in ether solution, but none of the expected 4-(β-aminoethyl)-pyrazole (II) could be isolated from the reaction mixture.

In view of these disappointing results, attention was turned to the reactions of 1-benzyl-4-hydroxymethylpyrazole, XI. With thionyl chloride, this yielded 1-benzyl-4-chloromethylpyrazole hydrochloride which could not be induced to crystallize, and an analytically pure sample was not obtained. This chloromethyl compound likewise was highly reactive. An absolute alcohol solution was allowed to react with aqueous potassium cyanide, and there was obtained a liquid product which appeared to consist of a mixture of 1-benzyl-4-cyanomethylpyrazole and 1-benzyl-4-ethoxymethylpyrazole. These could not be separated by distillation, and so the mixture was subjected to the action of lithium aluminum hydride. From this reaction there was isolated a liquid mixture of 1-benzyl-4-(β-aminoethyl)-pyrazole and the unchanged 1-benzyl-4-ethoxymethylpyrazole. When this mixture in dry ether solution was treated with carbon dioxide the β-aminoethyl compound was precipitated as a white crystalline solid which was apparently the ammonium carbamate salt.[7] The dihydrochloride of 1-benzyl-4-(β-aminoethyl)-pyrazole was obtained by treating the carbamate salt with hydrogen chloride in absolute alcohol. The benzyl group was removed from 1-benzyl-4-(β-aminoethyl)-pyrazole carbamate salt by sodium in liquid ammonia to yield compound II.

The condensation of 1-benzyl-4-chloromethyl-

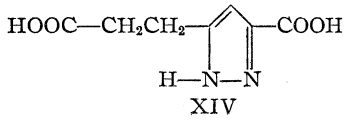
(7) For a recent discussion of ammonium carbamate salts of this type see Wright and Moore, THIS JOURNAL, **70**, 3865 (1948).

pyrazole hydrochloride with sodium acetaminomalonic ester led to the preparation of 1-benzyl-4-pyrazolealanine, XIII. This was converted through the agency of sodium in liquid ammonia to IV, which was purified by precipitation as an insoluble mercuric chloride complex.



XIII

In the early part of this work, another possible approach to the synthesis of the 3-substituted pyrazole compounds was considered. Diethyl α,γ-diketopimelate[8] was allowed to react with hydrazine to yield 5-(β-carbethoxyethyl)-3-pyrazolecarboxylate which was saponified to form the acid XIV.



XIV

When XIV was heated to about 200° in vacuum it sublimed unchanged. No method was discovered by which XIV could be decarboxylated to yield β-(3-pyrazole)-propionic acid which would have been a suitable intermediate for the synthesis of other 3-substituted pyrazoles.

Neither 3- nor 4-(β-aminoethyl)-pyrazole possessed any histamine-like action[9] or other observable pharmacological activity. 3-Pyrazolealanine was not inhibitory to *E. coli, L. arabinosis, Leuconostoc mesenteroides, Strep. viridans, Influenza virus or E. coli phages* T_2 and T_7.

Experimental[10]

3-Hydroxymethylpyrazole. (a) Reaction of Diazomethane with Propargyl Alcohol.—The diazomethane solution prepared in 1500 ml. of ether from 103 g. (1 mole) of nitrosomethylurea[11] was dried over potassium hydroxide pellets for three hours and then decanted into a dry two-liter flask. To the solution was added 56 g. (1.0 mole) of freshly distilled propargyl alcohol (b. p. 110–111°). The solution was allowed to stand at room temperature, and after sixty hours it had become colorless. The ether was evaporated, and the sirupy residue was distilled *in vacuo*. After a forerun of 31 g. (55%) of unreacted propargyl alcohol there was obtained 30 g. of viscous liquid, b. p. 120–150° (0.5 mm.), and about 2 g. of higher boiling material which partially crystallized upon cooling. After several recrystallizations from acetone–petroleum ether mixtures the crystalline substance melted at 121–122° and was identified by mixed melting point as 4-hydroxymethylpyrazole (see below).

The 30 g. of viscous liquid was dissolved in 50 ml. of water and added to a boiling-hot solution of 80 g. of picric acid in 1200 ml. of water. The resulting solution was boiled with 5 g. of decolorizing carbon, filtered and cooled to 40°. The yellow, crystalline precipitate of 3-hydroxymethylpyrazole picrate was collected, washed with a little absolute alcohol and air-dried. The yield was 78 g. (53% based upon unrecovered propargyl alcohol). It melted at 183.5–184.5°, and the melting point remained unchanged after recrystallization from water.

Anal. Calcd. for $C_{10}H_9N_5O_8$: N, 21.41. Found: N, 21.43.

The picrate, 75 g., was suspended in 200 ml. of nitrobenzene, and the mixture was vigorously shaken with 50 ml. of 12 *N* hydrochloric acid (6 *N* hydrochloric acid did not decompose the picrate). The hydrochloric acid layer was washed with three 50-ml. portions of chloroform, and then the nitrobenzene and chloroform solutions were extracted with a fresh 50-ml. portion of 12 *N* hydrochloric acid. After the total acid solution had been filtered, it was evaporated in vacuum to dryness. The residual solid was taken up in absolute alcohol, and the solution was evaporated to dryness in vacuum, leaving the 3-hydroxymethylpyrazole hydrochloride as a very hygroscopic, white, crystalline solid. It was dried in vacuum over potassium hydroxide, and the yield was 30 g. (97%); m. p. 113–115°. A sample recrystallized from absolute alcohol–ether and dried in vacuum melted at 117–118°.

To 0.5 g. (0.005 mole) of the crude 3-hydroxymethylpyrazole in 30 ml. of distilled water was added 1.05 g. (0.0067 mole) of potassium permanganate. The mixture was shaken and heated for one-half hour and then filtered. The colorless filtrate together with about 30 ml. of water used to wash the manganese dioxide was evaporated to a volume of about 5 ml. This solution was brought to *p*H 2 with hydrochloric acid and, after scratching, 0.35 g. of white crystalline precipitate separated, m. p. 216–217°. The product was identified as 3-pyrazolecarboxylic acid by a mixed melting point with an authentic sample,[12] m. p. 216–217°.

Anal. Calcd. for $C_4H_4N_2O_2$: C, 41.98; H, 3.60. Found: C, 42.16; H, 3.92.

(b) Reduction of Ethyl 3-Pyrazolecarboxylate with Lithium Aluminum Hydride.—3-Pyrazolecarboxylic acid[12] was esterified with ethanol and hydrogen chloride. The ethyl ester, obtained in 89% yield, melted[2] at 158°. In a Soxhlet thimble above a refluxing solution of 15 g. of lithium aluminum hydride[13] in 1 l. of ether was placed 28 g. (0.20 mole) of ethyl 3-pyrazolecarboxylate. After fifteen hours all of the ester had been dissolved and carried down into the lithium aluminum hydride solution. Very cautiously and with stirring, 50 ml. of water was added dropwise to the reaction mixture, and then the ether was almost all removed by evaporation. The residual, white, granular solid was treated with 300 ml. of methanol, and the mixture was thoroughly saturated with carbon dioxide. After the mixture had been heated to boiling it was filtered, and the solid was extracted with two more 300-ml. portions of boiling methanol. The total filtrate was evaporated in vacuum, and the residual sirup containing some solid was extracted with 50 ml. of dry methanol. This methanol solution was again filtered and evaporated, and the residual sirup was distilled in vacuum to yield 16.5 g. (84%) of pure 3-hydroxymethylpyrazole; b. p. 137–140° (0.5 mm.), $n^{25}D$ 1.5340, d^{25}_{25} 1.225.

Anal. Calcd. for $C_4H_6N_2O$: N, 28.56. Found: N, 28.42.

The 3-hydroxymethylpyrazole was a colorless, very viscous liquid which could not be induced to crystallize. It was highly soluble in water or alcohol, moderately soluble in ether, and it could not be extracted from its water solution with organic solvents. The picrate melted at 184–185°, and the melting point was not depressed when mixed with the picrate described above under (a).

3-Chloromethylpyrazole Hydrochloride.—To 40 ml. of thionyl chloride was added in small portions 30 g. (0.22 mole) of 3-hydroxymethylpyrazole hydrochloride. Reaction took place immediately, and a clear solution was formed. After the solution had been warmed on the steam-bath for fifteen minutes, the excess thionyl chloride

(8) Wislicenus, *Ber.*, **21**, 2583 (1888).

(9) Lee and Jones, *J. Pharmacol.*, **95**, 71 (1949).

(10) All melting points are corrected.

(11) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(12) Knorr, *Ann.*, **279**, 231 (1894).

(13) Obtained from Metal Hydrides Inc., Beverly, Mass.

was removed by evaporation in vacuum. The white, crystalline 3-chloromethylpyrazole hydrochloride was washed with anhydrous ether and stored in a vacuum desiccator over potassium hydroxide. The yield was 34 g. (100%), m. p. 155–156° dec. It was deliquescent.

Anal. Calcd. for $C_4H_5N_2Cl \cdot HCl$: N, 18.31. Found: N, 18.20.

3-Cyanomethylpyrazole.—To a well-stirred solution of 60 g. of potassium cyanide in 65 ml. of water cooled in an ice-bath was added a solution of 15.3 g. (0.10 mole) of 3-chloromethylpyrazole hydrochloride in 200 ml. of absolute alcohol over a period of one hour. The reaction mixture was removed from the cooling bath and stirred at room temperature for four hours. It was then filtered, the salts were washed with two 200-ml. portions of 95% alcohol and the total filtrate was evaporated in vacuum to a volume of about 100 ml. After the addition of a little water to bring some precipitated salts into solution, the mixture was extracted with four 100-ml. portions of chloroform. The chloroform extract was evaporated in vacuum leaving 9.5 g. of liquid residue. This was distilled in vacuum. It all came over at 117–120° (0.4 mm.) as a colorless liquid. The yield was 8.5 g. (80%) of 3-cyanomethylpyrazole; $n^{25}D$ 1.5138.

Anal. Calcd. for $C_5H_5N_3$: N, 39.23. Found: N, 38.94.

The picrate, m. p. 63–64°, was appreciably water soluble.

3-(β-Aminoethyl)-pyrazole.—A solution of 7.5 g. (0.07 mole) of 3-cyanomethylpyrazole in 50 ml. of dry ether was added dropwise to a solution of 5 g. of lithium aluminum hydride in 150 ml. of ether. After the mixture had stood for about one-half hour, 25 ml. of water was added dropwise through the condenser. The ether was then evaporated and 200 ml. of methanol was added. The mixture was saturated with carbon dioxide, heated to boiling and filtered. The solid was extracted with four additional 300-ml. portions of hot methanol, and the total methanol filtrate was evaporated in vacuum to dryness. The residue was dissolved in 200 ml. of warm methanol and the solution filtered and evaporated. The solid residue which appeared to be a 3-(β-aminoethyl)-pyrazole salt with carbon dioxide was dissolved in 50 ml. of water and the solution added to a hot solution of 35 g. of picric acid in 600 ml. of water. After cooling to 10° the crystalline solid was collected and recrystallized from 250 ml. of water to yield 21 g. (53%) of 3-(β-aminoethyl)-pyrazole dipicrate; m. p. 195–197°.

Anal. Calcd. for $C_{17}H_{15}N_9O_{14}$: N, 22.20. Found: N, 22.90.

The dipicrate, 20 g., was treated with concentrated hydrochloric acid in nitrobenzene and the mixture worked up as described above to yield 6.2 g. (96%) of 3-(β-aminoethyl)-pyrazole dihydrochloride; m. p. 223–224°. It was deliquescent, but only sparingly soluble in hot absolute alcohol.

Anal. Calcd. for $C_5H_9N_3 \cdot 2HCl$: N, 22.83; Cl, 38.52. Found: N, 23.21; Cl, 38.16.

3-Pyrazolealanine.—In a 500-ml. three-necked flask provided with a stirrer and dropping funnel was placed 150 ml. of absolute alcohol. In the alcohol was dissolved 6.9 g. (0.3 g. atom) of sodium. To the solution was added 43 g. (0.2 mole) of acetaminomalonic ester, and then the flask was surrounded with an ice-bath. With stirring a solution of 15.3 g. (0.1 mole) of 3-chloromethylpyrazole hydrochloride in 100 ml. of absolute alcohol was added. The ice-bath was removed, and the mixture was stirred at room temperature for one hour after which most of the alcohol was removed by evaporation in vacuum on the steam-bath. The residue was taken into 400 ml. of 2 *N* hydrochloric acid, the solution was extracted with ethyl acetate to remove unreacted acetaminomalonic ester, and then the aqueous solution was made basic with sodium carbonate and extracted with ether. Evaporation of the dried ether solution left a glass which did not crystallize. It was heated on the steam-bath for five hours with 100 ml. of concentrated hydrochloric acid. The solution was evaporated, the residual glass was taken up in water, and the solution was freed of chloride ion with silver carbonate and hydrogen sulfide in the usual way. The resulting aqueous solution was evaporated to small volume and alcohol was added to precipitate 13 g. (84% yield) of 3-pyrazolealanine as a white crystalline powder, m. p. 226–228° dec.

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.50; H, 6.38; N, 27.00.

Pyrazole.—A mixture of 220 g. (1 mole) of 1,1,3,3-tetraethoxypropane,[6] 105 g. (1 mole) of hydrazine dihydrochloride, 150 ml. of water and 100 ml. of alcohol was heated on the steam-bath for two hours. The solution was evaporated in vacuum to remove the alcohol. The brown residual sirup was taken up in 200 ml. of water, and 200 g. of sodium carbonate was added. The mixture was filtered and the salts were thoroughly washed with two 200-ml. portions of ether which were then used to extract the filtrate. The dried ether solution was evaporated and the residue was distilled in vacuum to yield 59–63 g. (87–93%) of very pure pyrazole; b. p. 95–97° (20 mm.); m. p. 70°.

1-Benzylpyrazole.—To a solution prepared by dissolving 14 g. (0.6 g. atom) of sodium in 500 ml. of absolute alcohol was added 34 g. (0.5 mole) of pyrazole. The solution was heated to gentle boiling under reflux and 150 g. (1.2 moles) of benzyl chloride was added slowly from a dropping funnel. After a few minutes the mixture had become neutral. It was filtered, and the filtrate was evaporated in vacuum to remove the alcohol. The residual liquid was poured into 100 ml. of 6 *N* hydrochloric acid. The aqueous layer was separated, washed with ether and then made basic with excess sodium hydroxide, cooled, and extracted with two 100-ml. portions of ether. After evaporation of the ether the residual 1-benzylpyrazole was distilled; b. p. 255–257° (750 mm.), 134–136° (15 mm.); $n^{25}D$ 1.5558; d^{25}_{25} 1.078. The yield was 62–68 g. (79–86%).

Anal. Calcd. for $C_{10}H_{10}N_2$: N, 17.71. Found: N, 17.59.

1-Benzylpyrazole failed to react with excess formalin. After heating the two together in a sealed tube at 120° for nine hours 95% of the 1-benzylpyrazole was recovered unchanged.

1-Benzyl-4-bromopyrazole.—A solution of 104 g. (0.65 mole) of 1-benzylpyrazole in 200 ml. of chloroform was cooled in an ice-bath and stirred well while 104 g. (0.65 mole) of bromine in 100 ml. of chloroform was slowly poured in. The chloroform solution was then shaken with excess aqueous sodium carbonate solution, dried over anhydrous sodium carbonate, and, after removal of the chloroform, the 1-benzyl-4-bromopyrazole was distilled in vacuum. It all came over at 169–170° (20 mm.) as a colorless liquid, which crystallized after cooling, m. p. 44–45°. The yield was 148–154 g. (94–98%).

Anal. Calcd. for $C_{10}H_9N_2Br$: N, 11.82. Found: N, 11.45.

1-Benzyl-4-cyanopyrazole.—A 200-ml. round-bottom flask was provided with a short Claisen head and wide-bore condenser set for distillation with a receiver attached to a vacuum line in such a way that the system could be immediately evacuated. In the flask was placed 23.7 g. (0.1 mole) of 1-benzyl-4-bromopyrazole and 13.4 g. (0.15 mole) of cuprous cyanide. The mixture was slowly and carefully heated with a soft flame and occasionally swirled until it had all melted. Local heating was avoided. As soon as the contents had become homogeneous the heating was stopped and the liquid was closely watched. Usually, at this point a slight bubbling of the liquid became evident indicating that an exothermic reaction had begun. If there was no evidence within about thirty seconds that the exothermic reaction was starting a little more heat was applied. At the first sign of spontaneous bubbling the vacuum of about 20 mm. was *immediately* applied being careful not to cause the material to bump over into the condenser. The mixture was then distilled as rapidly as possible at about 20 mm. using a flame until no more liquid

came over. The distillate of crude 1-benzyl-4-cyanopyrazole solidified upon cooling. The product was triturated with a little warm petroleum ether and then filtered and air-dried. The yield was 11–14 g. (60–76%). It was soluble in ether, alcohol, benzene or ethyl acetate, sparingly soluble in petroleum ether and insoluble in water. A sample for analysis was recrystallized from petroleum ether, m. p. 63–64°.

Anal. Calcd. for $C_{11}H_9N_3$: N, 22.21. Found: N, 22.33.

This experiment was carried out many times and it was possible to get satisfactory yields consistently. With larger-sized runs the yields were lower. If the distillation was begun as soon as the mixture had melted and before the exothermic reaction started then the distillate consisted mostly of unchanged 1-benzyl-4-bromopyrazole. However, it was essential to start the vacuum distillation just as soon as the exothermic reaction had become evident. On one or two occasions, a delay of only five or ten seconds resulted in the reaction getting out of control and leaving only charred decomposition products.

1-Benzyl-4-cyanopyrazole did not form a hydrochloride. A solution in ether was saturated with dry hydrogen chloride, but nothing precipitated. When the solution was evaporated pure, unchanged 1-benzyl-4-cyanopyrazole, m. p. 63–64°, remained.

1-Benzyl-4-pyrazolecarboxylic Acid.—1-Benzyl-4-cyanopyrazole was boiled with aqueous sodium hydroxide and alcohol until no more ammonia was evolved. The alcohol was removed by evaporation and the aqueous solution was acidified with hydrochloric acid to precipitate 1-benzyl-4-pyrazolecarboxylic acid in 94% yield. A sample was recrystallized from water containing a little alcohol, m. p. 151–152°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: N, 13.86. Found: N, 13.88.

Ethyl 1-Benzyl-4-pyrazolecarboxylate.—A solution of 1-benzyl-4-pyrazolecarboxylic acid in ten parts of absolute alcohol was saturated with hydrogen chloride, refluxed for eighteen hours and then worked up in the usual way to give the ethyl ester in 94% yield. A sample recrystallized from petroleum ether melted at 62–63°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: N, 12.17. Found: N, 12.27.

1-Benzyl-4-aminomethylpyrazole Hydrochloride.—A solution of 5 g. of 1-benzyl-4-cyanopyrazole in 50 ml. of dry ether was added to a stirred solution of 1.5 g. of lithium aluminum hydride in 100 ml. of ether. After one-half hour, 10 ml. of water was added dropwise. The mixture was filtered, and the solid was washed by suspension in another 50 ml. of ether. The combined ether filtrate was dried and saturated with dry hydrogen chloride. Recrystallization of the resulting precipitate from absolute alcohol–ether gave 5.0 g. (72% yield) of the monohydrochloride, m. p. 232–233°.

Anal. Calcd. for $C_{11}H_{13}N_3 \cdot HCl$: N, 18.78; Cl, 15.85. Found: N, 18.94; Cl, 16.28.

4-Pyrazolecarboxylic Acid. (a) Cleavage of 1-Benzyl-4-pyrazolecarboxylic Acid with Sodium in Liquid Ammonia.—A suspension of 2.02 g. (0.01 mole) of 1-benzyl-4-pyrazolecarboxylic acid in 30 ml. of liquid ammonia was treated with sodium in small pieces until a permanent blue color was formed (0.5 g. of sodium). The ammonia was allowed to evaporate, and then the residue was taken up in 20 ml. of water. After the aqueous solution had been washed with ether it was acidified to *p*H 2 with hydrochloric acid to precipitate 0.89 g. (80% yield) of 4-pyrazolecarboxylic acid. A sample was recrystallized from water; m. p. 279–280° dec. (lit.[5] 275 dec.).

Anal. Calcd. for $C_4H_4N_2O_2$: N, 25.00. Found: N, 25.20.

(b) Oxidation of 4-Methylpyrazole.—4-Methyl-3-pyrazolecarboxylic acid was prepared in a yield of about 50% by the condensation of methyl crotonate with diazomethane, followed by oxidation of the intermediate pyrazoline with bromine and saponification of the ester according to the method of v. Pechmann and Burkard.[14] The acid was decarboxylated by heating, to give a 70% yield of 4-methylpyrazole,[4] b. p. 202–203° (730 mm.).

4-Methylpyrazole was oxidized with potassium permanganate in the same way as has been described for the oxidation of the corresponding 3-isomer.[12] The yield of 4-pyrazolecarboxylic acid was 50–53%, m. p. 278–279° dec.

Ethyl 4-Pyrazolecarboxylate.—4-Pyrazolecarboxylic acid was esterified with ethanol and sulfuric acid, and the yield of ethyl ester was 70%; b. p. 138–140° (3 mm.), m. p. 78–79° from petroleum ether–ethyl acetate mixture.

Anal. Calcd. for $C_6H_8N_2O_2$: N, 19.99. Found: N, 20.18.

Methyl 4-Pyrazolecarboxylate.—This was prepared from the acid and diazomethane in methanol, m. p. 136–137°.

Anal. Calcd. for $C_5H_6N_2O_2$: N, 22.22. Found: N, 21.69.

1-Benzyl-4-hydroxymethylpyrazole.—A solution of 58 g. (0.25 mole) of ethyl 1-benzyl-4-pyrazolecarboxylate in 600 ml. of anhydrous ether was added dropwise to a solution of 15 g. of lithium aluminum hydride in 300 ml. of ether. After a few hours 50 ml. of water was added dropwise. The resulting mixture was filtered and the solid was extracted with three 400-ml. portions of hot methanol. The methanol and ether filtrates were evaporated in vacuum, the residue was extracted with three 200-ml. portions of dry ether, and the filtered ether solution was evaporated. Distillation of the residual liquid gave 43.5–45.3 g. (92–96% yield) of 1-benzyl-4-hydroxymethylpyrazole as a colorless, viscous liquid; b. p. 146–148° (0.2 mm.), $n^{25}D$ 1.5742, d^{25}_{25} 1.155.

Anal. Calcd. for $C_{11}H_{12}N_2O$: N, 14.89. Found: N, 14.60.

4-Hydroxymethylpyrazole. (a) Reduction of Ethyl 4-Pyrazolecarboxylate with Lithium Aluminum Hydride.—Ethyl 4-pyrazolecarboxylate was reduced with lithium aluminum hydride in ether and the mixture worked up in the manner described above for the corresponding ethyl 3-pyrazolecarboxylate. The 4-hydroxymethylpyrazole obtained in a yield of 86% was a solid. It was purified by dissolving in absolute alcohol, filtering and evaporating the solution, m. p. 120–122°. A sample was recrystallized from a mixture of absolute alcohol and chloroform, m. p. 126.5–127°. It was very soluble in water or alcohol, very sparingly soluble in chloroform and insoluble in ether.

Anal. Calcd. for $C_4H_6N_2O$: N, 28.56. Found: N, 28.25.

(b) Cleavage of 1-Benzyl-4-hydroxymethylpyrazole with Sodium in Liquid Ammonia.—To a solution of 9.4 g. (0.05 mole) of 1-benzyl-4-hydroxymethylpyrazole in 75 ml. of liquid ammonia was added small pieces of sodium (2.3 g.) until a permanent blue color was formed. Ammonium chloride, 6 g., was then added and the ammonia was allowed to evaporate. The residue was extracted with 300 ml. of hot acetone. The solution was filtered, evaporated to small volume, and 100 ml. of petroleum ether was added. There was thus obtained 4.5 g. (92% yield) of 4-hydroxymethylpyrazole; m. p. 125–126° and mixed with a sample prepared as described under (a), m. p. 126–127°. The picrate, recrystallized from water, melted at 149–150° dec.

1-Benzyl-4-(β-aminoethyl)-pyrazole.—Dry hydrogen chloride was passed into a mixture of 9.4 g. (0.05 mole) of 1-benzyl-4-hydroxymethylpyrazole and 75 ml. of anhydrous ether. The resulting oily hydrochloride could not be induced to crystallize. Therefore, the ether was removed by evaporation and 25 ml. of thionyl chloride was added. Reaction took place immediately. The resulting clear solution was warmed on the steam-bath for a short time, and then the excess thionyl chloride was evaporated in vacuum. The residual oily product, presumably 1-benzyl-4-chloromethylpyrazole hydrochloride, would not crystallize. It was readily soluble in absolute alcohol and was precipitated as an oil by the addition of dry ether.

(14) v. Pechmann and Burkard, *Ber.*, **33**, 3590 (1900).

A solution of the crude 1-benzyl-4-chloromethylpyrazole hydrochloride in 100 ml. of cold absolute alcohol was added to aqueous potassium cyanide and the mixture worked up as described above for the preparation of 3-cyanomethylpyrazole. The liquid reaction product distilled at 130–150° (0.2 mm.), and it proved to be a mixture containing the desired 1-benzyl-4-cyanomethylpyrazole together with 1-benzyl-4-ethoxymethylpyrazole (see below) which resulted from the reaction of the chloro compound with alcohol.

The liquid, 8.5 g., in 50 ml. of ether was added to a solution of 3 g. of lithium aluminum hydride in 200 ml. of ether. After this reaction mixture had been decomposed with 10 ml. of water it was filtered and the solid was extracted with three 200-ml. portions of ether. The liquid obtained after evaporation of the dried ether extract was distilled in vacuum, b. p. 110–140° (0.1 mm.). It weighed 6.2 g. This liquid was dissolved in 100 ml. of dry ether and the solution was saturated with carbon dioxide to precipitate a white, non-hygroscopic, crystalline solid. The product appeared to be the carbamate[7] formed by the reaction of one molecule of carbon dioxide with two molecules of 1-benzyl-4-(β-aminoethyl)-pyrazole. It melted with decomposition over the range 100–115°. The yield was 2.7 g. (24% based on 1-benzyl-4-hydroxymethylpyrazole).

Anal. Calcd. for $C_{25}H_{30}N_6O_2$: N, 18.83. Found: N, 18.65.

A solution of 2.0 g. of the carbamate in 20 ml. of absolute alcohol was saturated with dry hydrogen chloride; and after the addition of 30 ml. of dry ether, 2.3 g. (94% yield) of white, crystalline 1-benzyl-4-(β-aminoethyl)-pyrazole dihydrochloride separated, m. p. 177–179°. It was not hygroscopic. A sample was recrystallized from absolute alcohol, m. p. 179–180°.

Anal. Calcd. for $C_{12}H_{15}N_3 \cdot 2HCl$: C, 52.56; H, 6.25; N, 15.33. Found: C, 52.45; H, 6.51; N, 15.42.

The ether filtrate from the above carbamate was evaporated and the residual liquid was distilled in vacuum. After a small forerun 2 g. of colorless liquid was obtained, b. p. 115–117° (0.1 mm.). This was believed to be 1-benzyl-4-ethoxymethylpyrazole.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.96. Found: C, 71.94; H, 7.52; N, 13.31.

4-(β-Aminoethyl)-pyrazole.—To a suspension of 4.0 g. of the above carbamate of 1-benzyl-4-(β-aminoethyl)-pyrazole in 150 ml. of liquid ammonia was added small pieces of sodium until a permanent blue color was formed. This required 1.1 g. of sodium, and the reaction was very slow toward the end. After evaporation of the ammonia the residue was treated with 100 ml. of warm absolute alcohol, and the mixture was saturated with carbon dioxide and filtered. The filtrate was boiled for a few minutes, again filtered, then evaporated to dryness in vacuum. The residue, dissolved in 20 ml. of water, was added to a hot solution of 9 g. of picric acid in 150 ml. of water. The product which separated after cooling was recrystallized from 100 ml. of water to yield 8.1 g. (83%) of 4-(β-aminoethyl)-pyrazole dipicrate, m. p. 190–191°.

Anal. Calcd. for $C_{17}H_{15}N_9O_{14}$: N, 22.14. Found: N, 22.03.

The dipicrate, 7.0 g., was decomposed with hydrochloric acid and the reaction worked up as described above for the preparation of 3-(β-aminoethyl)-pyrazole dihydrochloride. There was thus obtained 1.72 g. (76% yield) of 4-(β-aminoethyl)-pyrazole dihydrochloride, m. p. 227–228°.

Anal. Calcd. for $C_5H_9N_3 \cdot 2HCl$: N, 22.83. Found: N, 22.82.

It was only sparingly soluble in hot absolute alcohol and was not deliquescent.

1-Benzyl-4-pyrazolealanine.—An absolute alcohol solution of crude 1-benzyl-4-chloromethylpyrazole hydrochloride (prepared from 0.1 mole of 1-benzyl-4-hydroxymethylpyrazole) was caused to react with sodium acetaminomalonic ester. The reaction was carried out and worked up as described above for the preparation of 3-pyrazolealanine except that the evaporated mixture was treated with 6 *N* instead of 2 *N* hydrochloric acid. The 1-benzyl-4-pyrazolealanine was rather sparingly soluble in water and, therefore, the precipitate formed by the addition of silver carbonate to the hydrochloride solution was washed several times with hot water before the treatment of the filtrate with hydrogen sulfide. There was obtained 5.4 g. (22%) of 1-benzyl-4-pyrazolealanine, m. p. 243–244° dec.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: N, 17.13. Found: N, 16.93.

4-Pyrazolealanine.—1-Benzyl-4-pyrazolealanine, 1.0 g. (0.004 mole), in 50 ml. of liquid ammonia was treated with small pieces of sodium until a permanent blue color was formed (0.30 g. sodium). Then 0.70 g. (0.013 mole) of ammonium chloride was added. After the ammonia had evaporated the residue was taken up in 25 ml. of hot water and to the solution was added 5 g. of mercuric acetate dissolved in 25 ml. of water. The resulting white precipitate was thoroughly washed by suspension in two 50-ml. portions of fresh water, and then it was suspended in 100 ml. of water and hydrogen sulfide was bubbled in until the mixture was saturated. The precipitate of mercuric sulfide was separated by filtration, and the filtrate was evaporated in vacuum to a sirup. This was taken up in 50 ml. of absolute alcohol and 100 ml. of dry ether was added, whereupon a white crystalline precipitate separated which proved to be a mixture of the mono- and dihydrochlorides of 4-pyrazolealanine, m. p. 235–236° dec. The yield was 0.60 g. (72%).

Anal. Calcd. for $C_6H_9N_3O_2 \cdot 1.44HCl$: C, 34.6; H, 5.1; N, 20.4; Cl, 24.7. Found: C, 34.2; H, 5.2; N, 21.0; Cl, 24.0.

The above hydrochloride, 0.40 g. (0.0019 mole) was dissolved in 25 ml. of water and 0.40 g. (one equivalent) of silver carbonate was added. The mixture was digested on the steam-bath for one hour, filtered, and the filtrate was saturated with hydrogen sulfide. The solution was clarified with carbon, filtered and evaporated to dryness in vacuum leaving 0.25 g. (80% yield) of white crystalline 4-pyrazolealanine. It was insoluble in alcohol and only sparingly soluble in water. A solution of the product in 4 ml. of hot water was filtered and the filtrate diluted with 8 ml. of alcohol to precipitate 0.15 g. of pure 4-pyrazolealanine, m. p. 304–306° dec.

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.23; H, 6.17; N, 26.81.

4-Cyanomethylpyrazole.—To 50 ml. of thionyl chloride was added 13 g. of powdered 4-hydroxymethylpyrazole. A vigorous reaction took place, but the resulting product, presumably 4-chloromethylpyrazole hydrochloride, was insoluble in the thionyl chloride. The excess thionyl chloride was evaporated in vacuum and the solid was washed with dry ether. It was extremely hygroscopic and no satisfactory analysis was obtained. A sample, dissolved in ice-water, appeared to be quickly hydrolyzed to form 4-hydroxymethylpyrazole which was obtained after evaporation of the water solution and identified by melting point and mixed melting point.

A cold absolute alcohol solution of the crude 4-chloromethylpyrazole hydrochloride was allowed to react with potassium cyanide and the reaction was worked up as described for the preparation of 3-cyanomethylpyrazole. There was obtained 4.0 g. (28% yield) of crude 4-cyanomethylpyrazole, b. p. 125–130° (0.2 mm.) which crystallized after cooling, m. p. 73–77°. A sample was recrystallized from a mixture of chloroform–petroleum ether and then from benzene–petroleum ether, m. p. 83–84°.

Anal. Calcd. for $C_5H_5N_3$: N, 39.23. Found: N, 38.68.

5-(β-Carboxyethyl)-3-pyrazolecarboxylic Acid and its Diethyl Ester.—Diethyl α,γ-diketopimelate, b. p. 183–185° (14 mm.), was prepared in 27% yield from ethyl levulinate and diethyl oxalate according to the procedure of Wislicenus.[8]

To a solution of 61 g. (0.25 mole) of the above diketo ester in 200 ml. of methanol was added 12.5 g. (0.25 mole) of 100% hydrazine hydrate. Heat was evolved, and the solution boiled spontaneously. After removal of the methanol the ethyl 5-(β-carbethoxyethyl)-3-pyrazolecarboxylate was distilled in vacuum to yield 56 g. (93.5%) of viscous colorless liquid which soon crystallized; b. p. 180° (0.5 mm.), m. p. 70–72°. A sample was recrystallized from petroleum ether, m. p. 72–73°.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: N, 11.66. Found: N, 12.17.

The above ester, 55 g., was saponified with sodium hydroxide solution and the 5-(β-carboxyethyl)-3-pyrazolecarboxylic acid was precipitated with hydrochloric acid. The yield was 42.5 g. (100%). A sample, recrystallized from water, melted at 243–244° dec.

Anal. Calcd. for $C_7H_8N_2O_4$: N, 15.23. Found: N, 15.15.

A sample of the acid was sublimed twice in vacuum at a temperature of about 200–230°. It remained unchanged, m. p. 243–244° dec.

Anal. Calcd. for $C_7H_8N_2O_4$: neut. equiv., 92.08. Found: neut. equiv., 93.57.

A sample of the acid was boiled for several hours in quinoline and another sample was boiled in glacial acetic acid. In neither case was there any evidence of decarboxylation.

Acknowledgment.—The author is indebted to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses reported here, and to Frank Streightoff and Dr. H. M. Lee for the biological tests.

Summary

3-Pyrazolealanine, 3-β-aminoethylpyrazole, 4-pyrazolealanine and 4-β-aminoethylpyrazole have been synthesized.

These pyrazole compounds appear to have no significant biological activity.

INDIANAPOLIS, INDIANA RECEIVED JUNE 2, 1949

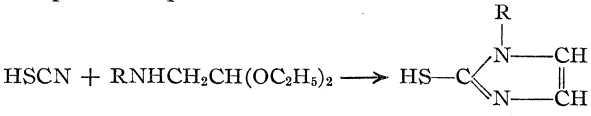
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Studies on Imidazoles. IV.[1] The Synthesis and Antithyroid Activity of Some 1-Substituted-2-mercaptoimidazoles

BY REUBEN G. JONES, EDMUND C. KORNFELD, KEITH C. MCLAUGHLIN AND ROBERT C. ANDERSON

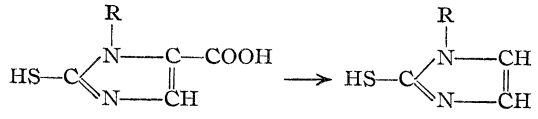
A large amount of synthetic work on antithyroid drugs appears to have been directed toward the preparation of 2-thiouracil types.[2] However, in 1945, Astwood[3] showed that 2-mercaptoimidazole had antithyroid activity about one and one-half times that of thiouracil when tested in rats. In connection with other work a number of 1-substituted-2-mercaptoimidazoles became available, and it appeared to be worthwhile to prepare others of this series and submit them to pharmacological testing.

Easson and Pyman have described a general method of preparing 1-substituted-2-mercaptoimidazoles by the reaction of primary amines with acetalylisothiocyanate.[4] Earlier, Marckwald and others had synthesized compounds of this type from isothiocyanates and aminoacetal.[5] The reaction of thiocyanic acid with N-substituted aminoacetals has proved to be a most useful method for obtaining the greater number of the compounds reported in Table I.



This is designated as method A in the table. The requisite N-substituted aminoacetals were readily prepared by heating chloro- or bromoacetal with primary amines.

Another satisfactory method (B) of synthesizing some of the compounds of Table I consisted of the decarboxylation of 1-substituted 2-mercapto-5-imidazolecarboxylic acids.



The acids were heated to about 250° at which temperature the decarboxylation was rapid, and the yields of the desired products were practically quantitative. Surprisingly the resulting 2-mercaptoimidazoles, in the absence of air, appeared to be quite stable at these elevated temperatures.

The antithyroid activities of a number of the compounds of Table I as determined by the rat test[6] are recorded in the last column. Although 2-mercaptoimidazole appears to be somewhat less active in rats than is propylthiouracil, Astwood has recently found[7] that in man 2-mercaptoimidazole and 1-methyl-2-mercaptoimidazole are much more active.

In addition to the compounds of Table I, three related members were synthesized (see Experimental) and tested. These together with their activities were: 4(or 5)-methyl-2-mercaptoimidazole,[8] 0.05; 4(or 5)-ethyl-2-mercaptoimidazole, 0.1; and 1-methyl-5-ethyl-2-mercaptoimidazole, 0.5. After the completion of this work

(1) For the preceding paper of this series see THIS JOURNAL, **71**, 2444 (1949).

(2) (a) Anderson, Halverstadt, Miller and Roblin, *ibid.*, **67**, 2197 (1945); (b) Jackman, Bergman and Archer, *ibid.*, **70**, 497 (1948); (c) Miller, Dessert and Anderson, *ibid.*, **70**, 500 (1948).

(3) Astwood, Bissell and Hughes, *Endocrinology*, **37**, 456 (1945).

(4) Easson and Pyman, *J. Chem. Soc.*, 1806 (1932).

(5) (a) Marckwald, *Ber.*, **25**, 2354 (1892); (b) Wohl and Marckwald, *ibid.*, **22**, 568, 1353 (1889).

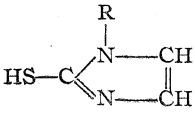
(6) Astwood, *J. Pharmacol.*, **78**, 79 (1943).

(7) Stanley and Astwood, *Endocrinology*, **44**, 588 (1949).

(8) Gabriel and Pinkus, *Ber.*, **26**, 2203 (1893).

TABLE I

1-SUBSTITUTED-2-MERCAPTOIMIDAZOLES



R	Empirical formula	Method of prepn.	Yield, %[a]	M. p., °C.[b]	Nitrogen, % Calcd.	Found	Activity Thiouracil = 1.0
H[c]	$C_3H_4N_2S$	A, B	78–91	218–220		[d]	0.5
CH_3[e]	$C_4H_6N_2S$	A, B	84–99	146–148	24.54	24.21	.5
C_2H_5	$C_5H_8N_2S$	A	98	79–80	21.86	21.60	.5
C_3H_5[f]	$C_6H_8N_2S$	A	36	73–74	19.99	19.99	
n-C_3H_7	$C_6H_{10}N_2S$	A	85	115–116	19.70	19.40	.05
i-C_3H_7	$C_6H_{10}N_2S$	B	95	168–169		[g]	
n-C_4H_9	$C_7H_{12}N_2S$	A	70	80–81	17.93	17.92	
i-C_4H_9	$C_7H_{12}N_2S$	A	90	137–138	17.93	17.69	.05
s-C_4H_9	$C_7H_{12}N_2S$	A	98	166–167	17.93	17.51	
t-C_4H_9	$C_7H_{12}N_2S$	A	19	189–190	17.93	17.77	
$(CH_3)_2NCH_2CH_2$[h]	$C_7H_{13}N_3S\cdot HCl$	A	53	188–189	20.23	20.27	
2-C_5H_4N[i]	$C_8H_7N_3S\cdot 2HCl$	A	66	159–160	16.80	16.28	
C_6H_5[e]	$C_9H_8N_2S$	A, B	85–97	179–180	15.90	16.55	
C_6H_{11}[j]	$C_9H_{14}N_2S$	B	89	173–174		[k]	
$C_6H_5CH_2$	$C_{10}H_{10}N_2S$	A, B	87–96	145–146		[l]	.2
$C_5H_{11}CH(CH_3)$[m]	$C_{10}H_{18}N_2S$	A	86	72–73	14.13	13.83	
$C_6H_5CH_2CH_2$	$C_{11}H_{12}N_2S$	A	80	166–167	13.72	14.00	

[a] Where two figures are given the yields are for methods A and B, respectively. [b] Melting points are not corrected. [c] See Ref. 5a. [d] Calcd.: S, 32.02. Found: S, 32.03. [e] See ref. 5b. [f] Allyl. After recrystallization from water this compound was white but upon exposure to air it gradually decomposed turning dark red. [g] Calcd.: S, 22.54. Found: S, 23.09. [h] This compound was isolated as the monohydrochloride by addition of one equivalent of hydrochloric acid to the reaction mixture followed by evaporation to dryness and extraction of the residue with hot absolute alcohol. It was recrystallized from absolute alcohol. [i] 2-Pyridyl. Isolated as the dihydrochloride. [j] Cyclohexyl. [k] S, 17.69. Found: S, 17.80. [l] See Jones, THIS JOURNAL, **71**, 383 (1949). [m] 2-Heptyl.

TABLE II

N-SUBSTITUTED AMINOACETALS, $RHNCH_2CH(OC_2H_5)_2$

R	Empirical formula	Yield, %	B. p., °C.	Mm.	$n^{25}D$	d^{25}_{25}	Nitrogen, % Calcd.	Found
CH_3[a]	$C_7H_{17}NO_2$	65	164–166	750				
C_2H_5	$C_8H_{19}NO_2$	55	71–73	16	1.4857	0.8792	8.69	8.74
C_3H_5[b]	$C_9H_{19}NO_2$	81	195–200	750				
n-C_3H_7[b]	$C_9H_{21}NO_2$	70	78–80	13				
n-C_4H_9[b]	$C_{10}H_{23}NO_2$	82	94–97	12				
i-C_4H_9	$C_{10}H_{23}NO_2$	59	85–87	12	1.4195	.8922	7.40	7.84
s-C_4H_9	$C_{10}H_{23}NO_2$	72	86–87	12	1.4224	.8687	7.40	7.54
t-C_4H_9	$C_{10}H_{23}NO_2$	90	190	750	1.4135	.8631	7.40	7.48
$(CH_3)_2NCH_2CH_2$	$C_{10}H_{24}N_2O_2$	70	104–106	12	1.4304	.8921	13.71	13.66
2-C_5H_4N[c]	$C_{11}H_{18}N_2O_2$	52	115–118	0.6	1.5123	1.043	13.32	13.20
C_6H_5[d]	$C_{12}H_{19}NO_2$	66	108–110	0.4				
$C_6H_5CH_2$[e]	$C_{13}H_{21}NO_2$	82	162–164	20				
$C_5H_{11}CH(CH_3)$[f]	$C_{13}H_{29}NO_2$	74	125–127	10	1.4265	0.8582	6.06	5.79
$C_6H_5CH_2CH_2$	$C_{14}H_{23}NO_2$	60	142–145	3	1.4122	0.9565	5.90	6.12

[a] See ref. 11. [b] See ref. 12. [c] 2-Pyridyl. [d] See ref. 13a. [e] See ref. 13b. [f] 2-Heptyl.

a paper by Jackman and others[9] appeared describing the synthesis and antithyroid activity of an additional number of 2-mercapto-4(or 5)-substituted-imidazoles.

The 1-substituted-2-mercapto-5-imidazole carboxylic acids of Table III (Experimental) and their methyl or ethyl esters[10] were tested and found to have no antithyroid activity.

(9) Jackman, Klenk, Fishburn, Tullar and Archer, THIS JOURNAL, **70**, 2884 (1948).

(10) Jones, *ibid.*, **71**, 644 (1949).

Acknowledgment.—The authors are grateful to Drs. Ewald Rohrmann, K. K. Chen and D. C. Hines for advice and to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses.

Experimental

N-Substituted Aminoacetals.—The preparation of the compounds presented in Table II consisted of heating diethyl chloro- or bromoacetal with an excess of the appropriate primary amine as de-

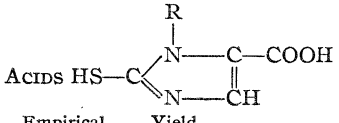
scribed by Knorr,[11] Paal and Gember[12] and others.[13] The following is a description of a typical experiment.

In a pressure vessel (autoclave or sealed tube) was placed 60 g. (0.3 mole) of bromoacetal and 88 g. (1.0 mole) of N,N-dimethylethylenediamine,[14] and the mixture was heated at 120° for sixteen hours. The product was removed from the reaction vessel, shaken with 100 ml. of 50% aqueous potassium hydroxide, and the organic layer was dried with potassium carbonate. Distillation of this liquid gave 35 g. of unreacted N,N-dimethylethylenediamine and 42 g. of dimethylaminoethylaminoacetal, b. p. 104–106° (12 mm.). The sample for analysis distilled at 105° (12 mm.).

1-Substituted-2-mercapto-5-imidazolecarboxylic Acids.—These acids, presented in Table III, were obtained by saponification of the corresponding methyl or ethyl esters[10] as has been described previously.[10]

TABLE III

1-SUBSTITUTED-2-MERCAPTO-5-IMIDAZOLECARBOXYLIC ACIDS



R	Empirical formula	Yield, %	M. p. °C.[a]	Nitrogen, % Calcd.	Found
H	$C_4H_4N_2O_2S$	96	235–236	19.43	19.43
i-C_3H_7	$C_7H_{10}N_2O_2S$	97	203–204	15.40	14.76
C_6H_{11}[b]	$C_{10}H_{14}N_2O_2S$	98	203–204	12.38	12.00
$C_6H_5CH_2$	$C_{11}H_{10}N_2O_2S$	97	221–222	11.96	11.69

[a] Melting points dec. are not corrected. [b] Cyclohexyl.

1-Substituted-2-mercaptoimidazoles. A. From Substituted Aminoacetals and Thiocyanic Acid.—The following example is illustrative of method A used for preparing the compounds of Table I.

To a solution of 19 g. (0.1 mole) of N-*n*-butylaminoacetal in 100 ml. of alcohol was added 12 g. (0.12 mole) of potassium thiocyanate and 55 ml. (0.11 mole) of 2 *N* hydrochloric acid. The mixture was heated on the steam-bath overnight and then evaporated to dryness *in vacuo*. The residue was extracted with hot acetone which, after evaporation, left the crude 1-*n*-butyl-2-mercaptoimidazole.

The crude products were purified in a number of ways. Those which were not too soluble in water, including the butyl and higher homologs, were taken up in dilute aqueous sodium hydroxide. The solution was treated with carbon, filtered and acidified to precipitate the product. Acetone, ethyl acetate or mixtures of one of these with petroleum ether were good solvents for recrystallizing the compounds.

B. Decarboxylation of 1-Substituted-2-mercapto-5-imidazolecarboxylic Acids.—Method B for the preparation of compounds in Table I is illustrated by the following typical experiment.

In a two-liter round-bottom flask was placed 300 g. of 2-mercapto-4(or 5)-imidazolecarboxylic acid. This was heated with a soft flame and stirred with a glass rod until all had melted and foaming had stopped. The melt was cooled under nitrogen or carbon dioxide and the solid was taken up in 2.5 l. of boiling absolute alcohol. The alcohol solution was boiled with a liberal quantity of decolorizing carbon, filtered, evaporated almost to dryness *in vacuo*, and 1 l. of petroleum ether was added to the residue. The white crystalline solid was collected on a filter and air-dried. It was analytically pure.

α-Bromobutyraldehydediethylacetal.—The method described by Kuhn and Grundmann[15] for the preparation of α-bromo-*n*-valeraldehydediethylacetal was employed using freshly distilled *n*-butyraldehyde. The product was obtained in 58% yield; b. p. 88–91° (21 mm.).

Anal. Calcd. for $C_8H_{17}BrO_2$: Br, 35.50. Found: Br, 35.59.

α-Aminobutyraldehydediethylacetal.—α-Bromobutyraldehydediethylacetal, 200 g., was mixed with 100 ml. of methanol in a 1-l. high pressure autoclave, and the bomb was cooled in Dry Ice–methanol. About 450 ml. of liquid ammonia was then added, and the bomb was closed. The reaction mixture was heated for seven hours at 120–130°. After the autoclave had been opened the ammonia was allowed to evaporate, and the methanol was distilled *in vacuo*. The mixture was diluted with ether, and a concentrated aqueous solution containing 70 g. of potassium hydroxide was added slowly with stirring. The ether solution was decanted, and the remaining sludge was extracted twice with ether. The extracts (600 ml.) were dried over potassium hydroxide, and the ether was evaporated. The residue was distilled *in vacuo;* b. p. 79–84° (24 mm.); yield, 98 g. (68%).

Anal. Calcd. for $C_8H_{19}NO_2$: N, 8.69. Found: N, 8.47.

2-Mercapto-4(5)-ethylimidazole.—This was prepared from butyraldehydediethylacetal and thiocyanate as described above. The yield was 38 g. (84%), and the product was recrystallized from either dilute ethanol or water; m. p. 165–167°.

Anal. Calcd. for $C_5H_8N_2S$: N, 21.86. Found: N, 21.26.

α-Methylaminobutyraldehydediethylacetal.—α-Bromobutyraldehydediethylacetal, 341 g., was charged into a cold 1-l. autoclave with 450 ml. of liquid methylamine, and the mixture was heated for seventeen hours at 115°. The product was isolated as described above for the amino homolog; b. p. 85–90° (25 mm.); yield, 189 g. (71%). The acetal contained a trace of the bromide starting material which was not removed by fractionation; however, it was adequately pure for conversion to the mercaptoimidazole.

2-Mercapto-1-methyl-5-ethylimidazole.—This compound was prepared as described above for the other 2-mercaptoimidazoles. The yield was 71%; m. p. 208–210°.

Anal. Calcd. for $C_6H_{10}N_2S$: N, 19.70. Found: N, 19.01.

Summary

A series of 1-substituted-2-mercaptoimidazoles has been synthesized, and some of the compounds have been tested for antithyroid activity in rats.

INDIANAPOLIS, INDIANA RECEIVED JUNE 9, 1949

(11) Knorr, *Ber.*, **32**, 729 (1899).

(12) Paal and Gember, *Arch. Pharm.*, **246**, 306 (1905).

(13) (a) Wohl and Lange, *Ber.*, **40**, 4727 (1907); (b) Rügheimer and Schön, *ibid.*, **41**, 17 (1908).

(14) Turner, THIS JOURNAL, **68**, 1607 (1946).

(15) Kuhn and Grundmann, *Ber.*, **70**, 1894 (1937).

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Hantzsch's Pyridine Synthesis

BY ARTHUR P. PHILLIPS

The Hantzsch pyridine synthesis[1] has been run using cinchoninaldehyde,[2] *m*-nitrobenzaldehyde, *p*-dimethylamino- and *p*-diethylaminobenzaldehydes as the aromatic aldehydic reactants, and with a variety of alkyl acetoacetates as the ester components. The first products obtained by this synthesis were all of the normal dihydropyridine type, and manifested weak analgesic and curare-like activities in laboratory animals.

A series of quaternary salts has been prepared from each of the original basic Hantzsch products (including the *m*-aminophenyl ones obtained by reduction of the *m*-nitrophenyl derivatives) by the addition of alkyl halides to the quinoline (or aminophenyl) nitrogen, (the dihydropyridine nitrogen being relatively non-basic[1,3]) hoping in this way to attain products with increased water solubility and enhanced curariform activity. The correlation of curare-like activity with quaternary ammonium salt structure represents one of the oldest and best examples of a relationship between chemical constitution and physiological action.

Many of the quaternary ammonium iodides were very sparingly soluble in water and some of the more active substances were converted to different salts, chlorides and ethanesulfonates, by reaction with the appropriate silver salts. The chlorides so obtained were not significantly more soluble in water than the iodides, but the ethanesulfonates were very readily soluble.

The chlorides, obtained from analytically pure iodides with silver chloride, after careful purification by repeated recrystallizations gave consistently low analyses for carbon, though the hydrogen, nitrogen and chloride results agreed well with the calculated figures.

Attempts at catalytic hydrogenations of I, Table I, with the object of reducing the dihydropyridine ring to a piperidine ring, using either palladium charcoal or Adams catalyst and hydrogen at three atm. overpressure, and temperatures from 30–70°, gave back only the unchanged starting material.

The pronounced steric hindrance to be expected in the quinoline dihydropyridine I, Table I, was confirmed by the almost complete lack of hydrolysis of the carbethoxy groups during prolonged refluxing with either aqueous or alcoholic alkali. Furthermore, treatment of the diethyl ester, I, Table I, with excess methanol containing hydrogen chloride gave no evidence of ester interchange. Resistance to saponification in this type of compound was reported by Hantzsch[1] in his original studies, and is surprising only because the true pyridine derivatives, resulting on mild oxidation of the dihydropyridines, are smoothly saponified by alcoholic alkali, even though steric effects of a similar order of magnitude should prevail here, too.

It is felt that the physiological activity observed in this series may be related to the particular steric structure involved here. Because of the saturated nature of the 4-carbon of the dihydropyridine ring to which the quinoline ring is attached the quinoline and dihydropyridine rings will be non-coaxial. Because of the substitution *ortho* to the 4-position of the pyridine ring of quinoline and the *di-ortho* substitution with respect to the 4-position of the dihydropyridine nucleus (by carbethoxy groups buttressed by methyl groups) free rotation about the quinoline-dihydropyridine juncture would be restricted to a marked degree (as in various *ortho*-substituted biphenyls) and the two rings would be distorted still further from anything approaching coplanarity by rotation of one ring about its not quite coaxial axis to the extent of approximately 90°. This property of non-coplanarity of rings is a feature held in common with morphine.

The *m*-nitrophenyl derivatives were reduced rapidly by Adams catalyst and hydrogen to the free primary aminophenyl compounds. The aminophenyldihydropyridines on treatment with excess alkyl iodide (methyl or ethyl) in the presence of potassium carbonate, to neutralize the hydrogen iodide formed, gave in nearly all cases the quaternary ammonium salt directly. In one case alkylation of the aminophenyl with ethyl iodide gave as the principal product the tertiary amine, the diethylaminophenyl compound VIII, Table II, which was then purified and subsequently converted to quaternary salts IX and XI, Table II, with methyl iodide and ethyl iodide in separate experiments.

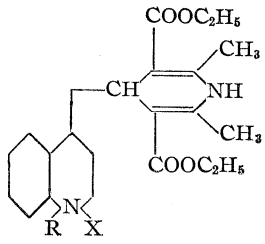
The aminophenyl dihydropyridine V, Table II (R = C_2H_5) when heated for some time with acetonylacetone gave the 4-(3′-(2″,5″-dimethylpyrryl-1″)-phenyl) dihydropyridine XII, Table II.

Reaction of the *p*-dimethylaminophenyl compounds with a series of alkyl (methyl through *n*-butyl) iodides gave excellent yields of the corresponding quaternary salts. With the *p*-diethylaminophenyl series, as might be expected, the alkyl iodides above methyl iodide reacted very much more slowly, if at all, because of enhanced steric hindrance. Yields with these higher iodides were usually much poorer and in certain

(1) Hantzsch, *Ann.*, **215**, 1 (1882), and many papers thereafter.
(2) (a) Phillips and Randall, U. S. Patent 2,359,329; (b) Heilbron, *et al.*, *J. Chem. Soc.*, 413 (1943).
(3) Hantzsch, *Ber.*, **18**, 2579 (1885).

TABLE I

COMPOUNDS DERIVED FROM THE HANTZSCH PYRIDINE SYNTHESIS USING CINCHONINALDEHYDE



Compd.	R X	Yield, %	M. p., °C.[a]	Crystn. solvent[b]	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	None	60	203–204	A	69.47	6.37	69.44	6.65
II	HCl	60	273	A	63.31	6.04	63.47	6.29
III	None[c]	100	122–123	H	69.86	5.86	69.86	5.87
IV	None[d]	65	234–235	Æ. H	68.14	5.74	68.13	5.79
V	CH_3I	92	248–249	M. E.	52.85	5.21	52.75	5.12
VI	C_2H_5I	71	248–250 (dec.)	M. E.	53.71[e]	5.45	53.42	5.46
VII	$C_6H_5CH_2Cl$	77	245	M. E.	63.68	6.18	68.30	5.98
VIII	$C_6H_5CH_2OSO_2C_2H_5 \cdot H_2O$	93	155–156	AqAcE	62.18	6.40	62.90	6.44
IX	$BrCH_2COOC_2H_5$	73	206–207	A. E.	57.01	5.70	57.19	5.78

[a] All melting points are uncorrected. [b] A = ethanol; Æ = ethyl acetate; Aq = water; Ac = acetone; E = ether; H = hexane; M = methanol. [c] True pyridine structure obtained by nitric oxidation of I. [d] Dimethyl ester. [e] Calcd.: I, 23.69. Found: I, 23.68.

cases some side-product of the original tertiary amine hydroiodide resulted.

Curare-like action seems to be enhanced, within these series, by accumulation of large alkyl groups both on the quaternary nitrogen and in the ester positions. Interest in these types of compounds has diminished with the noting of undesirable side effects during clinical trials, and with the advent of new and more potent drugs in the fields for which these were being evaluated.

Experimental

Most of these compounds were made by more or less uniform procedures. Thus experimental details are supplied for only one representative of a particular type of compound, while pertinent data for all are included in Tables I–III.

Part I (Table I)

Preparation of the Dihydropyridine, I.—(A) One mol of cinchoninaldehyde and two mols of acetoacetic ester were dissolved in an equal volume of ethyl alcohol. Two mols of concentrated aqueous ammonia were added and the mixture was heated for two hours on the steam-bath. Cooling of the reaction mixture gave I, yield 60%. (B) Alternatively two mols of β-aminocrotonic ester could be used in place of the acetoacetic ester and ammonia of (A); or (C). One mol of acetoacetic ester and one mol of β-aminocrotonic ester could be used with the cinchoninaldehyde. Yields by routes (B) or (C) were never as good as by route (A).

Oxidation of I to the True Pyridine, III.—One mol of I warmed with an excess of 3–6 *N* nitric acid gave a rapid solution of the originally suspended solid accompanied by evolution of oxides of nitrogen. When reaction was complete, in less than an hour, the mixture was cooled and basified with aqueous alkali precipitating the base III in quantitative yield.

Preparation of the Quaternary Salts.—In general one mol of I was dissolved in a little ethanol and heated several hours in presence of excess of the alkyl halide. Finally, the mixture was cooled and the product precipitated with ethyl acetate or ether.

Details concerning individual compounds are included in Table I.

Part II (Table II)

Preparation of the *m*-Nitrophenyl Compound, XIII.—A mixture of 16 g. of *m*-nitrobenzaldehyde, 34 cc. of *n*-butyl acetoacetate, 60 cc. of ethanol, and 10 cc. of concentrated aqueous ammonia was heated for three hours on the steam-bath, allowing alcohol to evaporate. Chilling and scratching converted the originally viscous oil to yellow crystals, yield 29 g. (68%). After recrystallization from benzene–hexane the yellow needles melted at 109–110°.

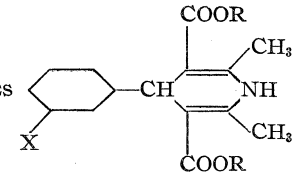
Hydrogenation of the Nitrophenyl Compound, XIII, to the Amino Compound, XIV.—A suspension of 8 g. of the nitro compound XIII in 50 cc. of methanol was hydrogenated in the presence of platinic oxide at room temperature and one to three atmospheres of hydrogen overpressure. Reduction was rapid, and the calculated amount of hydrogen was absorbed within an hour. After removal of the platinum by filtration, the methanol was evaporated to a small volume. All attempts to obtain this particular aminophenyl derivative crystalline, either as the base, the hydrochloride, oxalate or picrate failed. Thus it never was analyzed or characterized as such, but samples of the viscous, oily base were used directly for alkylations. Alkylations with methyl or ethyl iodides gave essentially quantitative yields of the corresponding quaternary ammonium salts, verifying in this way both the purity and identity of the otherwise uncharacterized oil.

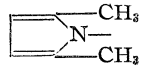
Preparation of the Quaternary Salt, XV, from XIV.—A sample of unpurified base XIV from the preceding experiment, 6 g., dissolved in 100 cc. of benzene, plus 10 cc. of methyl iodide was combined with a concentrated solution of 15 g. of potassium carbonate in 40 cc. of water. The mixture was refluxed on a steam-bath for ten hours. A third oily layer formed, during the reaction, insoluble in either benzene or the carbonate solution. Cooling and scratching converted this oily precipitate to a mass of white crystals; yield 8.3 g. (95%). After washing with water and recrystallization from methanol–ether these crystals melted at 178–179°.

Preparation of the *m*-Pyrrylphenyl Compound, XII.—A mixture of 3.3 g. of the aminophenyldihydropyridine V, 1.3 g. of acetonylacetone and 20 cc. of ethanol was heated

TABLE II

m-SUBSTITUTED PHENYL DIHYDROPYRIDINES



Compd.	X	Yield, %	M. p., °C.[a]	Crystn. solvent[b]	Analyses, % Calcd. C	Calcd. H	Found C	Found H
			A, Methyl esters, R = CH_3					
I	NO_2–	75	209–210	M	58.94	5.23	59.06	5.04
II	NH_2–	90	218–219	M. B. H.	64.52	6.39	64.53	6.67
III	$(CH_3)_3NI$–	83	205–208	M. E.	49.36	5.59	49.56	5.80
					I, 26.12		26.01	
			B, Ethyl esters, R = C_2H_5					
IV	NO_2–[c]	86	164–165	A. Aq				
V	NH_2–	98	151–153	A. Aq	66.28	7.03	66.22	7.38
VI	$(CH_3)_3NI$–	90	173–174	A. E.	51.36	6.08	51.26	6.36
VII	$(CH_3)_3NCl$–[d]	95	186–187	M. E.	62.44	7.39	61.80	7.23
					Cl, 8.40	N, 6.62	8.31	6.60
VIII	$(C_2H_5)_2N$–	54	162–163	M	69.00	8.06	69.12	7.82
IX	$(C_2H_5)_2(CH_3)NI$–	90	165–166	A. E.	53.11	6.51	53.33	6.52
X	$(C_2H_5)_2(CH_3)N$–$OSO_2C_2H_5$–[d]	80	164–165	A. E.	59.51	7.69	59.51	7.41
XI	$(C_2H_5)_3NI$–	50	162–163	Aq	53.93	6.71	53.80	6.52
				A. E.	I, 22.83		22.85	
XII		60	164–165	A	71.06	7.15	71.34	7.05
			C, Butyl esters, R = C_4H_9-*n*					
XIII	NO_2–	68	109–110	B. H.	64.16	7.02	63.85	6.98
XIV	NH_2–[e]	95						
XV	$(CH_3)_3NI$–	95	178–179	M. E.	54.71	6.89	54.73	6.76
XVI	$(CH_3)_3$–N–$OSO_2C_2H_5$–[d]	90	Gray crystals, oils out, no analysis					
XVII	$(C_2H_5)_3$–NI–	65	182–183	A. E.	56.83	7.41	56.74	7.30
XVIII	$(C_2H_5)_3$–N–$OSO_2C_2H_5$–[d]	100	125–126	Ac. E.	62.58	8.48	62.44	8.48

[a] All melting points are uncorrected. [b] A = ethanol; Ac = acetone; Aq = water; B = benzene; E = ether; H = Skelly B; M = methanol. [c] Known compound; Lepetit, *Ber.*, **20**, 1338 (1887); German Patent 42,295, *Friedl.*, **1**, 195. [d] This salt obtained from the iodide and the appropriate silver salt as described in Part II (see ref. 1). [e] Not analyzed; see experimental part for details.

for sixteen hours on the steam-bath, allowing solvent to evaporate. The crystalline residue after recrystallization from ethanol gave 2.5 g. (60%) of white crystals melting at 164–165°.

Other experimental details are to be found in Table II.

Part III (Table III)

Preparation of 2,6-Dimethyl-3,5-dicarbomethoxy-4-(4′-dimethylaminophenyl)-1,4-dihydropyridine (Compound II, Table III).—A mixture of 30 g. (1 mol) of *p*-dimethylaminobenzaldehyde, 50 g. (2.2 mols) of methyl acetoacetate, 20 cc. (excess) of concentrated aqueous ammonium hydroxide, and 60 cc. of methanol was allowed to stand one hour at room temperature. Next in a closed bottle, wired tight, the reaction mixture was heated for seven hours in a steam-bath. After cooling, scratching gave a yellow crystalline product. The yield was 30 g. (43%) of yellow crystals from methanol, m. p. 193–194°. Evaporation of the methanol mother liquors gave 12 g. more of product melting at 192°; total yield 42 g. (61%).

Preparation of the *n*-Butyl Iodide Adduct of II (Compound VI).—A suspension of 6 g. of the above tertiary base (II) in 10 cc. of methanol and 6 cc. of *n*-butyl iodide was refluxed on a steam-bath for sixty-four hours. The crystalline product, 10 g. (100%), was precipitated from the reaction mixture by addition of excess ether, and scratching to induce crystallization. After recrystallization from methanol–ether mixtures it melted at 186–187°.

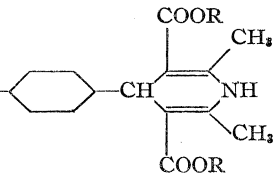
Preparation of the Chloride, VII, from the Iodide, VI.—A solution of 4 g. of the iodide (VI) in 200 cc. of methanol was digested for two hours on a steam-bath with 6 g. of freshly prepared silver chloride (washed well previously first with water, then with methanol). The mixture of insoluble silver chloride and silver iodide was then filtered off and the clear methanol filtrate was concentrated to about 20 cc. Addition of excess ether, with scratching, gave a white crystalline precipitate, 3 g. (94%) which after recrystallization from methanol–ether melted at 198–199°.

Preparation of the Ethanesulfonate, XXI, from the Iodide, XX.—Exactly equimolecular quantities of the quaternary iodide (XX) and silver ethanesulfonate were dissolved separately in methanol and the clear solutions were mixed. After digesting the mixture for about an hour on the steam-bath the precipitated silver iodide was removed by filtration and the clear filtrate was concentrated by evaporation. The quaternary ethanesulfonate was recovered by precipitation with ether, and was purified by recrystallization from ethanol–ether.

Preparation of the Oxidized, True Pyridine Compound, XIX.—The dihydropyridine quaternary salt, compound XVIII, 1.5 g. was heated for one hour on the steam-bath with 8 *N* nitric acid. Copious fumes of oxides of nitrogen

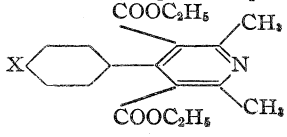
TABLE III

p-AMINOPHENYLDIHYDROPYRIDINES



Compd.	X	Yield, %	M. p., °C.[a]	Crystn. solvent[b]	Analyses, % Calcd. C	Calcd. H	Found C	Found H
			A, Methyl esters, R = CH_3					
I	H–	63	197–198	M	67.73	6.37	67.90	6.27
II	$(CH_3)_2N$–	61	193–194	B. H. or M. Aq.	66.24	7.03	66.11	6.89
III	$(CH_3)_3$–NI–	95	Starts 172–173	M. E.	49.36	5.59	48.75	5.82
			Final 202–203		I, 26.12	N, 5.76	26.03	5.55
IV	$(CH_3)_2(C_2H_5)$NI–	100	194–195	M. E.	50.38	5.84	50.10	5.70
					I, 25.39	N, 5.60	25.39	5.47
V	$(CH_3)_2(n\text{-}C_3H_7)$–NI–	100	196–197	M. E.	51.36	6.08	51.23	5.92
					I, 24.70		24.61	
VI	$(CH_3)_2(n\text{-}C_4H_9)$–NI–	100	186–187	M. E.	52.24	6.30	52.17	6.05
VII	$(CH_3)_2(n\text{-}C_4H_9)$–NCl–	94	198–199	M. E.	Cl, 8.13	N, 6.41	7.94	6.44
VIII	$(C_2H_5)_2N$–	53	209–210	M	67.71	7.58	67.94	7.29
IX	$(C_2H_5)_2(H)$NI–	40[c]	240–241	M	50.38	5.82	50.29	5.79
X	$(C_2H_5)_2(CH_3)$–NI–	100	193–194	M. E.	51.36	6.08	51.44	6.11
					I, 24.70		24.67	
XI	$(C_2H_5)_2(CH_3)$–NCl–	93	210–211	M. E. or Aq.	Cl, 8.40	N, 6.62	7.99	6.47
XII	$(C_2H_5)_3$NI–	60	235 (dec.)	M	52.24	6.30	51.61	6.08
					I, 24.04		23.92	
XIII	$(C_2H_5)_2(n\text{-}C_3H_7)$NI–	50[c]	167–168	M. E.	I, 23.42		23.25	
			B, Ethyl esters, R = C_2H_5					
XIV	$(CH_3)_2$–N–[d]	53	158.5–159.5	M				
XV	$(CH_3)_2(H)$NCl[e]	85	204–205	M. E.	61.66	7.14	61.21	7.01
					N, 6.85		6.68	
XVI	$(CH_3)_3$–NI–[f]	100	174–175	M. Æ. E.	51.36	6.08	51.61	6.01
				A. E.				
XVII	$(CH_3)_2(C_2H_5)$NI–	95	166–167	M. E.	I, 24.04		23.95	
XVIII	$(CH_3)_2(n\text{-}C_3H_7)$NI–	90	182–183	M. E.	53.11	6.51	53.08	6.52
					I, 23.42		23.54	
XIX	$(CH_3)_2(n\text{-}C_3H_7)$NI[g]	80	177–178	A. E.	53.30	6.16	53.73	6.03
XX	$(CH_3)_2(n\text{-}C_4H_9)$NI–	72	174–175	M. E.	53.93	6.71	53.70	6.35
					I, 22.83		22.80	
XXI	$(CH_3)_2(n\text{-}C_4H_9)$N–$C_2H_5SO_2O$–	60	205–210	A. E.	60.19	7.86	60.59	7.88
XXII	$(C_2H_5)_2N$–	50	158–159	M. Aq.	68.95	8.07	68.96	7.92
XXIII	$(C_2H_5)_2(CH_3)$NI–	100	127–128	M. Æ. E.	53.11	6.51	53.46	6.44
XXIV	$(C_2H_5)_3$NI–	93	174–175	M. Æ. E.	53.93	6.71	53.56	6.80

[a] All melting points are uncorrected. [b] A = ethanol; Æ = ethyl acetate; Aq = water; B = benzene; E = ether; H = Skelly B; M = methanol. [c] Based on tertiary amine used; recovered 75% of unused tertiary amine [d] Known, compound; see ref. 3 of text. [e] Isolated from the reaction of compound XIV with benzyl chloride. Hinkel and Cremer, reference 3, report m. p. 201° for this. [f] Hinkel and Cremer report m. p. 182–183°. [g] True pyridine structure



were evolved, and free iodine was liberated and steam distilled or sublimed out of the reaction mixture. The product, presumably the quaternary nitrate of the true pyridine structure, was isolated by reconversion to the iodide. The aqueous acid reaction mixture was basified to *p*H 8 with 40% aqueous potassium hydroxide, and 4 g. of potassium iodide was added precipitating the quaternary iodide. After purification by crystallization from water, then from ethanol–ether the yield of white crystals was 1.2 g. (80%), m. p. 177–178°.

The success of this nitric acid oxidation of the dihydro to the true pyridine structure gives evidence of stabilization of the molecule in the quaternary salt from. Hinkel and Cremer[4] reported that the tertiary amino derivative, compound XIV, could not be oxidized by nitrous fumes to the corresponding tertiary aminophenyl true pyridine, for under these conditions they observed decomposition of the molecule to form *p*-nitrosodimethylaniline nitrate.

(4) Hinkel and Cremer, *J. Chem. Soc.*, **117**, 137 (1920).

Acknowledgment.—The author is indebted to Mr. Samuel W. Blackman for the microanalytical results reported here.

Summary

A series of quaternary ammonium salts has been made for examination as potential curare substitutes. These were all derived from the Hantzsch pyridine synthesis employing aromatic aldehydes containing basic salt-forming groups or containing other substituents readily convertible to salt-forming groups.

TUCKAHOE 7, NEW YORK RECEIVED MAY 16, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

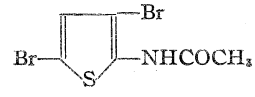
The 2-Aminothiazoles

BY CHARLES D. HURD AND H. L. WEHRMEISTER[1]

Some relationships were developed in the thiophene series, in particular with aceto-2-thiophenamide (I) and its derivatives, which were of an unexpected nature.[2] The 3,5-dibromo derivative (II), for example, underwent nitration to yield the same 3,5-dinitro derivative that was obtained by nitration of I. This substitution



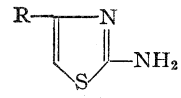
I



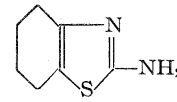
II

of bromine atoms by nitro groups is most unusual. Then again, II was found to couple readily with *p*-nitrobenzenediazonium chloride to form a dye with replacement of the 5-bromo group by azo. Coupling of I even occurred while the solution was strongly acidic. It is remarkable, as a matter of fact, that either I or II should yield azo dyes, since an amine group (not amide) is usually required to activate an aromatic molecule sufficiently for coupling.

The study of substitution reactions of amino and acetamido heterocyclic compounds now has been extended to the thiazoles. The 4-methyl- and 4-phenyl-2-aminothiazoles (III) were prepared by the reaction of thiourea with either the chloro ketone ($RCOCH_2Cl$) or with a mixture of the ketone ($RCOCH_3$) and iodine.[3] A similar procedure, using cyclohexanone, thiourea and iodine, was developed for the preparation of 2-amino-4,5,6,7-tetrahydrobenzothiazole (IV). The preparation of IV from 2-chlorocyclohexanone has been reported.[4]

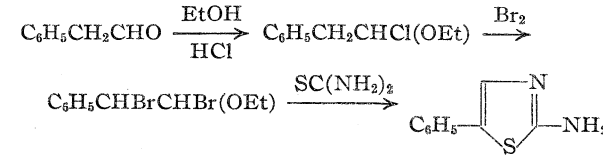


III



IV

5-Phenyl-2-aminothiazole was prepared from phenylacetaldehyde as outlined



The conventional procedure in the first step is to add the hydrogen chloride gas slowly with as little agitation as possible to avoid mixing of the water layer (formed in the reaction) with the organic layer. In the present work emulsions always were encountered, probably because of nearly identical densities of the two phases. Very dark products resulted. Some investigators[5] have designed special apparatus to perform this type of reaction so as to avoid the difficulty mentioned. In the present work, the addition of anhydrous sodium sulfate to the reaction mixture was found to be a simple solution to the problem. With this modification light colored products were obtained even when hydrogen chloride was introduced rapidly and with stirring.

Nitration of 2-acetamidothiazole is known[6] to yield 5-nitro-2-acetamidothiazole. The same compound was obtained in the present study by nitration of 5-bromo-2-acetamidothiazole, thus demonstrating that replacement of halogen does occur in the thiazole as in the thiophene series. Since the structure of the 5-bromo-2-acetamidothiazole is known,[7] the replacement reaction serves to establish the structure of the nitro compound as 5-nitro-2-acetamidothiazole.

Monomercuration of 2-acetamidothiazole occurred in position 5 with mercuric chloride in water, whereas 4,5-dimercuration took place with mercuric acetate in acetic acid. The position of the chloromercuri group in the first of these compounds (V) was established by cleavage with bromine to the known 5-bromo-2-acetamidothiazole. Conversion of V into 5-iodo-2-acetamidothiazole by reaction with iodine also proceeded

(1) University Fellow, 1946–1948. Present address, Commercial Solvents Corporation, Terre Haute, Indiana.

(2) Hurd and Priestley, THIS JOURNAL, **69**, 859, 1173 (1947).

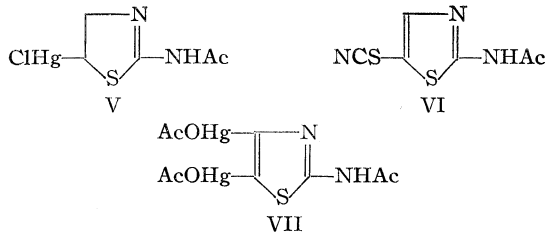
(3) Dodson and King, *ibid.*, **67**, 2242 (1945); **68**, 871 (1946).

(4) Erlenmeyer and Schoenauer, *Helv. Chim. Acta*, **24**, 172 (1941).

(5) Kok, Leendertse and Waterman, *Chem. Weekblad*, **37**, 579 (1940).

(6) Ganapathi and Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 343 (1945).

(7) Dahlbom and Ekstrand, *Svensk. Kem. Tids.*, **57**, 229 (1945).



readily.[8] Similar cleavage with thiocyanogen (sodium thiocyanate and bromine) yielded 5-thiocyanato-2-acetamidothiazole (VI). 4,5-Diiodo-2-acetamidothiazole was prepared from VII by use of iodine.

Direct thiocyanation of the 2-aminothiazoles (III, R = H, CH_3, or C_6H_5) or the corresponding acetamidothiazoles was readily achieved. Yields were highest for the 4-phenyl derivative.

That thiocyanation occurred in position 5 was established, since the compound from 2-acetamidothiazole was identical to that obtained from V. As might be expected, no product was obtained on attempted thiocyanation of 2-amino-4,5,6,7-tetrahydrobenzothiazole.

No sulfonate was obtained on oxidation of VI with either dilute nitric acid or hydrogen peroxide. Sulfate ion was identified.

Reduction of the thiocyanato group to the mercapto group (RSCN → RSH) was achieved by use of zinc and acetic acid, or of potassium sulfite. The melting point of the 5-mercapto-2-acetamidothiazole so produced differed from that reported by Faith[9] for the reduction product of the compound obtained by the action of chlorosulfonic acid on 2-acetamidothiazole. The assumption that this latter reaction yielded 2-acetamido-5-thiazolesulfonyl chloride evidently is not warranted. The similar reaction of chlorosulfonic acid with 4-methyl-2-acetamidothiazole is stated in one report[10] to yield N-acetyl-4-methyl-2-thiazolylsulfamyl chloride, while in another report[11] the product is described as 2-acetamido-4-methyl-5-thiazolesulfonyl chloride. The reported melting points are 156–157° and 159–160°, respectively. It seems possible that these two substances are identical and that the assignment of structure was in error in one of the papers. The assignment of a sulfamyl chloride was based on the hydrolysis of the compound to the known 4-methyl-2-thiazolylsulfamic acid. The assignment of the sulfonyl chloride structure was based on analogy with other electrophilic reactions (bromination, chlorination) and is probably in error.

Experimental

2-Amino-4,5,6,7-tetrahydrobenzothiazole (IV).—A mixture of 39 g. of cyclohexanone, 61 g. of thiourea and 102 g. of iodine was heated overnight at 100°, then dissolved in 200 ml. of hot water and filtered through Celite. The filter cake was rinsed with 100 ml. of boiling water. Chilling of the combined filtrates in an ice-bath yielded 63 g. of the hydroiodide of IV. Twenty grams of this salt was heated with 150 ml. of water and the mixture was filtered through Celite. The filtrate was cooled and 20 ml. of aqueous 28% ammonia was added. The precipitated solid, after recrystallization from ligroin, appeared as white needles, m. p. 90–90.5°. It was shown to be IV by analysis. The reported[4] m. p. is 87.5–88.5°.

Anal. Calcd. for $C_7H_{10}N_2S$: N, 18.2. Found: N, 18.2.

2-Acetamido-4,5,6,7-tetrahydrobenzothiazole.—Five grams of acetic anhydride and 1.7 g. of IV, after heating for twenty minutes at 100° and diluting with 50 ml. of water, yielded a solid of m. p. 141–142°. Repeated crystallization from ligroin yielded a product melting at 144.5–145°.

Anal. Calcd. for $C_9H_{12}N_2OS$: N, 14.27. Found: N, 14.28.

2-Phenyl-1-chloroethyl Ethyl Ether.—Dry hydrogen chloride (11.5 g.) was introduced rapidly into a chilled, stirred mixture of phenylacetaldehyde (32.5 g.), ethanol (12.5 g.) and anhydrous sodium sulfate (30 g.). The liquid product was decanted from the solid and calcium chloride (16 g.) was added. The mixture was then maintained at 20 mm. pressure for forty-five minutes to remove excess hydrogen chloride. The yield of crude chloro ether was 47 g., or 94%.

Bromination.—Thirty-five grams of the crude ether was cooled and stirred while 30.4 g. of bromine was added during twenty minutes. The yellow crystalline solid which formed was 2-phenyl-1,2-dibromoethyl ethyl ether.

5-Phenyl-2-aminothiazole.—The above yellow solid, stirred with 50 ml. of absolute alcohol, gradually dissolved to a homogeneous, dark green solution. A suspension of 14.5 g. of thiourea in 200 ml. of absolute alcohol containing 10.3 g. of sodium methoxide was then added. The mixture was stirred for two hours and set aside overnight. Most of the solvent was distilled off, it being replaced by 200 g. of water and 20 ml. of concd. hydrochloric acid. The mixture was heated. A green oily layer appeared which was separated and further removed by extraction with ether. The aqueous layer, containing the desired thiazole salt, was cooled in an ice-bath and 100 ml. of aqueous 28% ammonia was added. The precipitate was collected, washed with water and dried; yield, 9.5 g. This crude 5-phenyl-2-aminothiazole was recrystallized thrice from dilute alcohol to yield 6 to 7 g. of product of m. p. 207.5–208.5°.

Anal. Calcd. for $C_9H_8N_2S$: N, 15.9. Found: N, 15.4.

5-Phenyl-2-acetamidothiazole.—Acetylation of the amino compound with acetic anhydride produced the amide, m. p. 244–244.5° after crystallization from alcohol.

Anal. Calcd. for $C_{11}H_{10}N_2OS$: N, 12.8. Found: N, 12.6.

5-Nitro-2-acetamidothiazole.—2-Aminothiazole was brominated and acetylated, forming 5-bromo-2-acetamidothiazole.[7] A mixture of 1.2 ml. of red fuming nitric acid (sp. gr. 1.6) and 5 g. of acetic anhydride was added to a cold solution of 3.2 g. of 5-bromo-2-acetamidothiazole in 55 g. of glacial acetic acid. A 0.3-g. precipitate was separated after ten minutes. The yellow filtrate was evaporated to dryness, taken up in 100 ml. of hot absolute alcohol, decolorized (Norit), filtered and cooled to −10°. After several hours, 0.7 g. of solid was collected, m. p. 260–262°. Recrystallization from alcohol brought the m. p. to 264–265°. Halogen was absent by test.

Anal. Calcd. for $C_5H_5N_3O_3S$: C, 32.08; H, 2.69. Found: C, 32.13; H, 2.73.

5-Nitro-2-acetamidothiazole, m. p. 262–265°, was made for purposes of comparison, by nitration[6] of 2-acetamidothiazole. The mixed m. p. was 262–265°.

(8) The preparation of several monomercurated 2-acetamidothiazoles and their conversion to iodo compounds has been reported recently by Travagli, *Gazz. chim. ital.*, **78**, 592 (1948).

(9) Faith, THIS JOURNAL, **69**, 2063 (1947).

(10) Postovskiĭ and Belaya, *Compt. rend. acad. sci. U. R. S. S.*, **40**, 326 (1943); *C. A.*, **39**, 1152 (1945).

(11) Backer and Jonge, *Rec. trav. chim.*, **62**, 163 (1943).

2-Acetamido-5-thiazolemercuric Chloride[8] **(V).**—To a hot solution of 7.1 g. of 2-acetamidothiazole in 200 ml. of water there was added 250 ml. of an aqueous solution containing 16 g. of mercuric chloride and 32 g. of sodium acetate trihydrate. The mixture was boiled for fifteen minutes, cooled and filtered. The filter cake was washed with 100 ml. of water, 50 ml. of methanol and 50 ml. of ether; yield, 16.7 g. or 88%. The material did not melt below 300°.

Anal. Calcd. for $C_5H_5ClHgN_2OS$: N, 7.43. Found: N, 8.09.

5-Bromo-2-acetamidothiazole.—A mixture of 1 g. of V in 20 ml. of methanol saturated with sodium bromide was treated with 1 g. of bromine. After fifteen minutes some sodium sulfite was added and the mixture was heated to boiling and filtered. The filtrate was diluted with an equal volume of water and concentrated to about 5 ml. Water was added and the solid which separated was recrystallized from dilute acetic acid; yield, 0.24 g. (42%), m. p. 210–212°. Recrystallization from dilute acetic acid brought the m. p. up to 218–220°. A mixture of this product and an authentic sample of 5-bromo-2-acetamidothiazole, m. p. 225–226°, melted at 218–220°.

The authentic sample was prepared both by bromination of 2-aminothiazole[7] and of 2-acetamidothiazole.[12] The once recrystallized product melted at 218–220°. Reported melting points are 224–225°[7] and 229–231°.[12] Our samples melted at 225–226°.

2-Acetamido-4,5-thiazolebis-(mercuric Acetate) (VII).—Forty grams of mercuric acetate, 7.1 g. of 2-acetamidothiazole and 170 ml. of glacial acetic acid were heated together at 100° for eighteen hours. The hot mixture was filtered and the solid product was washed with acetic acid, water, methanol and acetone; yield 23.4 g. (74%). This material did not melt.

Anal. Calcd. for $C_9H_{10}Hg_2N_2O_5S$: N, 4.24. Found: N, 3.46.

5-Iodo-2-acetamidothiazole.—A mixture of 1 g. of V, 1.5 g. of potassium iodide, 10 g. of water and 0.5 g. of iodine was triturated and filtered. The solid was rinsed with water and treated with 30 ml. of alcohol. The mixture was filtered and the filtrate evaporated to 15 ml. On cooling, 0.4 g. (56% yield) of crystals separated; m. p. 210–212°. A constant melting point of 225–226° was achieved after five recrystallizations from dilute alcohol. The recorded m. p. for the 5-iodo-2-acetamidothiazole obtained[8] by a similar approach is 228°.

Anal. Calcd. for $C_5H_5IN_2OS$: C, 22.36; H, 1.88. Found: C, 22.42; H, 1.90.

2-Acetamido-5-thiocyanatothiazole (VI).—To a mixture of 1.2 g. of V and 0.65 g. of sodium thiocyanate in 20 ml. of acetic acid, there was added a solution of 0.58 g. of bromine in 10 ml. of acetic acid. After standing at room temperature overnight, the mixture was filtered and the solid was washed with 10 ml. of acetic acid. Approximately 35 ml. of water was added to the filtrate, and the mixture was evaporated to dryness. The solid residue was recrystallized from methanol. The product weighed 0.32 g. (50% yield) and melted at 195–198°. This material was twice recrystallized from methanol yielding 0.2 g. of a product melting at 212–214°. A mixture of this material and the product of direct thiocyanation of 2-acetamidothiazole melted at 212–214°.

2-Acetamido-4,5-diiodothiazole.—To 20.5 g. of VII there was added a solution of 15 g. of sodium chloride in 150 ml. of water. The stirred mixture was heated at 100° for five hours, cooled and filtered. The solid obtained was washed with 1 l. of water, 50 ml. of methanol and 50 ml. of acetone. The dried product weighed 18.5 g.

A mixture of 3.1 g. of this material, 7 g. of potassium iodide, 2.9 g. of iodine and 25 ml. of water was triturated for a few minutes. The solid obtained was washed with potassium iodide solution until free of iodine. This product was washed with water and dried; yield 1.6 g. A 1.2-g. portion of this material was heated with 60 ml. of 95% alcohol, decolorizing carbon was added, and the mixture was filtered through Celite. The filtrate was concentrated to 30 ml. and 20 ml. of water was added to yield a nearly saturated hot solution. On cooling, there was deposited 0.5 g. of crystalline material. This material decomposed at 222–232° when heated from 100°. When heated from 230°, the sample decomposed at 239–240°. The product was recrystallized from dilute alcohol yielding a sample which decomposed at 240° when inserted in an oil-bath at an initial temperature of 239°. Violet vapors were observed when the sample decomposed.

Anal. Calcd. for $C_5H_4I_2N_2OS$: C, 15.24; H, 1.02. Found: C, 15.20, 15.22; H, 1.08, 1.00.

5-Thiocyanato-4-phenyl-2-aminothiazole.—To a cooled (ice-bath) and stirred mixture of 2-amino-4-phenylthiazole (19 g.), sodium thiocyanate (27 g.) and methanol (100 ml.), there was added a solution of 17.3 g. of bromine in 25 ml. of methanol saturated with sodium bromide. The addition time was twelve minutes. After stirring the reaction mixture for two and one-quarter hours, it was poured onto 200 g. of crushed ice. Approximately 100 ml. of water was used to complete the transfer. A yellow solid was present. Twenty milliliters of concd. ammonium hydroxide was added and the solid was collected by suction filtration, washed with water and dried; weight 24.8 g., m. p. 168–173°.

A part of this product was dissolved in 550 ml. of boiling absolute alcohol to yield an almost saturated solution. The solution was cooled to room temperature and the precipitated solid was collected by filtration. The filtrate was used to dissolve a further portion of the product. This process was repeated a total of five times until all the material had been recrystallized. The recrystallized material weighed 19.5 g. (78% yield) and melted at 171–174°. A sample for analysis was recrystallized repeatedly from absolute alcohol to yield a product with a melting point of 186–187°.

Anal. Calcd. for $C_{10}H_7N_3S_2$: C, 51.48; H, 3.03. Found: C, 51.51; H, 3.11.

This identical procedure was used in the thiocyanation of the other 2-aminothiazoles and 2-acetamidothiazoles. Pertinent data are assembled in Table I. Yields refer to once-crystallized material. The m. p. listed in the table is for material which was crystallized two or more times to constancy. Crystallization was from ethanol, 2-propanol or benzene.

TABLE I

THIOCYANATION EXPERIMENTS

Compound formed: 5-thiocyanato deriv. of	Yield, %	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
2-Aminothiazole	32	142.5–143.5	$C_4H_3N_3S_2$	26.7	27.5
4-Methyl-2-aminothiazole	47	164.0–164.5	$C_5H_5N_3S_2$	24.5	24.5
4-Phenyl-2-acetamidothiazole	100	198–199	$C_{12}H_9N_3OS_2$	15.2	15.0
4-Methyl-2-acetamidothiazole	73	176–176.5	$C_7H_7N_3OS_2$	19.7	19.9
2-Acetamidothiazole	49	212–214	$C_5H_5N_3OS_2$	21.1	21.1

The acetylation of the thiocyanated 2-aminothiazoles with acetic anhydride gave the same products as were obtained by thiocyanation of the analogous 2-acetamidothiazoles. These acetamido compounds were soluble in alkali.

5-Mercapto-2-acetamidothiazole.—One and a half grams of zinc dust was added to a filtered solution of 2 g. of 5-thiocyanato-2-acetamidothiazole in 20–30 ml. of glacial acetic acid. The mixture was heated at 100° for an hour with stirring, then was cooled, poured into 100 ml. of water and evaporated to 40 ml. Then 100 ml. of glacial acetic acid and 20 ml. of water were added and the mixture was heated to 100° and filtered. The gray insoluble material was dissolved in 40 ml. of water and 10 ml. of concd. hydrochloric acid. After filtration, 40 ml. of concd. am-

(12) Backer and Buisman, *ibid.*, **63**, 226 (1944).

monium hydroxide was added to the filtrate. The initially-formed precipitate redissolved. After several hours 1.42 g. of solid separated. It was recrystallized from dilute acetic acid, using Norit, to yield 0.70 g. of 5-mercapto-2-acetamidothiazole, m. p. 255–257°. It decolorized iodine in warm acetic acid solution.

Anal. Calcd. for $C_5H_6N_2OS_2$: C, 34.46; H, 3.47; N, 16.08. Found: C, 34.61; H, 3.17; N, 16.11.

5-Mercapto-4-methyl-2-acetamidothiazole.—The synthesis was essentially by the above procedure. The yield of crude product was 1.15 g. from 2 g. It melted at 252–253° (dec.) after several crystallizations from acetic acid. It also decolorized iodine. Reduction with hot aqueous potassium sulfite also yielded the same product.

Anal. Calcd. for $C_6H_8N_2OS_2$: C, 38.07; H, 4.26. Found: C, 38.15; H, 3.94.

S-*p*-Chlorobenzylisothiuronium Sulfate.—This compound was obtained by adding an excess of an alcoholic solution of S-*p*-chlorobenzylisothiuronium chloride to aqueous sulfuric acid. The sulfate crystallized readily on cooling. It may be crystallized from water; m. p. 223–224° (dec.).

Anal. Calcd. for $C_{16}H_{20}Cl_2N_4O_4S_3$: N, 11.22. Found: N, 11.20.

Oxidation of the Thiocyanates to Sulfate Ion.—Heating of 2 g. of 5-thiocyanato-4-methyl-2-acetamidothiazole for one hour at 100° with 50 ml. of water and 10 ml. of concd. nitric acid produced a clear yellow solution. It was evaporated to dryness. A yellow oil remained. A test portion precipitated strongly with barium chloride solution. The bulk of the oil, dissolved in 15 ml. of water, was filtered and treated with 15 ml. of a 15% solution of S-*p*-chlorobenzylisothiuronium chloride in alcohol. There was formed 0.7 g. of S-*p*-chlorobenzylisothiuronium sulfate, m. p. 221–223°, or 223–224° after recrystallization from water. The mixed m. p. was also 223–224°.

Acknowledgments.—The several combustion analyses were performed by Misses J. Anderson, N. Mold, V. Hobbs and M. Hines.

Summary

Several 2-aminothiazoles and 2-acetamidothiazoles were prepared. Reactions of mercuration, halogenation, nitration and thiocyanation are reported. The bromine in 5-bromo-2-acetamidothiazole is replaced by nitro during nitration. Reduction of the 5-thiocyanato derivatives produces the 5-mercapto derivatives, but oxidation caused cleavage to sulfuric acid. S-*p*-Chlorobenzylisothiuronium sulfate is a new derivative of sulfuric acid.

EVANSTON, ILLINOIS RECEIVED JUNE 27, 1949

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Derivatives of Thianaphthene. III[1]

BY F. F. BLICKE AND DON G. SHEETS[2]

It was reported in a previous communication[3] that when thianaphthene-2-carboxylic, thianaphthene-2-acetic and thianaphthene-3-acetic acids were heated, in sodium carbonate solution, with Raney nickel for a short time, they were transformed into β-phenylpropionic (93%), γ-phenylbutyric (85%) and β-phenylbutyric acid (98%), respectively. These conversions offer simple, direct and conclusive proof of the structures of the original acids.

During this investigation we determined the suitability of this process for the determination of the structures of other derivatives of thianaphthene, thiophene and dibenzothiophene. The products obtained by the Raney nickel degradation are shown in Table I.

Compounds which contained a carboxyl group were dissolved in sodium carbonate solution, and then treated with Raney nickel. In other instances, methanol or ethanol was found to be a satisfactory solvent although methanol formed an azeotrope with one degradation product, namely, ethylbenzene.

The procedure was used to determine the structure of a product which had been obtained by Ancizar-Sordo and Bistrzycki[4] from the condensation of thianaphthene with benzilic acid. Although it might be expected that a 3-thianaphthenyl derivative would have been formed, at least one instance is known in which a substituent, other than a metal, entered the thianaphthene ring at the 2 position.[5] It was found that the condensation product was diphenyl-(3-thianaphthenyl)-acetic acid since, after degradation, α,α,β-triphenylbutyric acid was obtained.

From 3-hydroxythianaphthene (3-keto-2,3-dihydrothianaphthene) we expected to obtain either

TABLE I

DEGRADATION PRODUCTS OF DERIVATIVES OF THIANAPHTHENE, THIOPHENE AND DIBENZOTHIOPHENE

	Degradation product	Yield, %
Thianaphthene	Ethylbenzene	75.0
3-Hydroxythianaphthene	Ethylbenzene	86.0
Thianaphthene-3-carboxylic acid	α-Phenylpropionic acid	93.4
Diphenyl-(3-thianaphthenyl)-acetic acid	α,α,β-Triphenylbutyric acid	82.5
Thiophene-2-carboxylic acid	Valeric acid	70.0
2-Benzoylthiophene	Valerophenone	75.0
Dibenzothiophene	Biphenyl	97.5
Methylphenylcarbinol	Ethylbenzene	95.3
Acetophenone	Ethylbenzene	93.0

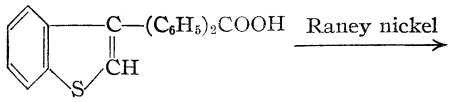
(1) This paper represents part of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Monsanto Chemical Company Fellow.

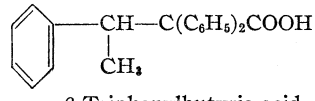
(3) Blicke and Sheets, THIS JOURNAL, **70**, 3768 (1948).

(4) Ancizar-Sordo and Bistrzycki, *Helv. Chim. Acta*, **14**, 141 (1931).

(5) Thianaphthene and phthalic anhydride condense, in the presence of aluminum chloride, to form 2-(*o*-carboxybenzyl)-thianaphthene (Mayer, Mombour, Lassmann, Werner, Landmann and Schneider, *Ann.*, **488**, 259 (1931)).



Diphenyl-(3-thianaphthenyl)-acetic acid



α,α,β-Triphenylbutyric acid

methylphenylcarbinol or acetophenone. The reaction product proved to be ethylbenzene. In separate experiments it was shown that, under the conditions employed, the carbinol, as well as the ketone, was converted into ethylbenzene. Mozingo, *et al.*,[6] found that benzaldehyde, under very similar experimental conditions, was reduced to toluene.

Experimental Part

Ethylbenzene from Thianaphthene, 3-Hydroxythianaphthene, Methylphenylcarbinol and Acetophenone.—A solution of 4.0 g. (0.03 mole) of thianaphthene in 250 cc. of methanol was refluxed for one-half hour with 45 g. of Raney nickel.[7] The cold mixture was filtered, and the catalyst washed with methanol. The filtrate and washings were diluted with 1.5 liters of water and extracted with three 100-cc. portions of chloroform. The chloroform extract was dried and fractionated. There was obtained 2.4 g. of ethylbenzene, b. p. 133–135°.[8]

The ethylbenzene was identified as *p*-ethylbenzenesulfonamide, m. p. and mixed m. p. 109°[9] after recrystallization from water.

Ethylbenzene was obtained from 3-hydroxythianaphthene, methylphenylcarbinol and acetophenone by the process described above, and, in each case, it was identified by the boiling point and by the melting point of the *p*-ethylbenzenesulfonamide. However, for the reduction of 0.04 mole of the carbinol and also of the ketone, only 35 g. of Raney nickel was used.

α-Phenylpropionic Acid from Thianaphthene-3-carboxylic Acid.—By the use of the procedure described previously[3] for the removal of sulfur from thianaphthene-2-carboxylic acid, 1.8 g. (0.01 mole) of thianaphthene-3-carboxylic acid was converted into 1.4 g. of α-phenylpropionic acid.

Anal. Calcd. for $C_9H_{10}O_2$: neut. equiv., 150.2. Found: neut. equiv., 150.0.

The amide, prepared by interaction of the acid chloride with ammonia water, melted at 91–92°[10] after recrystallization from dilute alcohol.

α,α,β-Triphenylbutyric Acid from Diphenyl-(3-thianaphthenyl)-acetic Acid.—By the use of the described procedure,[3] 3.4 g. (0.01 mole) of the diphenylthianaphthenylacetic acid, obtained by the method of Ancizar-Sordo and Bistrzycki,[4] and 40 g. of Raney nickel yielded 2.6 g. of α,α,β-triphenylbutyric acid, m. p. 157–158°[11] after recrystallization from petroleum ether (60–75°).

Anal. Calcd. for $C_{22}H_{20}O_2$: neut. equiv., 316.4. Found: neut. equiv., 315.1.

Valeric Acid from Thiophene-2-carboxylic Acid.—Subjected to the same process,[3] 2.6 g. (0.02 mole) of thiophene-2-carboxylic acid and 40 g. of Raney nickel yielded 1.4 g. of valeric acid, b. p. 180–186°.[12]

Anal. Calcd. for $C_5H_{10}O_2$: neut. equiv., 102.1. Found: neut. equiv., 104.0.

The *p*-bromoanilide, obtained from the acid chloride and *p*-bromoaniline, melted at 107–108°[13] after recrystallization from dilute alcohol; mixed m. p. 107–108°.

Valerophenone from 2-Benzoylthiophene.—A solution of 3.8 g. (0.02 mole) of 2-benzoylthiophene in 600 cc. of ethanol was refluxed for one-half hour with 40 g. of Raney nickel catalyst. The cold mixture was filtered, and the catalyst washed with ethanol. The filtrate and washings were fractionated. There was obtained 2.4 g. of valerophenone, b. p. 117–118° (10 mm.); semicarbazone, m. p. 165–166°[14] after recrystallization from dilute alcohol; 2,4-dinitrophenylhydrazone, m. p. 165–166°[15] after recrystallization from ethanol.

Biphenyl from Dibenzothiophene.—A mixture of 1.8 g. (0.01 mole) of dibenzothiophene, 500 cc. of ethanol and 35 g. of Raney nickel was refluxed for one-half hour. The mixture was cooled, filtered, and the catalyst washed with ethanol. The filtrate was concentrated to a volume of about 15 cc., and water was added until the solution became slightly turbid. Crystalline biphenyl (1.5 g.) separated from the cold solution; m. p. and mixed m. p. with an authentic sample 69–70°[16] after recrystallization from dilute alcohol.

Summary

It has been found that when thianaphthene, certain substituted thianaphthenes, dibenzothiophene and derivatives of thiophene are treated with Raney nickel, the nuclear sulfur atom is replaced by hydrogen, and a simple benzene derivative, which contains a saturated side chain, is formed. This process seems to represent a simple procedure for the determination of the structures of derivatives of these heterocycles.

ANN ARBOR, MICHIGAN RECEIVED JULY 11, 1949

(6) Mozingo, Spencer and Folkers, THIS JOURNAL, **66**, 1859 (1944).

(7) The catalyst was prepared by the process described by Mozingo, Wolf, Harris and Folkers (*ibid.*, **65**, 1013 (1943)).

(8) Perkin (*J. Chem. Soc.*, **69**, 1192 (1896)) reported 135.5°.

(9) Sempotowski (*Ber.*, **22**, 2664 (1889)) reported the same melting point. We found it advantageous to use chlorosulfonic acid for the preparation of the sulfonamide.

(10) Janssen (*Ann.*, **250**, 136 (1889)) reported the same melting point.

(11) Bergmann and Blum-Bergmann (*J. Chem. Soc.*, 727 (1938)) reported 158°. The isomeric α,α,γ-triphenylbutyric acid melts at 183.5–184° (Schlenk and Bergmann, *Ann.*, **479**, 86 (1930)).

(12) Lieben and Rossi (*ibid.*, **159**, 60 (1871)) found 184–185°.

(13) Robertson (*J. Chem. Soc.*, **115**, 1222 (1919)) reported 108°.

(14) Layroud (*Bull. soc. chim. France*, [3] **35**, 227 (1906)) found 166°.

(15) Evans (*J. Chem. Soc.*, 788 (1936)) reported 166°.

(16) Fittig (*Ann.*, **121**, 364 (1862)) found 70.5°.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF FREDERICK STEARNS AND COMPANY, DIVISION OF STERLING DRUG, INC.]

Alkamine Esters of Phenyl-2-thienylacetic Acid and Phenyl-2-thienylglycolic Acid[1]

BY R. F. FELDKAMP[2a] AND JOHN A. FAUST[2b]

A series of alkamine esters of substituted 2-thienylacetic acid and 2-thienylglycolic acid have been prepared by Blicke and Tsao[3] and the antispasmodic activity determined by Lands and co-workers.[3,4,5] This former study of basic alkyl esters included 2-thienyl, phenyl, 2-naphthyl, benzyl and 4-xenyl substituted 2-thienylacetic and 2-thienylglycolic acids. Of this group, the basic esters of the phenyl substituted acids showed the greatest diversity of activity and an enlarged series of esters of these acids have been prepared for pharmacological evaluation.

Both phenyl-2-thienylglycolic acid and phenyl-2-thienylacetic acid were prepared by the method previously described.[3]

The necessary basic alkyl chloride hydrochlorides were prepared by the action of thionyl chloride upon the corresponding basic alkanols in benzene solution. The bromide hydrobromides were prepared by the action of 48% hydrobromic acid on the alcohols in aqueous solution. In order to retard the cyclization of the free halides, ether extracts were used directly with subsequent solvent exchange as required. Most of the basic alkyl ester salts were obtained by refluxing the basic alkyl halide and acid in isopropyl alcohol for fifteen hours[6]; however, some of the esters required special methods as indicated.

We are indebted to Dr. A. M. Lands and coworkers in the Pharmacological Research Laboratories for the preliminary antispasmodic screening data reported herein. The compounds were tested by the Magnus technique against acetylcholine and barium chloride induced spasms in isolated strips of rabbit jejunum. In general, the glycolate esters were more anticholinergic than the corresponding acetates, whereas none of the compounds showed any appreciable activity against barium chloride. The modifications of the ester group produced approximately the same degree of difference in activity in each series. Some conclusions on the relationship between structure and activity, which refer equally well throughout each series, can best be summarized in the higher range of the glycolate series.

1. Quaternary salts increase the activity. The methobromides 21 and 27 are more active than the corresponding hydrochlorides 20 and 26.

2. Increasing the length of the carbon chain between the nitrogen and the carbonyl decreases the activity. Compound 20 is more active than compound 23. This relationship, however, is offset by branching. Actually compound 28 is more active than compound 26.

3. Alkyl substitutions on the nitrogen larger than ethyl diminish the activity as shown by comparing compound 20 with 25. Groups larger than isopropyl cause almost complete loss of activity. The four compounds 20, 25, 29 and 34 show this relationship.

4. The over-all effect of the ester group can best be shown by indicating the diminishing activity of compounds 28, 20, 23, 26, 25, 22, 30, 31 and 29. It is interesting that compound 31 with one methyl group on the nitrogen still retained appreciable activity.

Experimental

Phenyl-2-thienylacetyl Chloride.—Phenyl-2-thienylacetic acid was dissolved in ten times the theoretical quantity of purified thionyl chloride. The clear solution was refluxed for fifteen minutes during which time a deep purple color developed. Excess thionyl chloride was removed first by distillation under reduced pressure and finally by the successive addition and distillation of three 5–10-cc. portions of anhydrous benzene. The resulting deeply colored residual oil was used directly without further purification. Several attempts to purify the product by distillation resulted in total decomposition.

Methyl Phenyl-2-thienylacetate.—A solution of 28.2 g. (0.12 mole) of phenyl-2-thienylacetic acid, 400 cc. of anhydrous methanol and 2.0 cc. of 98% sulfuric acid was refluxed for five hours. The solvent was removed by distillation and the residual oil treated with water. The ester was extracted with ether and the extract washed with dilute sodium bicarbonate solution. The extract was dried with anhydrous magnesium sulfate, the solvent removed and the ester distilled; yield 24.6 g. (82.5%), b. p. 157–161° (0.8 mm.), m. p. 71–73° after recrystallization from *n*-heptane.

Anal. Calcd. for $C_{13}H_{12}O_2S$: S, 13.80. Found: S, 13.96.

N-Methyl-N-(2-hydroxyethyl)-phenyl-2-thienylacetamide.—A mixture of 23.2 g. (0.1 mole) of methyl phenyl-2-thienylacetate, 15.0 g. (0.2 mole) of 2-methylaminoethanol and 0.2 g. of sodium methoxide was heated in an oil-bath for two hours at 140–150°. The reaction mixture was dissolved in hot ethanol, cooled, the crystals collected and washed with cold alcohol; yield 20.4 g. (74.2%), m. p. 153–154° after recrystallization from the same solvent.

Anal. Calcd. for $C_{15}H_{17}NO_2S$: N, 5.09. Found: N, 4.83.

2-Methylaminoethyl Phenyl-2-thienylacetate Hydrochloride.—Hydrogen chloride was bubbled into a suspension of 15.2 g. (0.055 mole) of N-methyl-N-(2-hydroxyethyl)-phenyl-2-thienylacetamide in 400 cc. of isopropyl alcohol until all solid had dissolved. The solvent was removed by distillation and the residual gum solidified by rubbing several times with fresh portions of anhydrous ether; yield 10.55 g. (61.5%). (Analysis and properties in Table I.)

(1) Presented before the Division of Medicinal Chemistry at the American Chemical Society meeting, New York, N. Y., on September 17, 1947.

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(3) Blicke and Tsao, THIS JOURNAL, **66**, 1645 (1944).

(4) Lands and Nash, *Proc. Soc. Exptl. Biol. Med.*, **57**, 55 (1944).

(5) Lands, Nash and Hooper, *J. Pharmacol. Exp. Therap.*, **86**, vol. 2, 129 (1946).

(6) Horenstein and Pählicke, *Ber.*, **71**, 1654 (1938).

TABLE I

ALKAMINE ESTERS OF PHENYL-2-THIENYLACETIC ACID $C_6H_5CH(2\text{-}C_4H_3S)COOR$

Compd.	R	M. p. or b. p., °C.	Mm.	Formula	Analyses, % [b] Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found	Antispasmodic activity (Average values) [c] Acetylcholine	Barium chloride
1	$(C_2H_5)_2NCH_2CH_2$– [a]			$C_{18}H_{23}NO_2S\cdot HCl$					1-4M [d]	1-200T to 400T [e]
2	$(C_2H_5)_2NCH_2CH_2$–	197–199	0.2	$C_{18}H_{23}NO_2S$						
3	$(C_2H_5)_2NCH_2CH_2$–	115–117		$C_{18}H_{23}NO_2S\cdot HBr$	3.52	3.52	20.06	20.02	1-2M to 4M	1-40T to 100T
4	$(C_2H_5)_2NCH_2CH_2$–	65–66		$C_{18}H_{23}NO_2S\cdot CH_3Br$	3.40	3.60	19.33	19.26	1-2M to 4 M	
5	$C_5H_{10}N$ [f] CH_2CH_2– [a]			$C_{19}H_{25}NO_2S\cdot CH_3Br$					1-2M to 4M	1-200T
6	$(C_2H_5)_2NCH_2CH_2CH_2$– [a]			$C_{19}H_{25}NO_2S\cdot HCl$					1-2M to 4M	1-200T
7	$(C_4H_9)_2NCH_2CH_2CH_2$– [a]			$C_{23}H_{32}NO_2S\cdot CH_3Br$					1-200T to 500T	1-200T
8	$(i\text{-}C_3H_7)_2NCH_2CH_2$–	174–176	0.05	$C_{20}H_{27}NO_2S$						
9	$(i\text{-}C_3H_7)_2NCH_2CH_2$–	99–100		$C_{20}H_{27}NO_2S\cdot HCl$	3.67	3.78	9.28	9.40	1-2M	1-200T to 500T
10	$(CH_3)_2NCH_2CH_2$–	174–176	0.05	$C_{16}H_{19}NO_2S$						
11	$(CH_3)_2NCH_2CH_2$–	113–115		$C_{16}H_{19}NO_2S\cdot HCl$	4.29	4.16	10.88	10.79	1-500T to 1M	1-150T
12	$(CH_3)_2NCH_2C(CH_3)_2CH_2$–	126–128		$C_{19}H_{25}NO_2S\cdot HCl$	3.79	3.75	9.61	9.92	1-3M to 5M	1-100T
13	$(C_4H_9)_2NCH_2CH_2$–	180–183	0.01	$C_{22}H_{31}NO_2S$	3.75	3.65			1-50T to 100T	
14	$(C_2H_5)_2NCH_2CH(CH_3)$– [g]	162–165	0.01	$C_{19}H_{25}NO_2S$	4.23	4.26			1-1M to 2M	1-100T
15	$(CH_3)HNCH_2CH_2$–	132–134		$C_{15}H_{17}NO_2S\cdot HCl$	4.49	4.47	11.37	11.47	1-200T to 400T	1-50T to 100T
16	$(C_6H_5)HNCH_2CH_2$–	164–165		$C_{20}H_{19}NO_2S\cdot HCl$	3.75	3.67	9.48	9.36	1-200T to 500T	1-200T
17	$(C_6H_5)(C_2H_5)NCH_2CH_2$–	158–160		$C_{22}H_{23}NO_2S\cdot HBr$	3.14	3.12	17.90	17.72		
18	$(C_6H_{11})_2NCH_2CH_2$–	184–185		$C_{26}H_{35}NO_2S\cdot HCl$	3.03	2.95	7.67	7.46	1-10T	
19	$(C_6H_{11})HNCH_2CH_2$–	151–152		$C_{20}H_{25}NO_2S\cdot HBr$	3.30	3.25	18.83	18.94		
	ALKAMINE ESTERS OF PHENYL-2-THIENYLGLYCOLIC ACID $C_6H_5COH(2\text{-}C_4H_3S)COOR$									
20	$(C_2H_5)_2NCH_2CH_2$– [a]			$C_{18}H_{23}NO_3S\cdot HCl$					1-60M	1-200T to 400T
21	$(C_2H_5)_2NCH_2CH_2$–	141–142		$C_{18}H_{23}NO_3S\cdot CH_3Br$	3.27	3.40	18.66	18.68	1-50M to 100M	
22	$(C_5H_{10})N$ [f] CH_2CH_2 [a]			$C_{19}H_{23}NO_3S\cdot HCl$					1-20M to 40M	1-400T
23	$(C_2H_5)_2NCH_2CH_2CH_2$– [a]			$C_{19}H_{25}NO_3S\cdot HCl$					1-30 to 50M	1-200T
24	$(C_4H_9)_2NCH_2CH_2CH_2$– [a]			$C_{23}H_{33}NO_3S\cdot CH_3Br$					1-100T to 400T	1-100T
25	$(i\text{-}C_3H_7)_2NCH_2CH_2$–	156–157		$C_{20}H_{27}NO_3S\cdot HCl$	3.52	3.46	8.91	8.86	1-10M to 20M	1-200T
26	$(CH_3)_2NCH_2CH_2$–	159–161		$C_{16}H_{19}NO_3S\cdot HCl$	4.09	4.06	10.37	10.30	1-30M to 50M	1-200T
27	$(CH_3)_2NCH_2CH_2$–	189–191 dec.		$C_{16}H_{19}NO_3S\cdot CH_3Br$	3.50	3.61	19.97	20.22	1-40M to 80M	1-50T to 100T
28	$(CH_3)_2NCH_2C(CH_3)_2CH_2$–	142–144		$C_{19}H_{25}NO_3S\cdot HCl$	3.64	3.73	9.22	9.31	1-75M to 100M	1-100T
29	$(C_4H_9)_2NCH_2CH_2$–	119–120		$C_{22}H_{31}NO_3S\cdot HCl$	3.28	3.17	8.32	8.22	1-400T	1-400T
30	$(C_2H_5)_2NCH_2CH(CH_3)$– [g]	141–142		$C_{19}H_{25}NO_3S\cdot HCl$	3.65	3.62	9.24	9.22	1-10M to 20M	1-800T
31	$(CH_3)NHCH_2CH_2$–	139–140		$C_{15}H_{17}NO_3S\cdot HBr$	3.76	3.71	21.47	21.59	1-2M to 4M	1-100T to 500T
32	$(C_6H_5)HNCH_2CH_2$–	164–165		$C_{20}H_{19}NO_3S\cdot HCl$	3.60	3.42	9.09	8.82	1-400T	1-200T
33	$(C_6H_5)(C_2H_5)NCH_2CH_2$–	172–173		$C_{22}H_{23}NO_3S\cdot HCl$	3.35	3.45	8.46	8.37		
34	$(C_6H_{11})_2NCH_2CH_2$–	175–176		$C_{26}H_{35}NO_3S\cdot HCl$	2.93	2.84	7.42	7.20	1-100T to 200T	
35	$(C_6H_{11})HNCH_2CH_2$–	194–195 dec.		$C_{20}H_{25}NO_3S\cdot HBr$	3.18	3.41	18.15	18.05		

[a] Prepared by Blicke and Tsao.[3] [b] We are indebted to Elizabeth B. Macks for the analytical data on these compounds. [c] These figures are preliminary results only but are sufficiently accurate to permit a relative comparison of the compounds [d] 1:4,000,000 dilution. [e] 1:200,000–400,000 dilution. [f] $C_5H_{10}N$ = 1-Piperidyl. Compounds 3, 17, 18 and 25 were recrystallized from isopropyl alcohol; compounds 16, 27, 32, 33 and 35 from anhydrous ethanol; compound 4 from anhydrous ethanol and anhydrous ethyl acetate; compounds 8, 19, 21, 28, 31 and 34 from isopropyl alcohol and isopropyl ether; compounds 9, 26 and 30 from anhydrous ethanol and ethyl ether; compounds 11, 12 and 15 from anhydrous ethyl acetate; and compound 29 from ethyl acetate and isopropyl alcohol. [g] Alternative structure $[(C_2H_5)_2NCH(CH_3)\text{–}CH_2\text{–}]$ not excluded. Compounds 9, 12, 13, 14, 19, 25, 26, 28, 29, 30, 31, 32, 33, 34 and 35 were prepared by Method I; compounds 8, 10, 11, 16 and 18 by Method II; compound 17 by Method III; compound 3 by Method IV and compounds 4, 21 and 27 by Method V.

Preparation of Basic Esters and Salts

I. From Basic Alkyl Halides.[6]—Equimolar quantities of basic alkyl halide and acid were dissolved in an appropriate volume of isopropyl alcohol and the solution refluxed for fifteen hours. The solvent was removed by evaporation and the solid or gummy residue rubbed with anhydrous ether. The resulting solid was recrystallized from a suitable solvent as indicated in the tables.

II. From Phenyl-2-thienylacetyl Chloride.—The crude acid chloride from above was dissolved in anhydrous benzene and treated with an equivalent of the basic alcohol in the same solvent. After refluxing for one hour, the benzene was removed from the slurry by distillation and the residue dissolved in dilute hydrochloric acid. Insoluble material was extracted with ether. The clear solution was made alkaline to litmus with 10% sodium carbonate solution and the liberated basic-ester extracted with ether. The ether extract was dried with anhydrous magnesium sulfate. After filtration the ether was removed by distillation and the residual oil purified by distillation under reduced pressure. Hydrochlorides were obtained either by treating the dried ether extract or an ether solution of the distilled base with dry hydrogen chloride gas.

III. By Ester Exchange.—Equivalent amounts of methyl phenyl-2-thienylacetate and the basic alcohol were mixed with 0.1 g. of sodium methoxide and heated at 200° for twenty-four hours. The reaction mixture was cooled, dissolved in isopropyl alcohol and the solution treated with an equivalent amount of 48% hydrobromic acid. The product was worked up as in II.

IV. Hydrobromides.—A purified base was dissolved in isopropyl alcohol and treated with the theoretical quantity of 48% hydrobromic acid. The solvent was removed by distillation and the product purified as under I.

V. Methobromides.[7]—Either a purified base or a crude base obtained by neutralizing an aqueous solution of a hydrochloride with 10% sodium carbonate was dissolved in anhydrous ethanol. The solution was placed in a pressure bottle, cooled and treated with four to six equivalents of methyl bromide. After standing at room temperature for twenty-four hours the reaction mixture was worked up as under I.

Summary

Twenty-four new alkamine esters of phenyl-2-

(7) Blicke and Maxwell, THIS JOURNAL, **64**, 430 (1942).

thienylacetic acid and phenyl-2-thienylglycolic acid were prepared and characterized. From the results of some preliminary antispasmodic screening, brief conclusions are drawn on the relationship between structure and activity.

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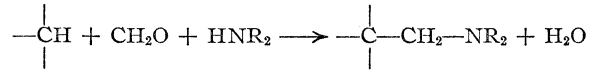
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

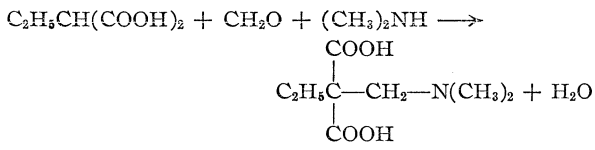
Studies on the Mechanism of the Mannich Reaction. I. Ethylmalonic Acid, A Methynyl Compound

BY ELLIOT R. ALEXANDER AND ELIZABETH J. UNDERHILL

When a compound containing an active hydrogen atom is treated with formaldehyde and ammonia or a primary or secondary amine, the active hydrogen atom is replaced by an aminomethyl group.



This reaction is commonly called the Mannich reaction,[1] and it has been used widely in synthesis. Its mechanism, however, has not been elucidated. Many types of active methylene and methynyl compounds undergo the reaction and it has been run in both acidic and basic media. The purpose of this investigation was to study the kinetics of the reaction of ethylmalonic acid with formaldehyde and dimethylamine.



Ethylmalonic acid, it will be observed, is a compound with only one replaceable hydrogen atom.

Experimental

Materials

Ethylmalonic Acid.—The ethylmalonic acid (m. p. 110–110.5°) used in this investigation was prepared by the saponification of commercial ethyl ethylmalonate.[2] Before commencing the preparation, however, the ester was shaken with half its volume of 25% aqueous potassium hydroxide for one half hour in order to remove any ethyl malonate which might have been present.

Formaldehyde.—In order to depolymerize any polyoxymethylenes present,[3a] commercial 37% formalin was diluted twenty-fold to give a solution approximately 2% in formaldehyde, which was allowed to stand for at least two days. The solution was standardized by the method outlined below.

Dimethylamine.—A solution, 2.616 *N* in dimethylamine, was made up by diluting commercial 25% aqueous dimethylamine. It was standardized with normal hydrochloric acid, using methyl orange as an indicator.

Nessler reagent (K_2HgI_4) was prepared according to the procedure given in the "Handbook of Chemistry and Physics."[4] It was found convenient to prepare it in quantities of 16 liters.

Dimethylaminomethylethylmalonic Acid.—The method used for the preparation of this acid was essentially that of Mannich and Ganz.[5] From 6.6 g. (0.05 mole) of ethylmalonic acid, 10 ml. (0.05 mole) of 22.5% dimethylamine solution, and 4.1 ml. (0.05 mole) of 37% formalin, was obtained 7.3 g. (77%) of the amino-acid, m. p. 100.5–101° (dec.).

Dimethylaminomethanol.—For the preparation of dimethylaminomethanol the procedure of Henry[6] was modified as follows. To 114 ml. (1.5 moles) of 37% formalin cooled in an ice–salt-bath, 270 ml. (1.5 moles) of 25% dimethylamine solution was added dropwise with stirring. The stirring was continued for two and one-half hours after addition was complete. Anhydrous potassium carbonate was then added in small portions until an oily layer formed. This was separated and dried over anhydrous potassium carbonate. During the entire preparation the temperature was kept below 5°, and the product was kept in a refrigerator. The yield of crude, undistilled material was 79 g. (70%), $n^{20}D$ 1.4060 (The refractive index changed to 1.4050 over a period of twenty four hours and then remained constant.). This substance was dissolved in water and analyzed as described for formaldehyde and dimethylamine.

Anal. Calcd. for C_3H_9NO: CH_2O, 40.0; $(CH_3)_2NH$, 60.0. Found: CH_2O, 36.8; $(CH_3)_2NH$, 61.2.

The infrared absorption spectrum of the substance showed only a very weak absorption band in the region characteristic of the OH group.

Procedures

Determination of Formaldehyde.—The determination of formaldehyde was carried out by a modification of the mercurimetric method of Bougault and Gros.[7] To 50 ml. of Nessler reagent was added a sample containing 0.0002 to 0.0006 equivalent of formaldehyde. A precipitate formed at once, the resulting mixture was shaken for five minutes, and it was then acidified by the addition of 30–40 ml. of 2 *N* acetic acid. Twenty-five ml. of 0.1 *N* iodine solution was added immediately and the precipitate was dissolved by agitation. The excess iodine was titrated with 0.1 *N* sodium thiosulfate solution. Care was taken to keep the mixture alkaline until the addition of the acetic acid by adding to the Nessler reagent 2–6 ml. of 10% sodium hydroxide solution in cases where the formaldehyde sample was strongly acidic. Blanks were run and corrections made for the effects of Nessler reagent, buffer, amine, ethylmalonic acid and dimethylaminomethylethylmalonic acid, on the thiosulfate titer. The corrections were not more than a few tenths of a ml. and were in such directions that they tended to cancel each other.

Determination of the Order of Reaction.—To study the kinetics of the formation of dimethylaminomethylethyl-

(1) Blicke in Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.

(2) Gattermann, "Laboratory Methods of Organic Chemistry," The Macmillan Co., New York, N. Y., 1937, p. 255.

(3) (a) Walker, "Formaldehyde," Reinhold Publishing Corp., New York, N. Y., 1944, p. 31; (b) p. 263.

(4) "Handbook of Chemistry and Physics," 27th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1943, p. 1277.

(5) Mannich and Ganz, *Ber.*, **55**, 3486 (1922).

(6) Henry, *Bull. Acad. roy. belg.*, [3] **28**, 355 (1894).

(7) Bougault and Gros, *J. pharm. Chim.*, **26**, 5 (1922) [*C. A.*, **16**, 3281 (1922)].

malonic acid from ethylmalonic acid, dimethylamine, and formaldehyde, the reaction was run in a solution kept at *p*H 4.20 ± 0.08 by the use of a buffer consisting of 4.102 g. of sodium acetate and 8–11 ml. of 12.56 *N* acetic acid, depending on the relative concentrations of amine and ethylmalonic acid.[8] The buffer, formaldehyde and amine were mixed in a 50-ml. volumetric flask, diluted to about 40 ml., and allowed to stand at room temperature for at least twelve hours. The solution was then cooled to 0°, ethylmalonic acid was added, the solution was made up to the mark, and the flask was immersed in a bath maintained at 0.09 ± 0.27°. Aliquots containing 0.0002 to 0.0006 equivalent of formaldehyde were withdrawn from time to time and analyzed immediately for formaldehyde in order to determine the extent of reaction. In each run the reaction was allowed to proceed to 52–80% of completion. The results are summarized in Table I and a typical reaction curve is shown in Fig. 1. Included in Table I is one run (54) in which the ionic strength was approximately doubled by adding 5.0 g. of potassium chloride.[9] When the reaction was run without allowing the amine and formaldehyde to stand at room temperature, complex curves (Fig. 1) were obtained.

TABLE I

DETERMINATION OF THE ORDER OF THE REACTION AT 0.09 ± 0.27°

Run	*p*H	*M* CH_2O	*M* $(CH_3)_2NH$	*M* $C_2H_5CH(COOH)_2$	*k*, (liter²/mole² hr.)
27	4.26	0.2056	0.2616	0.1971	0.434
30	4.23	.2056	.2616	.3942	.353
31	4.14	.2056	.1308	.3942	.300
32	4.12	.3541	.2616	.3942	.364
33	4.15	.1028	.2616	.3946	.330
35	4.26	.2056	.5232	.3940	.295
36	4.28	.2056	.2616	.1062	.455
44[a]	4.22	.2090[b]	.2324[b]	.3942	.431
49[a]	4.15	.2210	.1831	.3942	.410
51	4.18	.2238	.2616	.3942	.370
53	4.18	.1119	.2616	.3942	.337
54[c]	4.16	.2210	.2616	.3942	.360
				Average[d]	.360 ± 0.033

[a] Temperature is 0.48 ± 0.17°. [b] Formaldehyde and dimethylamine in the form of dimethylaminomethanol. [c] Ionic strength doubled by the addition of 5.0 g. of potassium chloride. [d] Excluding runs 44 and 49.

To investigate the reversibility of the reaction, a solution made up of the buffer and 3.78 g. (0.02 mole) of dimethylaminomethylethylmalonic acid was diluted to 50 ml. After maintaining this solution at 0° for one week, no precipitate characteristic of formaldehyde was formed upon analysis of an aliquot. Control runs were also made to discover whether there was an independent reaction between formaldehyde and either dimethylamine or ethylmalonic acid. A 50-ml. solution containing 0.02 mole of ethylmalonic acid, 0.01 mole of formaldehyde and the buffer was left at 0° for three days, and the loss in formaldehyde content was found to be 3%. In another run the acid was replaced by 0.013 mole of dimethylamine, and the formaldehyde content decreased by only 1.5% in three days.

In order to ascertain that ethylmalonic acid did not react with formaldehyde to form a compound which was decomposed under the basic conditions of the formaldehyde analysis, hydroxymethylethylmalonic ester was prepared[10] and tested for formaldehyde with Nessler reagent and also with methone.[3b] In the former case it gave formaldehyde quantitatively, but in the latter case, under acidic conditions, only a negligibly small trace of formaldehyde was detected. The control with ethylmalonic acid and formaldehyde was repeated at 0–5°, and when followed by the methone analysis it was found that 5% reaction occurred in three days.

(8) The volumes of acetic acid necessary to attain a *p*H of 4.2 were determined by previous experiments.

(9) The ionic strength was calculated by assuming that the sodium acetate and potassium chloride were completely dissociated, and that the dissociation constants of ethylmalonic acid and dimethylamine are 1.09×10^{-4} and 5.2×10^{-4}, respectively. The second dissociation constant of ethylmalonic acid was assumed to be negligible.

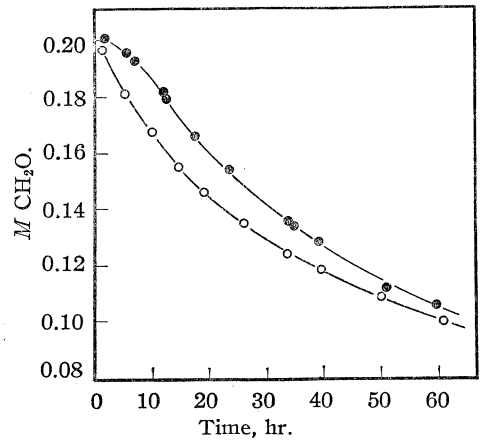


Fig. 1.—Course of the Mannich reaction at 0.16 ± 0.10° using solutions 0.2056 *M* in formaldehyde, 0.2616 *M* in dimethylamine and 0.1971 *M* in ethylmalonic acid: ⊙, Run 27, in which the formaldehyde and amine were mixed twelve hours before the addition of the ethylmalonic acid; ●, all the reagents mixed at once.

Dependence of the Specific Rate Constant, *k*, on *p*H.—By following the procedure outlined above, the dependence of the specific rate constant on *p*H was determined. In all cases the quantities of reagents used were: 2.6011 g. (0.01971 mole) of ethylmalonic acid, 5.00 ml. (0.01308 mole) of 2.616 *N* dimethylamine solution, 16.25 ml. 0.01028 mole) of 0.6324 *M* formaldehyde solution. The *p*H was varied by changing the composition of the buffer, and the temperature was held at 0.48 ± 0.04°. The buffers used and the rate constants calculated are summarized in Table II and Fig. 3. Control runs were made to determine the extent of the independent reactions of formaldehyde with dimethylamine and with ethylmalonic

TABLE II

DEPENDENCE OF REACTION RATE ON *p*H

Run	*p*H	Buffer	*k*, (liter²/mole² hr.)
39	2.90	3.728 g. KCl	0.342
40	3.95	4.102 g. NaOAc + 16.1 ml. 12.56 *N* HOAc	.455
41	4.60	4.102 g. NaOAc + 2.5 ml. 12.56 *N* HOAc	.306
42	5.03	4.102 g. NaOAc	.222
46	5.50	4.102 g. NaOAc + 4 ml. 10% NaOH	.121
47	1.00	4.102 g. NaOAc +16 ml. 5 *N* HCl	No reaction
59	11.57	20 ml. 10% NaOH	No reaction[a]
62	8.37	10 ml. 10% NaOH	0.007[b]

[a] No reaction in excess of the reaction between formaldehyde and dimethylamine. [b] Calculated roughly from the extent of reaction after three days.

(10) Welch, *J. Chem. Soc.*, 257 (1930).

acid over the *p*H range investigated. In acid solutions these reactions were found to be negligible, but in strongly basic solutions there was a noticeable reaction between formaldehyde and the amine.

Reaction of Dimethylaminomethanol with Ethylmalonic Acid.—The buffer, 2.6011 g. (0.01971 mole) of ethylmalonic acid, and 1.0 ml. of dimethylaminomethanol (corresponding to 0.01045 mole of formaldehyde and 0.01162 mole of dimethylamine), were mixed and diluted to 50 ml. at 0°. The reaction was followed in the usual way, and the results are included in Table I. Identical results were obtained when an induction period of twelve hours was allowed before the addition of the ethylmalonic acid.

Results

By plotting the function

$$\frac{2.303}{(a-b)(b-c)(c-a)}\left[(b-c)\log\frac{a-x}{a}+(c-a)\log\frac{b-x}{b}+(a-b)\log\frac{c-x}{c}\right]$$

against the time for the runs listed in Table I, straight lines were obtained. A typical line is shown in Fig. 2. In the above expression,

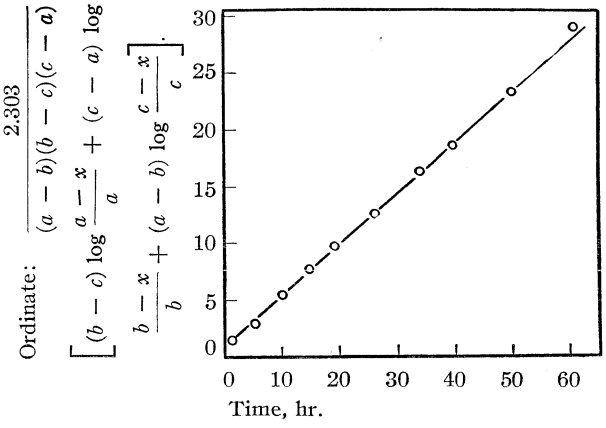


Fig. 2.—Plot for determining the order of the reaction, Run 27(see Fig. 1).

a is the initial concentration of formaldehyde, b the initial concentration of dimethylamine, c the initial concentration of ethylmalonic acid, and x is the change in concentration of any of these components as calculated from the formaldehyde remaining in the solution. All concentrations are expressed in moles per liter. In no case was the scattering of points from the straight lines greater than experimental error, or was there a trend away from these lines as the reaction proceeded, even in the case where it was allowed to proceed to 80% of completion. This relationship indicates that at constant *p*H the reaction obeys the rate equation

$$dx/dt = k(a-x)(b-x)(c-x)$$

where t is the time in hours and k is the specific rate constant in liters^2/mole^2 hr. The kinetics of the reaction is, therefore, first order in each of the components and third order over-all. A value of 0.360 ± 0.033 was obtained for k at 0.09 ± 0.27°. Third order kinetics was followed only when the formaldehyde and amine were mixed and allowed to stand for twelve hours before the addition of the ethylmalonic acid. When all three components were mixed at once, complex reaction curves were obtained (Fig. 1). Although the ionic strength in these runs varied from 1.16 to 1.39, it can be seen that the rate constant is independent of ionic strength over this range, since an increase from 1.26 (runs 30 and 51) to 2.60 (run 54) in otherwise similar runs had no effect upon k. The ionic strength was not increased further because of the insolubility of potassium chloride, the neutral salt added. The reaction is non-reversible, and since no appreciable reaction was detected between formaldehyde and either dimethylamine or ethylmalonic acid in the *p*H range of 3 to 8, the disappearance of formaldehyde from the reaction solution was taken as a true measure of the extent of the Mannich reaction under these conditions.

In Table II are listed the third order rate constants calculated for runs at various *p*H values. It can be seen that the rate is critically dependent on *p*H, and passed through a maximum at about *p*H 3.8. In Fig. 3 the specific rate constant, k, is plotted against *p*H.

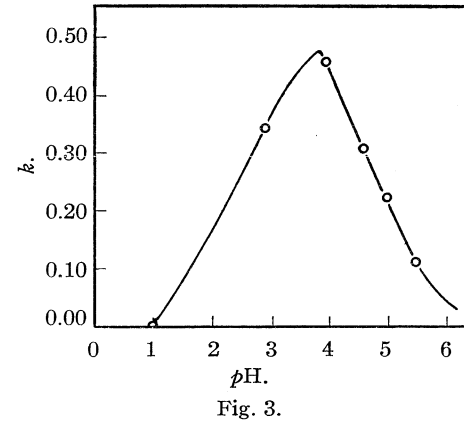


Fig. 3.

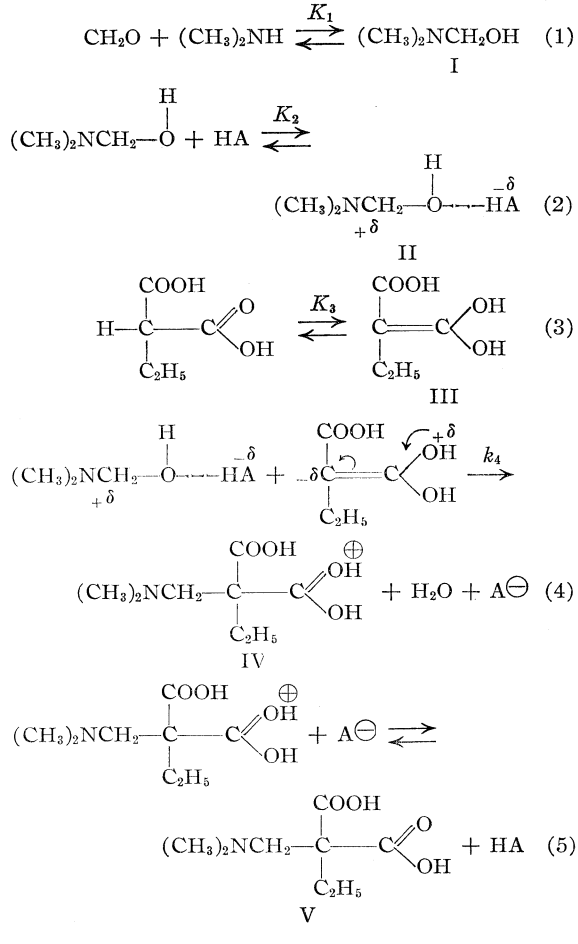
From runs 44 and 49 made at 0.48 ± 0.17°, it can be seen that the use of dimethylaminomethanol in place of formaldehyde and dimethylamine has no effect on the kinetics or on the rate constant of the reaction. The third order rate constants obtained were 0.431 (run 44) in which dimethylaminomethanol was used) and 0.410 (run 49 in which formaldehyde and dimethylamine were used), and these values are within the limits of experimental variation.

Discussion

Since it is quite possible that the Mannich reaction proceeds by different mechanisms depending on the number of replaceable hydrogen atoms and on the experimental conditions, this phase of our study was limited to an investigation of the behavior of a compound containing a methynyl group. Several compounds were tested in attempting to find one suitable for kinetic studies. In acid solution, antipyrine and indole

condense with formaldehyde even in the absence of dimethylamine. Isobutyraldehyde interferes with the formaldehyde determination, and phenylacetylene reacts best in a non-aqueous, heterogeneous system. Ethylmalonic acid was used since it has none of these disadvantages, and it reacts in good yields under mild conditions. The temperature was kept at 0° to avoid decarboxylation of the dimethylaminomethylethylmalonic acid.

The most striking feature of the experimental data is that the Mannich reaction of ethylmalonic acid follows third order kinetics. Any mechanism must take this fact into consideration. While there are other reaction sequences which follow third order kinetics, two of which will be mentioned later, one mechanism consistent with our results is



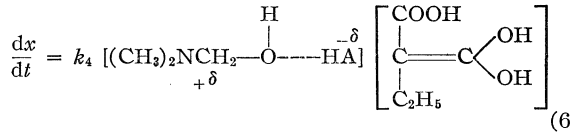
In these equations HA represents any acid present in the system.

Thus the reaction may be considered to be initiated by the reversible addition of dimethylamine and formaldehyde to give dimethylaminomethanol (I). In the presence of an acid HA, a reactive, hydrogen bonded addition complex (II) could be formed. A properly oriented collision of II with ethylmalonic acid, probably in the transitory enol form (III), would produce water, the conjugate base $A^{\ominus}$ and a protonated molecule of dimethylaminomethylethylmalonic acid (IV). Reaction of IV with the conjugate base $A^{\ominus}$ would give the free amino acid V.

The rate determining step of the over-all process is that represented by equation 4 since the rate is dependent upon the concentration of all three components and upon the concentration of acid present in the reaction mixture (Fig. 3).

Apparently, however, the rate of the establishment of the equilibrium of equation 1 is faster than but still in the same range as that of equation 4 since the initial over-all rate of the reaction was slower when all of the reagents were mixed at once than when the amine and formaldehyde were allowed to stand together for twelve hours before adding the ethylmalonic acid (Fig. 1). Presumably, in those reactions in which the amine and formaldehyde were not allowed to come to equilibrium, the initial concentration of complex II was small. Once equilibrium was established, however, it was not disturbed by the reaction of II with ethylmalonic acid. In order to obtain pure third order kinetics all of the equilibria must be established and maintained throughout the reaction.

From the above scheme it can be seen that



(6)

and, making the appropriate substitutions

$$dx/dt = K_1K_2K_3k_4[CH_2O][(CH_3)_2NH][C_2H_5CH(COOH)_2][HA] \quad (7)$$

At constant acid concentration this reduces to:

$$dx/dt = k[CH_2O][(CH_3)_2NH][C_2H_5CH(COOH)_2] \quad (8)$$

The complex variation of the rate of reaction upon *p*H indicates general acid catalysis.[11] Qualitatively, the reaction is acid catalyzed as shown by equation 7, but an increase in acid concentration decreases the concentration of the free amine and the free amine also enters into the reaction. It is presumably a superposition of these two effects which gives rise to the type of curve illustrated in Fig. 3). General acid catalysis explains the spread in rate constants at constant *p*H as the concentrations of ethylmalonic acid and dimethylamine are varied. To maintain a *p*H of 4.2 the amount of acetic acid in the buffer was varied, and thus the concentration of at least one of the acid catalysts was changed without being considered in the rate equation. It is therefore not surprising that there is a small spread in the rate constants (Table I).

While third order kinetics for the Mannich reaction merely supports the mechanism which was

(11) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 329–333.

proposed in equations 1–5, two facts strongly imply the formation of dimethylaminomethanol as an intermediate. First, under the experimental conditions employed, the reaction of formaldehyde with ethylmalonic acid was found to be negligible when followed by the methone method of analysis for formaldehyde. Since this method gave a negative test for formaldehyde in the presence of ethyl hydroxymethylethylmalonate, it is probable that any reaction between formaldehyde and ethylmalonic acid to form the corresponding hydroxymethyl acid would be detected by this method. Consequently, mechanisms based upon the preliminary condensation between these two components have been eliminated from consideration. Second, not only is the formation of some necessary intermediate between the amine and formaldehyde indicated (Fig. 1), but also it appears to be of the methylolamine type. It is particularly significant that smooth third order curves are obtained from formaldehyde, dimethylamine and ethylmalonic acid only after allowing the amine and formaldehyde to stand together for twelve hours. With dimethylaminomethanol, however, the preliminary equilibration may be omitted and the rate constant is identical with that obtained from dimethylamine, formaldehyde and ethylmalonic acid. It is clear, therefore, that dimethylaminomethanol does not react by a preliminary hydrolysis to dimethylamine and formaldehyde, and the identity of the rate constants suggests that dimethylaminomethanol is an actual intermediate in the process. Equations 2–5 illustrate the sequence which seems to be the most probable for the reaction of dimethylaminomethanol with ethylmalonic acid.

There are a number of other mechanisms which we have considered and rejected. The reaction may be assumed to proceed by the attack of a free carbonium ion upon the enol form of ethylmalonic acid

$$(CH_3)_2NH + CH_2O \overset{K_1}{\rightleftharpoons} (CH_3)_2NCH_2OH \quad (9)$$

$$(CH_3)_2NCH_2OH + HA \overset{K_4}{\rightleftharpoons} (CH_3)_2\overset{\oplus}{N}CH_2 + H_2O + A^{\ominus} \quad (10)$$

$$(CH_3)_2\overset{\oplus}{N}CH_2 + \begin{matrix}COOH\\|\\C\\\|\\C\\|\\C_2H_5\end{matrix}\!\!<\!\!\begin{matrix}OH\\OH\end{matrix} \overset{K_5}{\rightleftharpoons}$$

$$(CH_3)_2NCH_2-\begin{matrix}COOH\\|\\C\\|\\C_2H_5\end{matrix}\!\!-\!\!\begin{matrix}\overset{\oplus}{C}\!<\!\begin{matrix}OH\\OH\end{matrix}\end{matrix} \quad (11)$$

$$(CH_3)_2NCH_2-\begin{matrix}COOH\\|\\C\\|\\C_2H_5\end{matrix}\!\!-\!\!\begin{matrix}\overset{\oplus}{C}\!<\!\begin{matrix}OH\\OH\end{matrix}\end{matrix} + A^{\ominus} \xrightarrow{k_6}$$

$$(CH_3)_2NCH_2-\begin{matrix}COOH\\|\\C\\|\\C_2H_5\end{matrix}\!\!-\!\!\begin{matrix}C\!<\!\begin{matrix}O\\OH\end{matrix}\end{matrix} + HA \quad (12)$$

This series of equations, however, requires equation 12 to be the slowest step in the sequence for if equation 11 were non-reversible and rate determining the over-all rate equations would be

$$\frac{dx}{dt} = k_5[(CH_3)_2\overset{\oplus}{N}CH_2]\left[\begin{matrix}COOH\\|\\C\\\|\\C\\|\\C_2H_5\end{matrix}\!\!<\!\!\begin{matrix}OH\\OH\end{matrix}\right]$$

$$= k_5K_1K_3K_4[CH_2O][(CH_3)_2NH][C_2H_5CH(COOH)_2]\frac{[HA]}{[A^{\ominus}]}$$

and since

$$[OH_3^{\oplus}][A^{\ominus}]/[HA] = Ka$$

this reduces to specific oxonium ion catalysis which does not explain the complex variation of rate constant with pH which was found. It seems improbable that reaction 12 could be considered the rate determining step of the entire sequence since this involves a reaction between the conjugate acid of a carboxylic acid group (presumably a very strong acid) and a base such as acetate ion.

Another attractive mechanism[12] suggests that reaction occurs between a carbanion formed from ethylmalonic acid and the carbonium ion shown in equation 10. This hypothesis also has certain disadvantages. First, if the transition complex of the rate determining step involves the neutralization of unit charges, an increase in ionic strength should decrease strongly the rate of reaction.[13] This was not observed (run 54, Table I). Second, if carbanion formation exhibits general acid-base catalysis

$$H-\begin{matrix}C_2H_5\\|\\C\\|\\COOH\end{matrix}\!\!-\!\!COOH + A^{\ominus} \overset{K_7}{\rightleftharpoons}$$

$$HA + \left[\begin{matrix}\ominus\ C_2H_5\\|\\:C\\|\\COOH\end{matrix}\!\!-\!\!COOH \longleftrightarrow \begin{matrix}C_2H_5\\|\\C\\\|\\C\\|\\COOH\end{matrix}\!\!<\!\!\begin{matrix}O^{\ominus}\\OH\end{matrix}\right]$$

and if the rate determining step is between a carbonium ion and a carbanion

$$(CH_3)_2-N-\overset{\oplus}{C}H_2 + :\begin{matrix}\ominus C_2H_5\\|\\C\\|\\COOH\end{matrix}\!\!-\!\!COOH \xrightarrow{k_8}$$

$$(CH_3)_2N-CH_2-\begin{matrix}C_2H_5\\|\\C\\|\\COOH\end{matrix}\!\!-\!\!COOH$$

then the rate of reaction can be expressed by the equation

$$\frac{dx}{dt} = k_8[(CH_3)_2\overset{\oplus}{N}CH_2]\left[\begin{matrix}\ominus C_2H_5\\|\\:C\\|\\COOH\end{matrix}\!\!-\!\!COOH\right]$$

(12) Lieberman and Wagner, Abstracts of Papers, Third Meeting-in-Miniature of the American Chemical Society, Philadelphia, Pennsylvania, 1949, p. 49.

(13) Hughes, *Trans. Faraday Soc.*, **37**, 609 (1941).

Upon making the appropriate substitutions the expression becomes independent of the concentration of acid HA. This is also contrary to fact.

The mechanism outlined in equations 1–5 is interesting in view of the fact that in basic solution antipyrine has been reported to give a poorer yield of 4-dimethylaminomethylantipyrine with dimethylaminomethanol than with dimethylamine and formaldehyde under similar conditions.[14] This was interpreted to mean that the reaction did not proceed through the primary condensation of the amine with formaldehyde. We have repeated the experiments and have verified these results. While we do not, as yet, understand their significance to the base catalyzed transformation, it is clear that they have no bearing on our reaction carried out in acid solution. We have shown that the kinetics is unchanged when formaldehyde and dimethylamine are replaced by dimethylaminomethanol.

(14) Bodendorf and Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

Summary

1. In acid solution the Mannich reaction of ethylmalonic acid, formaldehyde and dimethylamine, follows third order kinetics, first order in each of the three components.

2. The rate of reaction shows a critical dependence on *p*H. It passes through a maximum at about *p*H 3.8.

3. Under the conditions of our experiments, no reaction takes place between ethylmalonic acid and formaldehyde.

4. Smooth, third order curves are obtained for the reaction only if the amine and formaldehyde are mixed and allowed to stand for twelve hours before adding the ethylmalonic acid, but if the formaldehyde and dimethylamine are replaced by dimethylaminomethanol, the reagents may all be mixed at once.

These facts are in agreement with an ionic mechanism for the Mannich reaction of methynyl compounds, based upon a primary condensation of formaldehyde with the amine.

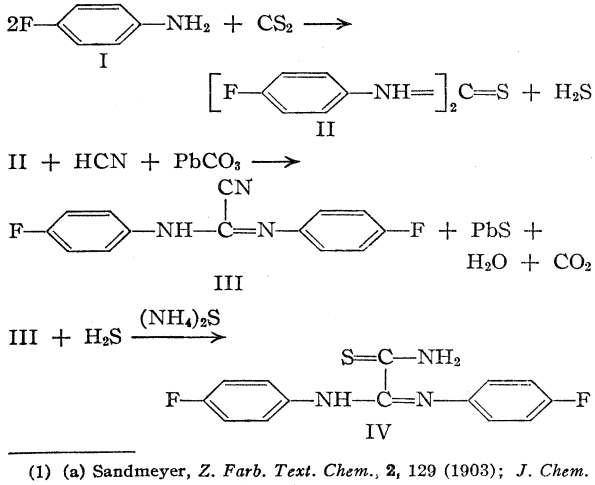
URBANA, ILLINOIS RECEIVED APRIL 4, 1949

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

The Preparation of 5,5′- and 7,7′-Difluoroindigo

BY ARTHUR ROE AND CLAUDE E. TEAGUE, JR.

The preparation of several fluoroindigos was undertaken as part of a study of aromatic and heterocyclic fluorine compounds being carried out in this Laboratory. The method of Sandmeyer[1] was found to be the most satisfactory way to prepare these compounds; 5,5′- and 7,7′-difluoroindigo were prepared from *p*-fluoroaniline and *o*-fluoroaniline, respectively, by this method. The preparation of 5,5′-difluoroindigo is outlined in the accompanying equations.



(1) (a) Sandmeyer, *Z. Farb. Text. Chem.*, **2**, 129 (1903); *J. Chem. Soc. Abst.*, **84**, I, 486 (1903); (b) Fierz-David, "Dye Chemistry," J. A. Churchill, London, 1921, p. 161–167.

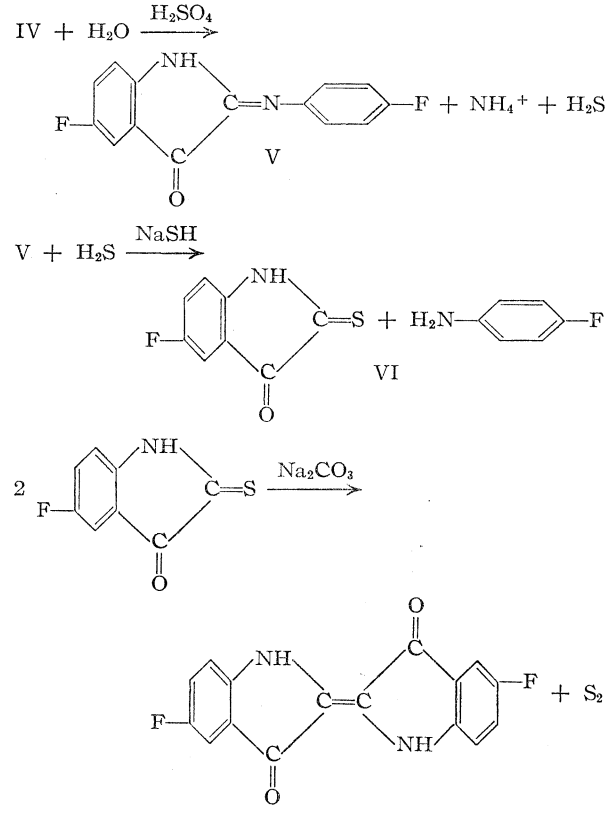


TABLE I

	Compound	Formula	M. p., °C.	Yield, %	Nitrogen, % Calcd.	Found
1	*s*-Di-*p*-fluorophenylthiourea[2,3]	$C_{13}H_{10}F_2N_2S$	187.5	94	10.6	10.7
2	*s*-Di-*o*-fluorophenylthiourea	$C_{13}H_{10}F_2N_2S$	188	97	10.6	10.6
3	N,N′-bis-(*p*-Fluorophenyl)-cyanoformamidine	$C_{14}H_9F_2N_3$	128	99	16.3	16.3
4	N,N′-bis-(*o*-Fluorophenyl)-cyanoformamidine	$C_{14}H_9F_2N_3$	128	98	16.3	16.3
5	α-(N,N′-Di-*p*-fluorophenylguanyl)-thioformamide	$C_{14}H_{11}F_2N_3S$	119	73	14.4	14.5
6	α-(N,N′-Di-*o*-fluorophenylguanyl)-thioformamide	$C_{14}H_{11}F_2N_3S$	106	98	14.4	14.6, 14.7
7	5,5′-Difluoroindigo	$C_{16}H_8F_2N_2O_2$	...	28[a]	9.4	9.3, 9.4
8	7,7′-Difluoroindigo	$C_{16}H_8F_2N_2O_2$	...	37[b]	9.4	9.3

[a] Yield based on compound (5). [b] Yield based on Compound (6).

The attempted preparation of 4,4′- or 6,6′-difluoroindigo starting with *m*-fluoroaniline was not possible because *m*-fluoroaniline would not react with carbon disulfide to form a difluorodiphenylthiourea; after one hundred and fifty hours refluxing the *m*-fluoroaniline was recovered almost quantitatively. The reaction of carbon disulfide with *o*- and *p*-fluoroaniline was complete in forty and seventy hours, respectively.

The *s*-di-*p*-fluorophenylthiourea formed by the action of carbon disulfide on *p*-fluoroaniline is not a new compound; conflicting reports of its melting point appear in the literature, however. Browne and Dyson[2] prepared it from *p*-fluoroaniline and thiocarbonyl chloride, and reported a melting point of 145°; Lubs and Fox[3] prepared it by the reaction of *p*-fluorophenyl isothiocyanate with *p*-fluoroaniline and report a melting point of 186.5–188°. The third synthesis here reported gives a product melting at 187.5°.

Attempts to prepare 5,5′-difluoroindigo by Baeyer's method[4] were not too successful. The preparation of 5-fluoro-α-isatin chloride from *p*-fluoroaniline was accomplished satisfactorily; attempted conversion of this to the fluoroindigo, however, resulted in the formation of large amounts of a difluoroindirubin contaminated with traces of 5,5′-difluoroindigo.

Attempts to use the Heumann method[5] starting with *p*-fluorophenylglycine were not too satisfactory; very poor yields of 5,5′-difluoroindigo were obtained in this way.

A comparison of the two new difluoroindigos with 5,5′-dibromoindigo[6] was made. No difference in the ease of vatting with hydrosulfite and the stability of the reduced form of the three dyes was noted. The dibromoindigo was absorbed on cotton cloth more rapidly than either of the difluoroindigos; both difluoroindigos were markedly more light-fast than was the dibromo derivative, however.

Experimental[6]

Directions given[1a,b] for the preparation of indigo were followed in the synthesis of 5,5′- and 7,7′-difluoroindigo; compounds involved in the synthesis which were stable enough to be analyzed are shown in the table below along with the final products. The fluoroanilines used as starting materials were prepared by the Schiemann reaction.[7]

Vatting of the dyes was carried out as follows: 0.15 g. of the dye was placed in a beaker with 100 ml. of 10% sodium hydroxide and the solution warmed to about 90°; 1 g. of sodium hydrosulfite was added with stirring. The dyes went into solution immediately, forming a light yellow solution.

Summary

The synthesis of 5,5′- and 7,7′-difluoroindigo is reported.

CHAPEL HILL, NORTH CAROLINA RECEIVED MAY 6, 1949

(2) Browne and Dyson, *J. Chem. Soc.*, 3285 (1931).

(3) Lubs and Fox, U. S. Patent 2,061,243 (1937); *C. A.*, **31**, 885 (1937).

(4) Baeyer, *Ber.*, **3**, 514 (1870); **11**, 1296 (1878); **12**, 456 (1879).

(5) Heumann, *ibid.*, **23**, 3043 (1890).

(6) A sample of 5,5′-dibromoindigo was kindly furnished by E. I. du Pont de Nemours and Company.

(6) All melting points are corrected.

(7) Balz and Schiemann, *Ber.*, **60**, 1186 (1927).

[CONTRIBUTION FROM THE ROSS CHEMICAL LABORATORY, ALABAMA POLYTECHNIC INSTITUTE]

Orientation in Aromatic Compounds of Phosphorus. II. Nitration of Diethyl Benzenephosphonate

BY GENNADY M. KOSOLAPOFF

Although the results of nitration of benzenephosphonic acid have been reported,[1,2] the esters of this acid have not been subjected to this reaction. A study of the aromatic reactions of such esters is of importance because of the ready availability of these derivatives by the modified Friedel–Crafts reaction.[3] In addition, the observations on the possible effect of the ester grouping, in comparison with the free acid, may be expected to be of interest.

Nitration of benzenephosphonic acid with fuming nitric acid has been reported to yield the *m*-nitro isomer.[2] The early work of Michaelis and his co-workers,[1] in which the product was separated from the unreacted material by a tedious crystallization of its barium salt, indicated the formation of a product, which melted at 140°, described as the para-derivative, without further proof of structure. Nijk,[2] in making a more thorough investigation, showed that the compound reported by Michaelis was the *m*-isomer; it should be noted that the yield of the purified product was only 50–60%.[2]

Preliminary experiments indicated that diethyl benzenephosphonate nitrates much more sluggishly than dibutyl benzylphosphonate[4] in the cold with either fuming nitric acid or with mixed acid. Satisfactory nitration was performed, however, with fuming nitric acid at somewhat above room temperature. Separation of the nitrated product from the original material was readily accomplished by fractional distillation. The boiling point spread of more than thirty degrees permitted a much more rapid and convenient method for the separation of unreacted material than the previously reported procedures.[1,2] The product of nitration showed a boiling range of several degrees, which indicated the presence of isomeric nitro derivatives; this range was much too narrow, however, for a practical separation of the isomers by distillation. The nitrated product, therefore, was either hydrolyzed to the free acid (mixture) and the latter reduced to the amino derivative, or first reduced to the amino acid ester (mixture) and then hydrolyzed. The results were identical in either case: 3-aminobenzenephosphonic acid was isolated in pure state along with the 2-amino isomer, which could not be obtained completely free from the 3-isomer. The over-all yield of the amino acid mixture from the nitro ester averaged 86%. Although the *p*-amino isomer was not detected, the formation of the *p*-nitro compound in the nitration mixture is not excluded, because of the possibility of decomposition of the phosphanilic acid. Unfortunately, no data on such decomposition are available at this time; however, it has been noted that the yields of phosphanilic acid are severely reduced if the ammonolysis, used in its synthesis, is unduly prolonged. It is of interest to note that the mixture of the nitrobenzenephosphonic acids melts at the same temperature as the *m*-nitro isomer, as reported by Nijk,[2] and several attempts to separate this mixture by crystallization (from water or from organic solvents), were fruitless. This fact calls for a re-examination of the nitration products of the free acid, particularly in view of the fact that the total yield of positively identified products from such nitrations has been far below the theoretical.

Experimental Part

Nitration of Diethyl Benzenephosphonate.—Nitration of the ester under previously reported conditions[4] gave but 15–20% conversions. However, addition of 42.8 g. (0.2 mole) of diethyl benzenephosphonate to 130 ml. of fuming nitric acid (d. 1.5) over one hour at 30–35° and stirring at this temperature for one hour, followed by quenching with ice-water, washing with water and dilute sodium carbonate solution (after dilution with 300 ml. of benzene), and distillation *in vacuo*, resulted in isolation of the nitration products in the form of a pale yellow liquid, which boiled at 135–145° at 0.5 mm.; the original ester boils at 99–100° at 0.5 mm. In several experiments the average yield of the product was 35 g. (67.5%), with recovery of 7 g. of unreacted ester.

Identification of the Products.—Reduction of the nitrated product (15 g.) by addition to a mixture of 38 g. of iron filings and 45 ml. of 8% acetic acid with vigorous stirring at 60–70°, followed by stirring at 80° for forty-five minutes, resulted in isolation, after neutralization with sodium carbonate, extraction with benzene and washing with water, of the isomer mixture of diethyl aminobenzenephosphonates in the form of an oil, which could not be distilled or crystallized. Hydrolysis of this mixture by boiling concentrated hydrochloric acid (150 ml.) for four hours, followed by the removal of the bulk of hydrochloric acid *in vacuo* and careful neutralization of the residue to a weak congo red end-point by means of sodium carbonate, gave 8.6 g. (86%) of the mixed 2- and 3-aminobenzenephosphonic acids, in the form of a colorless, very sparingly soluble, crystalline powder. The decomposition range, 290–296°, of this material indicates the absence of appreciable amounts of the para isomer, which develops a characteristic blue decomposition color at lower temperatures. In addition, its characteristic acetyl derivative could not be detected following Bauer's method of preparation.[5]

Treatment of this mixture (1.73 g.), in water containing just enough hydrochloric acid to give a clear solution, with bromine resulted in isolation of 0.9 g. of 2,4,6-tribromoaniline (27%), m. p. 118°, and 2.5 g. of 2,4,6-tribromo-3-aminobenzenephosphonic acid (61%), which decomposed at 222–223° (Nijk[2] reports 222°). The former substance forms as a result of dephosphonation of

(1) Michaelis, *Ber.*, **8**, 493 (1875); Michaelis and Benzinger, *Ann.*, **188**, 278 (1877).

(2) Nijk, *Rec. trav. chim.*, **41**, 461 (1922).

(3) Kosolapoff and Huber, THIS JOURNAL, **69**, 2020 (1947).

(4) Kosolapoff, THIS JOURNAL, **71**, 1876 (1949).

(5) Bauer, THIS JOURNAL, **63**, 2137 (1941).

2-aminobenzenephosphonic acid. Repeated fractional crystallization of the amino acid mixture from water resulted in isolation of the 3-isomer, in the form of colorless needles, which decomposed at 290–292° (heated block); this product gave no detectable amounts of tribromoaniline on treatment with bromine water. The 2-isomer could not be freed of the 3-isomer completely and the material always gave small amounts of the abovementioned tribromoaminobenzenephosphonic acid with bromine water, in addition to the normally expected tribromoaniline; this imperfect material showed a decomposition range of 294–296° (heated block).

Hydrolysis of the mixed diethyl nitrobenzenephosphonates (20 g., 0.0775 mole) by boiling with concentrated hydrochloric acid (175 ml.) for five hours resulted in isolation of 11–12.5 g. (78.5–89.5%) of the free acid mixture, which after crystallization from benzene–ether–ligroin mixture melted at 138–139°. This mixture, in the form of fine, almost colorless needles, could not be resolved into its components by crystallization. Reduction with alkaline sulfide, according to the previously described procedure,[6] gave the amino acid mixture similar to the one described above.

Acknowledgment.—The writer wishes to express his gratitude to Professor R. L. Shriner, who pointed out some time ago the possibility of non-homogeneous nature of Nijk's nitrobenzenephosphonic acid.

Summary

Nitration of diethyl benzenephosphonate results in the formation of appreciable amounts of the *o*-nitro isomer, along with the *m*-nitro isomer.

(6) Kosolapoff, THIS JOURNAL, **69**, 2112 (1947).

AUBURN, ALA. RECEIVED JUNE 13, 1949

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Some Steric Effects of the Cyclohexyl Group in Organosilicon Compounds

BY W. H. NEBERGALL[1,2] AND O. H. JOHNSON

In earlier studies[3,4] the writers found that chlorotricyclohexylgermane, $(C_6H_{11})_3GeCl$, was the sole product of the action of a large excess of cyclohexyllithium upon germanium tetrachloride, no tetracyclohexylgermane apparently being formed. However, the halogen atom of this substituted germane was found to be replaceable by normal alkyl, benzyl and phenyl groups. Attempts to substitute the chlorine atom by the sterically hindered isopropyl, cyclohexyl and *o*-tolyl groups were unsuccessful.

Efforts to prepare tricyclohexylphenylsilane, $(C_6H_{11})_3SiC_6H_5$, by the action of a large excess of cyclohexylmagnesium bromide on phenyltrichlorosilane were reported as unsuccessful by Cusa and Kipping.[5] Instead of the expected tricyclohexyl derivative, they obtained dicyclohexylphenylsilane, $(C_6H_{11})_2SiH\cdot C_6H_5$. This compound was brominated and then alkylated, using ethylmagnesium bromide at 160–180° to form dicyclohexylphenylethylsilane. The failure to obtain tricyclohexylphenylsilane was attributed to the steric effect associated with the cyclohexyl group.

These results led the authors to investigate the extent of substitution of the cyclohexyl group in the silane molecule by the use of cyclohexyllithium upon silicon tetrachloride. Under conventional experimental conditions three cyclohexyl groups are substituted for chlorine atoms in the reaction of cyclohexyllithium in large excess with silicon tetrachloride.

$$3C_6H_{11}Li + SiCl_4 \longrightarrow (C_6H_{11})_3SiCl + 3LiCl$$

The reaction of the tricyclohexylsilicon compound, however, differed from its germanium analog in that efforts to replace the chlorine atom by methyl, ethyl and phenyl groups were unsuccessful.

$$(C_6H_{11})_3SiCl + RLi \longrightarrow \text{No reaction}$$

Both Grignard and organolithium compounds were employed as alkylating agents and the ether was replaced by higher boiling solvents in an endeavor to force the reaction. In addition, since the Si–Br bond is reported[6] as weaker than the Si–Cl bond, bromotricyclohexylsilane was prepared and its alkylation attempted but still no evidence of further substitution was observed.

Chlorotricyclohexylsilane failed to respond to sodium condensation in boiling toluene, whereas bromotricyclohexylgermane condensed to form hexacyclohexylgermane,[3] $(C_6H_{11})_3Ge–Ge(C_6H_{11})_3$, under similar conditions.

Chlorotricyclohexylsilane was reduced to tricyclohexylsilane, $(C_6H_{11})_3SiH$, by lithium aluminum hydride in ether solution. This silane was brominated and iodinated to form the corresponding halides. Hydrolysis of the chloride yielded tricyclohexylsilanol, $(C_6H_{11})_3SiOH$, which was esterified by boiling with acetic anhydride to form acetoxytricyclohexylsilane.

Experimental

Synthesis of Chlorotricyclohexylsilane Using Cyclohexyllithium.—Cyclohexyllithium was prepared by adding, over a period of four hours, 95 g. (0.8 mole) of chlorocyclohexane to 500 ml. of low-boiling petroleum ether containing an excess of lithium metal shot in a one-liter, three-necked flask fitted with a mercury-sealed, air-driven stirrer, a reflux condenser protected by a calcium chloride tube, and a dropping funnel containing the chlorocyclohexane. The reaction mixture was stirred and heated on a warm water-bath to initiate the reaction, after which

(1) Part II from a thesis submitted by W. H. Nebergall to the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy. See THIS JOURNAL, **71**, 1720 (1949), for Part I.

(2) Present address: Indiana University.

(3) Johnson and Nebergall, THIS JOURNAL, **70**, 1706 (1948).

(4) Johnson and Nebergall, *ibid.*, **71**, 1720 (1949).

(5) Cusa and Kipping, *J. Chem. Soc.*, 1040 (1933).

(6) Linus Pauling, "The Nature of the Chemical Bond," 2d ed., Cornell University Press, Ithaca, New York, 1940, p. 53.

the heat of reaction caused continuous refluxing for two hours after all of the chlorocyclohexane had been added. Without filtering out the lithium chloride and excess lithium, 17.0 g. (0.1 mole) of silicon tetrachloride in 50 ml. of petroleum ether was added dropwise to the solution of cyclohexyllithium which was stirred and cooled in an ice–water-bath during the entire addition. After allowing the reaction mixture to stand overnight at room temperature, the lithium chloride and excess lithium were filtered out and the excess cyclohexyllithium was destroyed with 6 *N* hydrochloric acid while the reaction mixture was stirred and cooled in an ice–water-bath. The organic layer was separated, dried over anhydrous calcium chloride, and the solvent was removed by distillation leaving a viscous oily liquid. The product which was crystallized from glacial acetic acid and recrystallized from petroleum ether proved to be chlorotricyclohexylsilane, $(C_6H_{11})_3SiCl$, m. p. 101–102°,[7] yield 15 g. (60%).

Anal. Calcd.: Si, 8.97. Found: Si, 8.8.

Attempted Preparation of Methyltricyclohexylsilane by the Grignard Method.—Methylmagnesium iodide was prepared by treating 3 g. (0.13 mole) of magnesium turnings with 14.2 g. (0.1 mole) of methyl iodide in 150 ml. of absolute ether. On completion of the reaction, 3.1 g. (0.01 mole) of chlorotricyclohexylsilane dissolved in 20 ml. of dry toluene was added to the Grignard reagent. The reaction mixture was refluxed for one hour and then the uncombined ether was replaced by dry toluene. After heating the mixture on a steam-bath for three hours, the Grignard reagent was destroyed by pouring the reaction mixture into a mixture of cracked ice and dilute hydrochloric acid. The organic layer was separated and dried over anhydrous calcium chloride. The toluene was removed by air evaporation, yielding 2.5 g. of colorless crystals, which were recrystallized from low-boiling petroleum ether; m. p. 100–101°. A test for the chloride ion following hydrolysis with alcoholic potassium hydroxide was positive, indicating that the original chlorotricyclohexylsilane had undergone no change.

Attempted Substitution of Chlorotricyclohexylsilane Using Organolithium Compounds.—Methyllithium was prepared from 14.2 g. (0.1 mole) of methyl iodide and an excess of lithium metal shot in 150 ml. of anhydrous ethyl ether by the general procedure outlined for the preparation of cyclohexyllithium. On completion of the reaction, 3.1 g. (0.01 mole) of chlorotricyclohexylsilane dissolved in 25 ml. of ether was added to the solution of methyllithium. The mixture was brought to the reflux temperature and held there for two hours. The ethyl ether was replaced by petroleum ether (50–60°) and the reaction mixture was refluxed overnight. After hydrolyzing the methyllithium with dilute hydrochloric acid, the ether layer was separated and the ether was removed by evaporation. The product, recrystallized from glacial acetic acid, melted at 100–101°; test for the chloride ion was positive following hydrolysis with alcoholic potassium hydroxide. Again the methyl group failed to replace the chlorine atom of chlorotricyclohexylsilane.

Using similar procedures, attempts were made to replace the chlorine atom with ethyl and phenyl groups by the organolithium method. In each case, failure was encountered.

Suspecting that the resistance of the chlorine to substitution might be due to the stability of the Si–Cl bond, the less stable bromo derivative was prepared and an attempt was made to alkylate it, using ethyllithium. Once again, bromotricyclohexylsilane was reclaimed, unaltered, at the end of the experiment.

An Attempt to Synthesize Hexacyclohexyldisilane.—A solution of 6 g. of chlorotricyclohexylsilane in 100 ml. of dry toluene was heated with an excess of metallic sodium in a 200-ml., three-necked flask, fitted with a reflux condenser and adapted for flushing with nitrogen. The mixture was held at the reflux temperature for four hours during which time no indications of a reaction were apparent. The toluene solution was then removed from the sodium and upon evaporation of the solvent, 5.8 g. of the original chlorotricyclohexylsilane was reclaimed; m. p. 100–101°; test for the chloride ion was positive.

Reduction of Chlorotricyclohexylsilane by Lithium Aluminum Hydride.—A solution of 6 g. (0.019 mole) of chlorotricyclohexylsilane in 50 ml. of anhydrous ethyl ether was added dropwise to an excess of lithium aluminum hydride in 100 ml. of ethyl ether contained in an apparatus adapted for refluxing and excluding moisture. The reaction mixture was refluxed for one-half hour and then the ethyl ether was replaced by low-boiling petroleum ether. The excess lithium aluminum hydride and the chlorides of lithium and aluminum as products of the reaction are insoluble in petroleum ether, whereas the desired product, tricyclohexylsilane is soluble. After warming the petroleum ether solution, the insoluble substances were filtered out and most of the petroleum ether was removed by distillation at atmospheric pressure and the rest of the ether was taken off under reduced pressure. The tricyclohexylsilane, $(C_6H_{11})_3SiH$, obtained was an oily liquid which boiled at 183–185° (9 mm.), $n^{25}D$ 1.5132, yield 5 g. (90%). The compound did not freeze in a bath of Dry Ice and ethanol.

Anal. Calcd.: Si, 10.08. Found: Si, 10.0.

Bromination of Tricyclohexylsilane.—A solution of 1 g. of this silane in 50 ml. of carbon tetrachloride was treated with a slight excess of bromine. A carbon tetrachloride solution of the bromine was added dropwise to the silane solution until the bromine color no longer disappeared and the formation of hydrogen bromide ceased. The reaction mixture was heated to boiling for a few minutes and then the product was crystallized by air evaporation of the solvent. The yield of bromotricyclohexylsilane, $(C_6H_{11})_3SiBr$, m. p. 112–113°, was quantitative.

Anal. Calcd.: Si, 7.85. Found: Si, 7.9.

Iodination of Tricyclohexylsilane.—A sample of 2.8 g. of this compound was dissolved in 50 ml. of carbon tetrachloride and a slight excess of iodine crystals was added to the solution. The reaction mixture was refluxed for two hours, at the end of which time hydrogen iodide ceased to be evolved. The excess iodine was removed by combining it with powdered antimony and filtering. The carbon tetrachloride was replaced by low-boiling petroleum ether and the product, $(C_6H_{11})_3SiI$, was crystallized from this solvent and recrystallized from absolute ethanol; m. p. 97–98°, yield 2.1 g. (52%).

Anal. Calcd.: Si, 6.94. Found: Si, 7.0.

Iodotricyclohexylsilane appears to be quite unstable in view of the fact that samples of the crystalline product soon turn brown and its solutions take on a violet coloration on exposure to the air.

The Hydrolysis of Chlorotricyclohexylsilane.—A sample of 10 g. (0.032 mole) of this chloride was dissolved in 200 ml. of boiling, 5% alcoholic potassium hydroxide. Immediately a white precipitate of potassium chloride began to form and the reaction was complete in a few minutes. An equal volume of water was added to the solution which caused the formation of a white precipitate of tricyclohexylsilanol, $(C_6H_{11})_3SiOH$. This product was filtered out, crystallized from ethyl ether, and recrystallized from low-boiling petroleum ether; m. p. 176–177°, yield 8.2 g. (87%).

Anal. Calcd.: Si, 9.53. Found: Si, 9.4.

The Esterification of Tricyclohexylsilanol.—A solution of 3 g. (0.01 mole) of this silanol in 20 ml. of acetic anhydride was held at the reflux temperature for two hours. The solution was then cooled in an ice–water-bath and upon agitation of the mixture, a crop of colorless crystals formed. The product was collected on a sintered-glass filter crucible and washed with ethanol. The dried crystals melted at 82–83° and analysis indicated acetoxytricyclohexylsilane, $(C_6H_{11})_3Si—OCOCH_3$, yield 2.7 g. (80%).

Anal. Calcd.: Si, 8.34. Found: Si, 8.5.

(7) All melting points are uncorrected.

Summary

1. It has been found that cyclohexyllithium in large excess reacts with silicon tetrachloride to form chlorotricyclohexylsilane but no tetracyclohexylsilane.

2. Attempts to replace the chlorine atom of chlorotricyclohexylsilane by methyl, ethyl and phenyl groups using both Grignard and organolithium compounds as alkylating agents failed. In addition, this chlorosilane failed to respond to sodium condensation to give the disilane. These results may be due to the steric properties of the three cyclohexyl groups attached to the silicon atom in chlorotricyclohexylsilane.

3. Six new compounds have been prepared and some of their properties described. These compounds are: chlorotricyclohexylsilane, bromotricyclohexylsilane, iodotricyclohexylsilane, acetoxytricyclohexylsilane, tricyclohexylsilane and tricyclohexylsilanol.

MINNEAPOLIS 14, MINN. RECEIVED JUNE 20, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY, CALIFORNIA]

Photochemical Studies of the Porphyrins. II. The Photoöxidation of Chlorins by Various Quinones

BY FRANK M. HUENNEKENS[1] AND M. CALVIN

Calvin and Dorough[2] have previously established that zinc tetraphenylchlorin is photooxidized in the presence of quinones to zinc tetraphenylporphin. This reaction was studied in great detail for 1,2-naphthoquinone and the following observations made: (1) There is no dark complex formed between the quinone and chlorin. (2) Light adsorbed by the chlorin (6225 Å.) is required. (3) Oxygen inhibits the reaction. (4) The reaction rate is directly independent to the light intensity and inversely related to the temperature. (5) The reaction rate is independent of the naphthoquinone concentration in the range 10^{-3} to 10^{-6} M. (The chlorin concentration is initially about 10^{-5} M.) (6) A function of the chlorin concentration gives a straight line when plotted against time.

This work has now been extended to include both ortho- and para-quinones (eight in all), as well as measurements on magnesium tetraphenylchlorin.

Experimental

Part 1. Apparatus.—The apparatus and methods were essentially the same as those employed by Calvin and Dorough. The reader is referred to the preceding paper in this series for complete details.[2]

Light Source.—The actinic light was obtained from the tungsten filament lamp (operated at 9 volts) and the monochromator system of a Beckman Quartz Spectrophotometer, Model DU. With the wave length set at 6225 Å. and the slit width at 0.8 mm. the spectral segment was 28.8 Å. In the case of certain para-quinones the reaction was slow; this necessitated focussing the Beckman lamp with great care so that an appreciable reaction could be observed in a matter of a few hours.

Light Intensity Measurements.—After the lamp had been on for at least thirty minutes, the thermostatted cell compartment and phototube housing were removed and a small thermopile (without window) was placed at a fixed, reproducible distance from the front face of the Beckman. At this distance the light beam had an area of 1.77 sq. cm.; the opening of the thermopile was centered in this beam. The intensity of the beam was determined at the beginning and end of each run and the average computed for the mid-point of that run. The thermopile and galvanometer were calibrated with a U. S. Bureau of Standards radiation lamp; the sensitivity was found to be 119.4 watts/sq. cm./cm. deflection. Using the same principles as in the previous paper[2] but with slightly different constants I_0 (in photons/sec.) may be calculated from the galvanometer deflection, D (in cm.), by the following equation: $I_0 = 6.56 \times 10^{14} \times D$.

Reaction Vessel.—The reaction vessel was an ordinary 1-cm. square Pyrex mandrel cell with a magnetic stirrer and an evacuation stopcock built into the cell top (see Fig. 6, reference (2)).

Temperature Control.—Scrupulously clean water, maintained in a large thermostat at 25.0 ± 0.1°, was circulated slowly through the modified Beckman cell compartment with quartz windows. The top of the reaction cell above the water was enclosed in a light-proof cover and heated by a stream of hot air to *ca.* 40°; the heating prevented the benzene solution in the evacuated cell from distilling and condensing on the stirring motor in the upper part of the cell.

Routine Procedure.—In the dark the quinone and chlorin solutions in benzene were mixed: 2.56 cc. of the resultant solution was delivered via a calibrated overflow cup to the reaction cell. The ground glass connection between the top and the bottom of the cell was susceptible to leaks due to striations in the grease caused by the heat and mechanical vibrations of the stirrer. This was remedied by using Cello-Grease No. 14-637, manufactured by the Fisher Scientific Company; the product is guaranteed to maintain its consistency up to 120°. Perfect seals were obtained as follows: The ground glass surfaces at the joint were heated and a thin film of melted grease applied with a brush. The joint was clamped together under light pressure and allowed to cool for thirty minutes. The cell and solution were de-oxygenated by the method of freezing the assembly in liquid nitrogen and evacuating the cell. After thawing the solution, purified hydrogen (passed over hot copper according to the method of Michaelis)[3] was admixed with the vapor phase and the process repeated. Six sweepings with hydrogen were used.

(1) University of California Fellow in Chemistry, 1947–1948. Present address: The Enzyme Institute, University of Wisconsin, Madison, Wisconsin.

(2) Calvin and Dorough, THIS JOURNAL, **70**, 699 (1948), Paper I of this series.

(3) Michaelis in "Physical Measurements of Organic Chemistry," Vol. II, edited by A. Weissberger, Interscience Publishers, Inc., New York, N. Y., 1946, p. 1096.

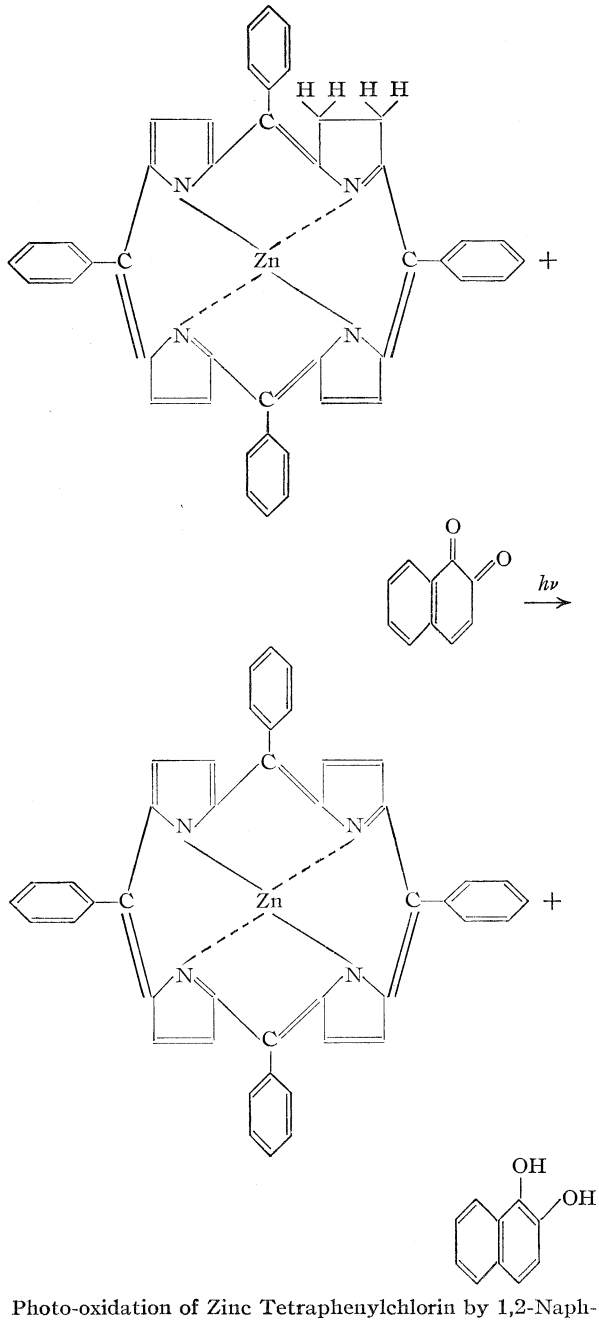


Photo-oxidation of Zinc Tetraphenylchlorin by 1,2-Naphthoquinone

Analytical Method.—After the light intensity had been measured and temperature equilibria established, the cell was illuminated with stirring for several time intervals. At the end of an illumination period the slit width was closed to 0.02 mm., the stirring motor stopped, and the log $1/T$[4] of the solution read for the wave lengths 6225, 5510 and 4650 Å.

Part 2. Materials.—Pure crystalline tetraphenylporphin, tetraphenylchlorin and the corresponding zinc salts were prepared by the methods of Ball, Dorough and Calvin.[5]

Magnesium Tetraphenylchlorin and Porphin.—The reaction was carried out in a standard Grignard apparatus with a bubbler system to remove traces of oxygen in the nitrogen.[6] The reaction flask was charged with 2.5 g. of pure magnesium turnings and the assembly gently heated and swept with nitrogen. Fifteen cc. of an absolute ether solution containing 6.9 cc. of methyl iodide was placed in the separatory funnel and 5 cc. admitted to the flask with gentle stirring. As soon as the reaction began, the remainder of the ethereal solution was added slowly enough to keep the reaction under control. Ten cc. of carefully purified dioxane[7] containing about 1 mg. of tetraphenylporphin was added dropwise through the separatory funnel. The reaction went smoothly, the porphin being converted quantitatively to the magnesium complex and the dioxane causing the magnesium iodide to precipitate. At the conclusion of the reaction 50 cc. of 1 *M* ammonium chloride was added in small portions to decompose the unused Grignard reagent (caution—violent evolution of methane!). The mixture was quantitatively transferred to a separatory funnel, shaken with 35 cc. of benzene and the benzene layer washed three times with 1 *M* ammonium chloride, twice with water and dried over anhydrous sodium sulfate. The benzene solution was concentrated under reduced pressure to about one-third its original volume to remove any residual methyl iodide, ether or dimethylmagnesium and then diluted to 50 cc.

Magnesium tetraphenylchlorin was prepared in the same manner except that all reactions were carried out in near darkness and the product, being photosensitive, had to be stored in a dark-box. Both magnesium porphin and chlorin decompose readily in the presence of acids, or even upon being evaporated to dryness. In addition, the chlorin complex decomposes spontaneously, even in

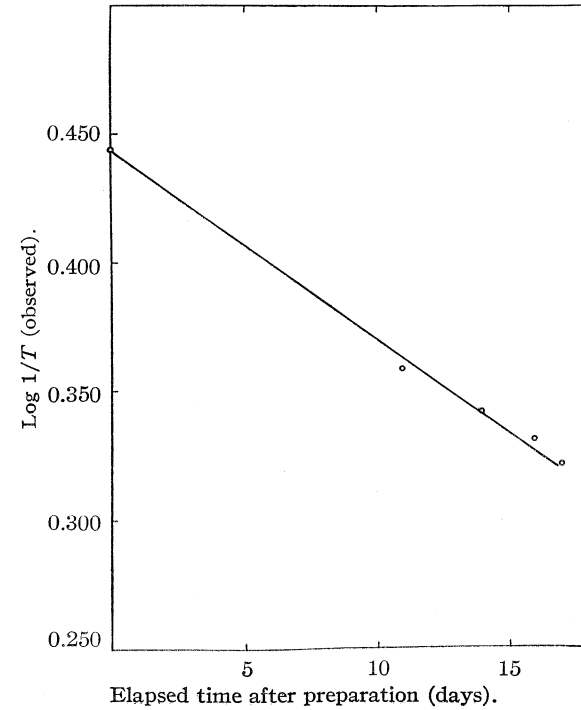


Fig. 1.—Decay of magnesium tetraphenylchlorin as a function of time.

(4) If T is the fraction of light transmitted and I_0 and I are the incident and outgoing light intensities, respectively, the value of log I_0/I read directly from the Beckman Spectrophotometer is equivalent to log $1/T$.

(5) Ball, Dorough and Calvin, THIS JOURNAL, **68**, 2278 (1946).

(6) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, Boston, 1941, pp. 395–404.

(7) *Ibid.*, p. 369.

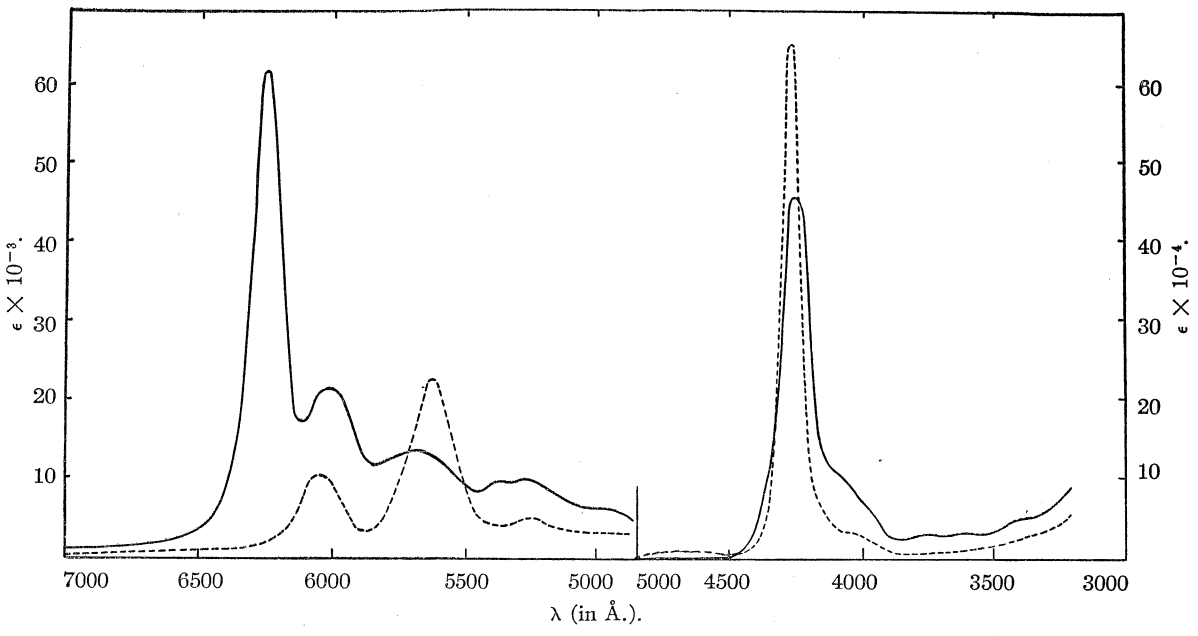


Fig. 2.—- - - - Magnesium tetraphenylporphin; — magnesium tetraphenylporphin in benzene.

the dark. The almost linear decrease of concentration with time is shown in Fig. 1. For rate runs the solutions were used within two days after preparation and the initial concentration of magnesium chlorin determined spectrophotometrically.

The concentrations of the magnesium metal complexes were determined by converting an aliquot to the free base. Five cc. of the benzene solution was placed in a separatory funnel and extracted with two 1-cc. portions of concentrated hydrochloric acid. The benzene layer was then washed twice with 5 cc. of water, twice with 5 cc. of concentrated ammonium hydroxide and finally three times with 5 cc. of water. After drying over sodium sulfate, the benzene solution was diluted to 10 cc. The concentration of the free base was determined spectrophotometrically. The absorption spectra of the magnesium complexes are shown in Fig. 2.

Quinones.—9,10-Anthraquinone, 1,2-benz-9,10-anthraquinone, 9,10-phenanthraquinone, 1,4-benzoquinone and 1,4-naphthoquinone were all obtained as stock substances recrystallized from ether or ethyl alcohol.

1,2-Benzoquinone was prepared by oxidizing pyrocatechol with freshly prepared silver oxide in anhydrous ether.[8] The product was a red crystalline powder which decomposed without melting in the range 60–80°. The compound was unstable and decomposed in hydroxylated solvents within a few hours. A solution in anhydrous benzene at 0° stood for several days without decomposition.

1,2-Naphthoquinone (Sample A) was prepared by oxidizing 1-amino-2-naphthol hydrochloride with ferric chloride.[9] The dark golden product was kept as an amorphous cake as recommended by Fieser. At 110–114° the substance darkened and complete decomposition occurred in the region 135–140°.

1,2-Naphthoquinone (Sample B).—The Eastman Kodak product was purified by two sublimations *in vacuo*. The orange needles darkened and decomposed at 110–115°.

Diphenoquinone.—A suspension of 1.0 g. of 4,4'-dihydroxydiphenyl and 20.0 g. of lead dioxide in 50 cc. of anhydrous benzene was boiled gently for five minutes and filtered. The filtrate evaporated to about one-third its original volume, and cooled in an ice-bath yielded crystals of diphenoquinone which were removed by filtration and dried *in vacuo*. Recrystallized once from benzene, the product consisted of orange-red needles with a steely luster and melted at 163–165°.

Part 3. Calculations.—At various times during a rate run log $1/T$ values for three different wave lengths were read from the spectrophotometer. The band at 6225 Å. is characteristic of the zinc chlorin, the band at 5510 Å. is characteristic of the zinc porphin and the band at 4650 Å. is due to the zinc chlorin–oxygen product. The extinction coefficients of these complexes are given in Table I. From the 6225 and 5510 Å.

TABLE I

MOLAL EXTINCTION COEFFICIENTS OF ZINC COMPLEXES

Substance	$\epsilon \times 10^{-3}$ 6225 Å.	5510 Å.	4650 Å.
Zinc chlorin	54.9	5.9	2.0
Zinc porphin	1.0	22.2	1.8
Zinc chlorin–oxygen product	1.9	7.5	38.7

bands the decrease in chlorin concentration (or, conversely, the increase in porphin concentration) may be calculated. A rise in the 4650 Å. band indicates that oxygen is present and competing with the quinone for the chlorin. This effect can be corrected for and the true rate for the quinone–chlorin reaction can be determined. The oxygen–chlorin reaction is treated in another paper.[10]

Any proposed mechanism for the reaction must be consistent with the observations of Calvin and Dorough as set forth in the first section of this paper. Furthermore, anticipating the experimental results, the mechanism must explain why the quantum yield does not vary with quin-

(8) Willstätter and Pfannenstiel, *Ber.*, **37**, 4745 (1904); Willstätter and Muller, *Ber.*, **44**, 2171 (1911).

(9) Fieser, "Organic Syntheses," **17**, 68 (1937).

(10) Huennekens and Calvin, THIS JOURNAL, **71**, 4031 (1949).

one concentration over a wide range, but, nevertheless, is different for each particular quinone. The key step in the mechanism (No. 6) was suggested to one of the authors (F. H.) by Prof. G. K. Rollefson. The symbols have the following significance: CH_2 = zinc chlorin in the ground state, CH_2^* = zinc chlorin in the excited singlet state, $CH_2^{\pm}$ = zinc chlorin in the triplet state, C = zinc porphin, Q = quinone, QH_2 = hydroquinone, S = solvent and wall.

$$CH_2 + h\nu = CH_2^* \quad (1)$$

$$CH_2^* = CH_2 + h\nu_f \quad (2)$$

$$CH_2^* + S = CH_2 + (S + kT) \quad (3)$$

$$CH = CH_2^{\pm} \quad (4)$$

$$CH_2^{\pm} + Q = C + QH_2 \quad (5)$$

$$CH_2^{\pm} + Q = CH_2 + (Q + kT) \quad (6)$$

Making the usual assumptions about the existence of steady states for both the excited singlet and triplet state molecules, we may write for the disappearance of zinc chlorin

$$\frac{d(CH_2)}{dt} = -\frac{k_5}{k_5 + k_6} \times \frac{k_4}{k_2 + k_3(S) + k_4} \times k_1 I_{abs.} \quad (7)$$

since the rate of formation of (CH_2^*) is dependent solely on the rate of absorption of light, *i. e.*

$$r_1 = d(CH_2^*)/dt = k_1 I_{abs.} \quad (8)$$

The conversion factor k_1 must transform photons absorbed per second into moles per liter per second of photons absorbed.

$$k_1 = 10^3/NV \quad (9)$$

where N is Avogadro's number and V is the volume of the solution (in cc.) The apparent volume delivered to the cell is 2.56 cc.; during pumping some of the solvent is evaporated and the true volume is obtained by employing the equation

$$V = 2.56 \times (C_m/C_0) \quad (10)$$

where C_m = theoretical concentration of the chlorin solution (allowing for dilution by the quinone solution) and C_0 = the concentration actually determined by the initial reading before illumination.

$I_{abs.}$ may be determined from I_0, the intensity from the Beckman, and an experimental molal extinction coefficient, Σ, of the chlorin

$$I_{abs.} = I_0 (1 - 10^{-\Sigma(CH_2)d}) = I_0 A \quad (11)$$

As previously, (CH_2) = the concentration of zinc chlorin and d = the thickness of the cell = 1 cm.

The quantum yield, γ, is expressed by the product of the fractions

$$\gamma = \frac{k_6}{k_5 + k_6} \times \frac{k_4}{k_2 + k_3(S) + k_4} \quad (12)$$

Substituting equations (8) and (12), equation (7) becomes

$$-d(CH_2)/dt = \gamma k_1 I_0 A \quad (13)$$

Transposing and integrating, letting π represent the integration constant

$$(CH_2) + (1/\Sigma) \log A = -k_1 \gamma I_0 t + \pi \quad (14)$$

The values of (CH_2) are determined from the readings at 6225 Å. Since neither the porphin nor the oxygenated product have any appreciable absorption at this wave length

$$(CH_2) = (\log 1/T)_{obs.}/54.9 \times 10^3 \quad (15)$$

The values of $(CH_2) + (1/\Sigma) \log A$ are plotted as a function of time and a straight line is obtained. Let M be the slope of the line.

The quantum yield is obtained from the slope of the concentration function–time curve by the equation

$$\gamma = -M/k_1 I_0 \quad (16)$$

The apparent molal extinction coefficient, Σ, was measured from a chlorin solution with the thermopile–galvanometer under conditions identical with those prevailing during the rate run. The value obtained, $\Sigma = 20.3 \times 10^3$, is smaller than would be expected simply by changing logarithmic bases

$$\Sigma = 54.9 \times 10^3/2.303 = 23.8 \times 10^3$$

The low experimental value is due to the method of measurement. $\epsilon = 54.9 \times 10^3$ was obtained in the usual manner on the spectrophotometer with the slit width set at 0.025 mm. admitting the incident light as a spectral segment of 0.9 Å. When Σ was measured, the slit was opened to 0.8 mm. corresponding to a segment of 28.8 Å. The sharpness of the absorption band and the width of the illuminating band gave rise to the low value of the apparent extinction coefficient.

In the case of magnesium tetraphenylchlorin Σ was 20.5×10^3.

A correction factor of 0.98 was applied to I_0 to compensate for light lost through absorption and scattering by the quartz windows and water of the thermostatted cell compartment.

Part 4. Tabulation of Data.—To avoid unnecessary repetition only one run, no. 54, will be considered in detail. Table II illustrates the data obtained when zinc chlorin was photooxidized by 9,10-phenanthraquinone. The plot of the function $(CH_2) + (1/\Sigma) \log A$ against time is shown in Fig. 3. The results of all runs are summarized in Table III. It is estimated that the quantum yields are accurate to 5–10%, hence the results are expressed only to two significant figures.

TABLE II

RUN NO. 54—ZINC CHLORIN WITH 9,10-PHENANTHRAQUINONE

Time	log 1/T 6225 Å.	5510 Å.	4650 Å.	Chlorin concn.	$(CH_2) + (1/\Sigma) \log A$
0	0.508	0.087	0.079	0.926×10^{-5}	-1.30×10^{-5}
15	.471	.093	.075	.857	−1.51
30	.438	.098	.068	.798	−1.70
45	.406	.105	.063	.738	−1.89
96	.314	.123	.052	.572	−2.53

TABLE III

QUANTUM YIELDS OF ZINC TETRAPHENYLCHLORIN

Run	Chlorin concn. $\times 10^5$	Quinone	Quinone concn.	Slope (M) $\times 10^9$	V	$k_1 \times 10^{22}$	D	$I_0 \times 10^{14}$	γ
70	1.25	1,4-Benzo-	2.57×10^{-2}	1.20	2.28	7.23	1.25	8.19	0.0020
71	1.25	1,4-Naphtho-	1.20×10^{-2}	0.819	2.37	6.96	1.13	7.42	.0016
47	1.25	1,4-Naphtho-	3.48×10^{-3}	.567	2.22	7.43	0.84	5.51	.0014
45	1.25	9,10-Anthra-	2.50×10^{-3}	.523	2.14	7.71	0.87	5.71	.0012
59	1.25	9,10-Anthra-	5.00×10^{-5}	.500	2.19	7.53	1.03	6.76	.0010
75	1.25	1,2-Benz-9,10-anthra-	2.33×10^{-3}	1.11	2.39	6.95	1.42	9.32	.0017
76	1.03	Dipheno-	1.30×10^{-4}	1.74	2.40	6.87	1.49	9.77	.0026
46	1.25	9,10-Phenanthra-	2.98×10^{-3}	1.24	2.49	6.62	0.84	5.51	.0034
54	1.25	9,10-Phenanthra-	2.98×10^{-3}	2.08	2.34	7.05	1.10	7.22	.0041
53	1.25	1,2-Naphtho- (A)	4.82×10^{-4}	12.3	2.25	7.33	1.13	7.42	.023
74	1.25	1,2-Naphtho- (B)	7.71×10^{-4}	2.88	2.42	6.82	1.32	8.65	.0049
60	1.09	1,2-Benzo-	1.00×10^{-3}	4.17	2.20	7.50	0.98	6.43	.0086
62	1.25	1,2-Benzo-	3.66×10^{-5}	4.17	2.21	7.47	1.03	6.76	.0083
		Quantum Yields of Magnesium Tetraphenylchlorin							
64	0.658	1,2-Naphtho- (A)	6.50×10^{-4}	Not calculated: —; curved line: $(CH_2) + (1/\Sigma) \log A$ *vs.* time plot					
65	.558	1,2-Naphtho- (A)	7.71×10^{-4}	Not calculated: —; curved line: $(CH_2) + (1/\Sigma) \log A$ *vs.* time plot					
66	.480	1,2-Naphtho- (A)	4.86×10^{-3}	2.07	2.30	7.17	1.50	9.84	.0030
69	.455	1,4-Benzo-	1.27×10^{-2}	0.467	2.20	7.50	1.32	8.66	.00072

Discussion

The energy levels involved in this photochemical transformation may be represented by a Jablonski diagram (Fig. 4). The ground state of the chlorin molecule is a singlet since there are no unpaired electrons; the excited level, due to absorption at 6225 Å., is also a singlet as evidenced by the high transition probability ($\epsilon = 54.9 \times 10^3$). Calvin and Dorough[2] have shown that the chlorin molecules could not be reacting from the S′ state, for not only is the lifetime of this state too short (*ca.* 10^{-9} sec.) compared to the mean time between chlorin–quinone collisions (*ca.* 10^{-5} sec.), but also the chlorin–quinone reaction would compete against fluorescence and solvent deactivation and the quantum yields, therefore, should increase with increasing quinone concentration. Their identification of the triplet as the reactive level was based upon agreement with the kinetic data, direct demonstration of the triplet or phosphorescent state and the greatly reduced quantum yield in the case of the paramagnetic copper chlorin.

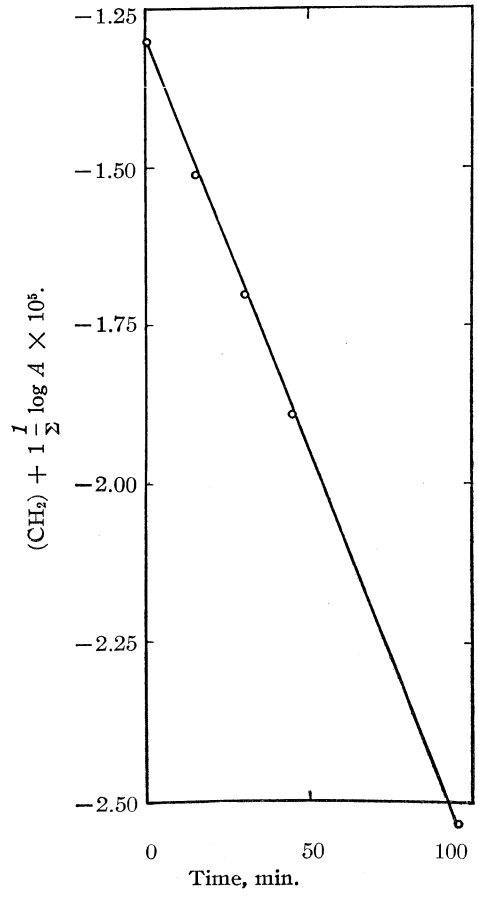


Fig. 3.—Run no. 54.

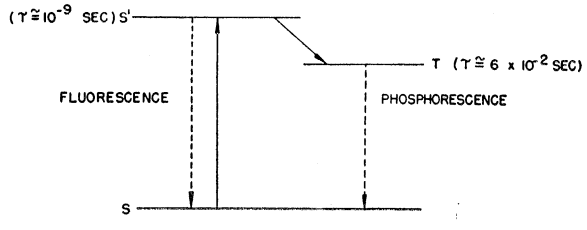


Fig. 4.—Jablonski energy-level diagram.

A very interesting observation, made by these authors, was that the reaction had a negative temperature coefficient. The average quantum yield of four runs at 25° was 0.021 whereas the average of two runs made at 10° was 0.024. In

TABLE IV

QUANTUM YIELDS AND OXIDATION POTENTIALS OF VARIOUS QUINONES

No.	*o*-Quinones	γ	E^{0a}	No.	*p*-Quinones	γ	E_0
1	9,10-Phenanthra-	0.0035	0.41	4	9,10-Anthra-	0.0011	0.25
2	1,2-Naphtho-	.0049	.51	5	1,2-Benz-9,10-anthra-	.0017	.36
3	1,2-Benzo-	.0085	.71	6	1,4-Naphtho-	.0015	.53
				7	1,4-Benzo-	.0021	.71
				8	Dipheno-	.0026	.95

[a] Quinone potentials are taken from G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1941, pp. 311–312. The values are those of E^0 (cor.) rather than E^0 (exp.). The potential is negative when the half-reaction is written: $H_2Q = Q + 2H^+ + 2e^-$.

a later section it will be shown that the absolute value of these quantum yields reported for 1,2-naphthoquinone are subject to an uncertainty. Nevertheless, we shall assume that these relative quantum yields reflect the true behavior of the system and that the magnitude of the temperature effect is beyond normal experimental error.

Kasha and Powell,[11] from an analysis of the rates of the various processes which could occur in the S′ state, have shown that for a maximum probability of interaction between the S′ and T states the "crossing over" must occur at the lowest point of the S′ curve (Fig. 5). Molecules excited to the S′ state may arrive at high vibrational levels but the cascade downward is rapid until a Boltzmann temperature distribution is established among the lower vibrational levels. Since lowering the temperature results in increased quantum yields, it follows that the crossing over point in this case must be located near the bottom of the S′ curve.

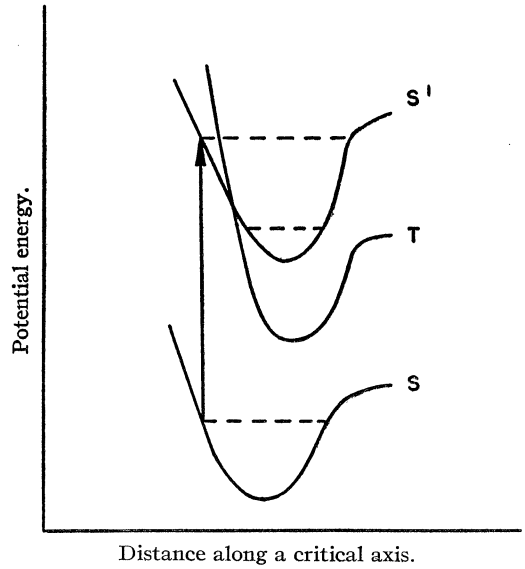


Fig. 5.—Potential energy diagram.

Another effect of lowering the temperature would be to decrease the probability of the back reaction caused by long-lived molecules in the triplet state being thermally reactivated to the S′ state. The separation of the S′ and T minima, estimated from the spectral data, is about 10 kcal.

As illustrated by Table III each quinone has a different quantum efficiency in the photo-oxidation of zinc chlorin. The photo-activation of the chlorin molecules to the triplet level merely loosens the two hydrogen atoms on the β-positions of the pyrrole nucleus. The quinone, which functions as the hydrogen acceptor, removes the hydrogens during collisions with the chlorin. Each quinone–triplet chlorin collision is not effective but the relative efficiency of this process among the various quinones should depend upon the decrease of free energy involved in the reduction of the quinone to the hydroquinone. Thus, the quantum yields should be proportional to some function of the free energy changes. In Table IV a tabulation has been made of the quantum yields and the standard oxidation potentials of the quinones. Plotting these quantities against each other, as in Fig. 6, two straight lines are obtained, one for the ortho-quinones and one for the para-quinones.

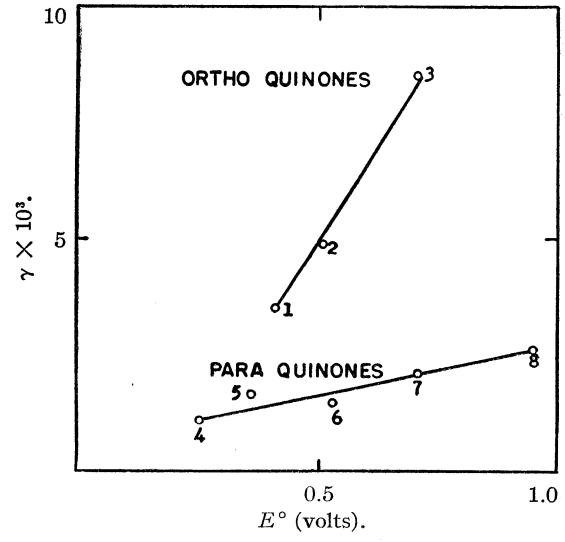


Fig. 6.—Plot of γ *vs.* E° for quinones.

The fact that there are two lines rather than one indicates that the ortho and para-quinones react by different mechanisms. An ortho-quinone may be capable of removing both hydrogens, even in a stepwise manner, during one energetically effective collision, whereas a para-quinone, unable

(11) Kasha and Powell, THIS JOURNAL, **69**, 2909 (1947).

to re-orient during the life-time of the activated complex, would require several collisions.

Previous work by Calvin and Dorough[2] on 1,2-naphthoquinone had given a quantum yield of about 0.021. The disagreement between this value and the present results was investigated briefly. The 1,2-naphthoquinone used in the early work had been prepared by the ferric chloride oxidation of 1-amino-2-naphthol hydrochloride. A portion of this material, labeled Sample A, was purified by vacuum sublimation and employed in run no. 53. The quantum yield of 0.023 is in good agreement with the previous value. Next, a sample of Eastman Kodak Co. 1,2-naphthoquinone, labeled Sample B, was purified by vacuum sublimation and, in run no. 74, gave a quantum yield of 0.0049. This value fitted in the *o*-quinone curve of Fig. 6. Samples A and B were compared further on the basis of melting point, analysis and absorption spectra. The results, listed in Table V, indicate only that A had partially decomposed. Sample A was the

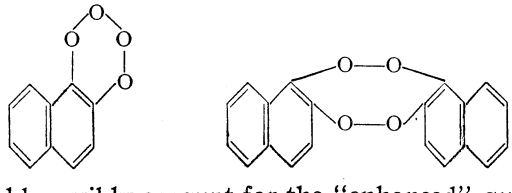
TABLE V

COMPARISON OF PHYSICAL PROPERTIES OF 1,2-NAPHTHOQUINONE

	Sample A	Sample B
Preparation	Ferric chloride oxidation of 1-amino-2-naphthol. Crystallization from water solution	Eastman Kodak Co. stock purified by two sublimations *in vacuo*
Melting point	Darkens at 110–114°, decomposes (to a black oil) 135–140°	Darkens and decomposes 113–114°
Analysis[a]	Calcd. for $C_{10}H_6O_2$ (m. w. 158.2): C, 75.8; H, 3.79%. Found: C, 71.38; H, 4.02; residue, 10.1	Found: C, 76.17; H, 4.29
Absorption spectrum (in benzene)	In the visible region (7000–3500 Å.) both samples displayed the same spectrum. The extinction coefficients were slightly higher for Sample B	

[a] Analysis performed by Mr. C. Koch.

only quinone, in the series of eight, that was prepared in an aqueous medium. Traces of occluded ferric compounds or quinone peroxides of the types[12] shown



could possibly account for the "enhanced" quantum yields obtained with Sample A.

Less extensive experiments were carried out with magnesium tetraphenylchlorin because of its unstability and the low quantum yields which were difficult to measure.

Runs no. 64 and 65 made with 1,2-naphthoquinone (Sample A) and magnesium chlorin exhibited a curved line plot of $(CH_2) + (1/\Sigma)$ log A against time. At these quinone concentrations (*ca.* 5×10^{-4} *M*) an insufficient number of collisions occurred during the triplet lifetime of the magnesium chlorin causing the rate to deviate from the expected straight-line plot. When the concentration was increased to *ca.* 5×10^{-3} *M* as in run no. 56, the rate curve was once again a straight line. In the case of zinc chlorin this concentration "breakdown" did not occur until the quinone concentration had been reduced to about 10^{-6} *M*. Hence, either the lifetime of the magnesium chlorin in the triplet state is shorter than the 10^{-2} sec. observed for zinc chlorin or the quantum efficiency of phosphorescence is less for the magnesium complex, *i. e.*, fewer of the molecules reach the triplet state.

A comparison of magnesium and zinc chlorins may be seen in Table VI. The discrepancy of the ratio for 1,4-benzoquinone could be explained

TABLE VI

COMPARISON OF ZINC AND MAGNESIUM CHLORINS

Oxidant	γ_{Zn}	γ_{Mg}	Ratio γ_{Zn}/γ_{Mg}
1,4-Benzoquinone	0.0021	0.00072	2.9
1,2-Naphthoquinone (Sample A)	.023	.0030	7.7
Oxygen[10]	.0074	.00094	7.9

simply as a difference between the two classes of quinones or the quantum yield for the reaction with the magnesium chlorin could be in error since the rate was so slow and irregular, in that one run, that the assignment of a slope to the individual points was only an approximation.

An attempt was made to determine the life-time of the phosphorescent state for magnesium chlorin using a rotating shutter phosphoroscope in conjunction with a photomultiplier tube and an oscilloscope. No decay curve could be observed corroborating the above conclusions regarding the phosphorescence life-time or phosphorescence efficiency of the magnesium chlorin. However, the magnesium chlorin does have a phosphorescent state, for when a sample was placed in a rotating shutter phosphoroscope and exposed to an ammonia-sensitized plate for three hours, a phosphorescence spectrum was obtained qualitatively similar to that of zinc chlorin.[13]

Acknowledgment.—The authors appreciate the many helpful suggestions made by their colleagues, notably Professors G. K. Rollefson and J. Cason and Drs. G. D. Dorough, M. Kasha, D. McClure, W. Simpson and H. W. Alter.

Summary

1. The zinc and magnesium complexes of tetraphenylchlorin may be photoöxidized to the corresponding porphins by both *o*- and *p*-quinones.

2. Plotting the standard oxidation potential of the quinone against the quantum yield produces one straight line for the *o*-quinones and

(12) Goldschmidt and Graef, *Ber.*, **61**, 1858 (1928).

(13) These measurements were made in the laboratory of Drs. M. Kasha and D. McClure.

another straight line for the *p*-quinones.

3. The rates of photoöxidation for magnesium tetraphenylchlorin are lower than the corresponding zinc chlorin reactions by a factor of almost eight.

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

Photochemical Studies of the Porphyrins. III. The Photoöxidation of Chlorins by Oxygen

BY FRANK M. HUENNEKENS[1] AND M. CALVIN

In the previous paper of this series[1a] it was established that the zinc and magnesium complexes of tetraphenylchlorin may be photooxidized to the corresponding porphin utilizing various ortho- and para-quinones as the hydrogen acceptors. Traces of oxygen were found to interfere with the normal quinone–chlorin reaction and a method of de-oxygenating the solution with purified hydrogen was devised. From a biological point of view, molecular oxygen is of great importance for although it possesses a high oxidation potential and is the final electron acceptor in aerobic systems it is, nevertheless, unable to directly oxidize certain compounds; *e. g.*, reduced pyridinoproteins or cytochrome c. It was of interest to ascertain whether in this case oxygen might be competing with the quinone as an oxidant for the photoactivated zinc chlorin.

Experimental

Part 1. Apparatus and Materials.—The apparatus and materials used in these experiments were the same as described in the previous two papers of this series.[1,2]

The ultimate reaction product, called the zinc chlorin–oxygen complex, obtained when oxygen reacts with photo-activated zinc chlorin, was not isolated in pure form. For absorption spectra purposes a known solution of zinc chlorin, in a sealed Pyrex 1-cm. square cuvette, was exposed to bright sunlight for five minutes. The absorption spectrum of this "unbleached," straw-yellow solution was determined as rapidly as possible (within five minutes) using a Cary Recording Spectrophotometer. The molal extinction coefficients were calculated on the basis that conversion of the initial chlorin was quantitative. The "bleached" product was quite stable since the absorption spectrum of a solution, exposed to diffuse laboratory light for several days, did not change appreciably; furthermore, several different zinc chlorin solutions exposed to light under a variety of conditions yielded the identical product.

The absorption spectrum of the metal-free chlorin–oxygen product was obtained by removing the zinc from a known solution of the "bleached" complex by means of the hydrochloric acid–ammonium hydroxide treatment described in a previous paper.[1]

Rate runs in the presence of both oxygen and a quinone were made inadvertently during the early part of this investigation when imperfectly sealed reaction cells permitted small quantities of oxygen to enter. Since the reaction rate is independent of the concentration of the oxidant provided it exceeds a certain minimum (*ca.* 10^{-6} *M* for zinc chlorin), it is, therefore, unnecessary to know the exact amount of oxygen present.

When oxygen alone was the oxidant, 2 cc. of the chlorin solution and 1 cc. of benzene were delivered directly to the reaction vessel and since the solution was not de-oxygenated by freezing, evacuating and sweeping with hydrogen, no volume correction was required.

Part 2. Calculations.—As will be discussed more thoroughly in a later section, oxygen differs from the quinones in that after the primary oxidation of the chlorin to the porphin a secondary reaction takes place in which the hydrogen peroxide reacts further with the porphin to produce a "bleached" yellow product. This does not interfere with the normal measurement of the quantum yield, since of all the substances in solution only the chlorin absorbs the irradiating light (6225 Å.) and the method of following the reaction depends only upon the disappearance of the chlorin.

In the case of 1,4-benzoquinone and 9,10-phenanthraquinone several runs were made in the presence of oxygen. For these runs, the observed quantum yields (γ) has been multiplied by a correction factor (f) to give the hypothetical quantum yield (γ') which would have been obtained if the quinone alone had reacted with the porphin. This correction factor is derived as follows: consider an entire rate run and let

n = total number of chlorin molecules that have reacted (with quinone and oxygen)
n' = number of chlorin molecules that have reacted with oxygen alone
Q = total number of quanta absorbed
γ = measured quantum yield
γ' = quantum yield of the quinone–chlorin reaction only
$A_0 - A$ = change in the log $1/T$ (the usual log I_0/I from the Beckman Spectrophotometer) reading at 6225 Å. for the entire run

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(1a) Huennekens and Calvin, THIS JOURNAL, **71**, 4024 (1949).

(2) Calvin and Dorough, *ibid.*, **70**, 699 (1948).

$C - C_0$ = change in the log $1/T$ reading at 4650 Å. (the expression is written as $C - C_0$ to keep it positive since $C > C_0$)
ϵ_a = extinction coefficient of zinc chlorin at 6225 Å.
ϵ_c = extinction coefficient of the zinc chlorin–oxygen product at 4650 Å.
$K = V \times N \times 10^3$, a conversion factor, which when multiplied by a concentration change, will give the change in number of molecules. (V is the volume of the solution in cc., N is Avogadro's number)

Now

$$\gamma = n/Q \text{ by definition} \quad (1)$$
$$n = [(A_0 - A) \times K]/\epsilon_a \quad (2)$$

Let us assume, as a first approximation, that the oxygen merely reacted with the chlorin to give the chlorin–oxygen product whose absorption spectrum has been measured and characterized by a band at 4650 Å. and, furthermore, that the rise in the 4650 Å. band is a measure of the oxygenation. Then

$$n' = (C - C_0) \times K/\epsilon_c \quad (3)$$
$$\gamma' = (n - n')/Q \quad (4)$$

Substituting Q from equation (1)

$$\gamma' = \frac{(n - n')}{n} \times \gamma \quad (5)$$

Replacing n and n' from equations (2) and (3) and cancelling K

$$\gamma = \gamma' = \left\{\frac{[(A - A_0)/\epsilon_a] - [(C - C_0)/\epsilon_c]}{(A_0 - A)/\epsilon_a}\right\} \times \gamma \quad (6)$$

This simple correction, applied to oxygenated runs, will give a corrected quantum yield approaching that of a run made in the absence of oxygen. A further improvement is possible. We have assumed that in the absence of oxygen, the 4650 Å. band should remain stationary. Since the extinction coefficient is greater for zinc chlorin than zinc porphin (*ca.* 2.0×10^3 compared to 1.8×10^3) a change from chlorin to porphin, without considering oxygenation, should result in a slight decrease of the 4650 Å. band. Thus, the term $(C - C_0)/\epsilon_c$ should be amended to read $[(C - C_0) + P]/\epsilon_c$ where P represents the number of log $1/T$ units that have been lost through the chlorin going to porphin. P is obviously some function of $(A - A_0)$ and we may let $P = f'(A_0 - A)$. f' is very difficult to evaluate since a rigorously derived expression must take into account not only the change in all three bands (6225, 5510 and 4650 Å.), but also the extinction coefficients of the chlorin, porphin and oxygenated product at these three wave lengths. Because of the complexity of this expression and the uncertainty of the numerical values for several of the nine extinction coefficients, it was decided to accept an empirical value of 0.037 for f'. Inserting this correction and knowing that $\epsilon_a = 54.9 \times 10^3$ and $\epsilon_c = 38.7 \times 10^3$, equation (6) becomes

$$\gamma' = \left\{\frac{\frac{(A_0 - A)}{54.9 \times 10^3} - \frac{(C - C_0) + 0.037\,(A_0 - A)}{38.7 \times 10^3}}{\frac{(A_0 - A)}{54.9 \times 10^3}}\right\} \times \gamma \quad (7)$$

which reduces to

$$\gamma' = \{0.948 - [1.42\,(C - C_0)/(A_0 - A)]\} \times \gamma \quad (8)$$

Part 3. Tabulation of Results.—Table I lists the data for a typical run, No. 48, in which both oxygen and 1,4-benzoquinone were present. The symbols are the same as those employed in the preceding paper.[1] The rate curve for this run, shown in Fig. 1, is essentially a straight line even though two competing reactions are being summed.

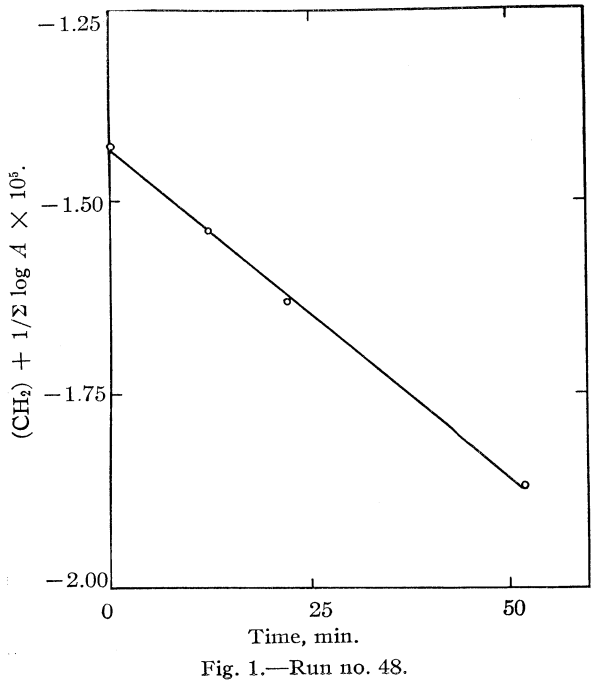

Fig. 1.—Run no. 48.

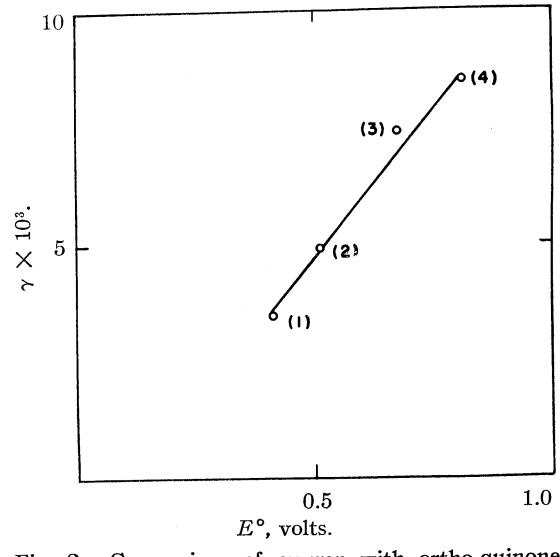

Fig. 2.—Comparison of oxygen with ortho-quinones: (1), 9,10-phenanthraquinone; (2), 1,2-naphthoquinone: (3) oxygen; (4) 1,2-benzoquinone.

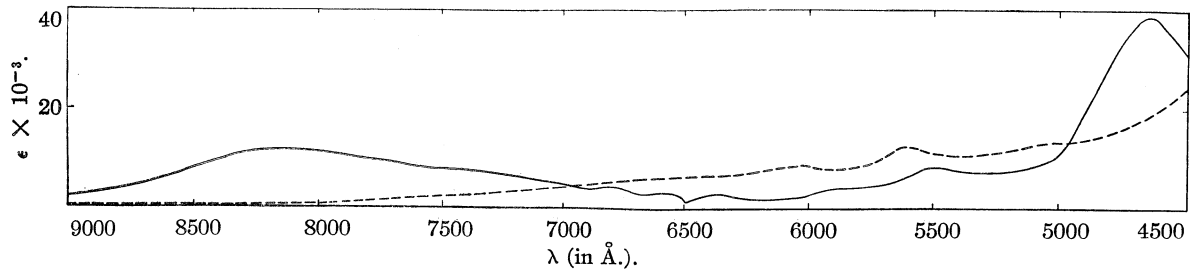

Fig. 3A.—- - - - Magnesium tetraphenylchlorin-oxygen product in benzene; — zinc tetraphenylchlorin-oxygen product in benzene.

TABLE I

RUN NO. 48—ZINC CHLORIN WITH 1,4-BENZOQUINONE AND OXYGEN

Time	Log 1/T 6225 Å.	5510 Å.	4650 Å.	Chlorin concn.	$(CH_2) + 1/\Sigma \log A$
0	0.484	..	0.046	0.881×10^{-5}	−1.43
12	.465	..	.053	.845	−1.54
22	.448	..	.059	.817	−1.63
52	.408	..	.086	.744	−1.87

A summary of all the oxygenated runs, showing the correction factor (f) is presented in Table II. For comparison, a non-oxygenated run, indicated by a blank in the correction factor column, has been included for each quinone.

Summarized data and quantum yields for rate runs made with oxygen alone are listed in Table III.

Discussion

The experimental data suggest that as an oxidant for zinc and magnesium chlorins oxygen is similar in nature to the quinones. Oxygen is reduced to hydrogen peroxide, corresponding to the reduction of a quinone to the hydroquinone. Using 0.68 volt[3] as the standard oxidation potential of the latter couple and 0.0074 as the quantum yield for the oxidation of zinc chlorin by molecular oxygen a comparison is made, in Fig. 2, of oxygen with the ortho-quinones. The quinone values are taken from the preceding paper in this series.[1] While some doubt exists as to the accuracy of the value for the oxygen–peroxide couple, it would seem, nevertheless, that the agreement of oxygen with the ortho-quinone line is too good to be accidental.

In the case of oxygen, a secondary reaction takes place between the hydrogen peroxide and porphin in which the porphin is probably attacked at one of the methine bridges causing the great ring to open to a tetrapyrrole.

In addition to being above to act as a hydrogen acceptor, oxygen, because of its paramagnetism, might conceivably exert another effect upon the reaction. The selection rule which prohibits transitions from the triplet to the ground singlet state is easily broken down in the presence of inhomogeneous magnetic fields or heavy atoms. The non-reactivity of copper chlorin toward

(3) W. M. Latimer, "Oxidation Potentials," Prentice-Hall Inc., New York, N. Y., 1938, p. 38.

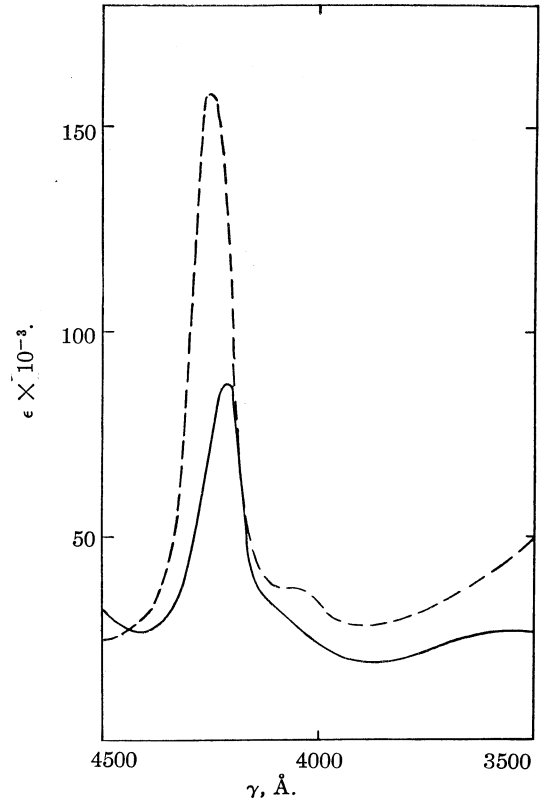

Fig. 3B.

quinones was attributed to the paramagnetism due to the one unpaired electron in the copper orbitals.[2] By similar reasoning, one might expect the paramagnetism of the oxygen molecule to shorten the lifetime of the triplet chlorin molecules causing any oxygenated run to have a slower rate than the corresponding quinone–chlorin reaction without oxygen. From the experimental evidence this is not the case for an ortho-quinone of lower potential than oxygen (*e. g.*, 9,10-phenanthraquinone). The presence of oxygen actually increases the over-all rate; furthermore, it has been demonstrated that oxygen does not inhibit, but competes with, a quinone–chlorin reaction. The oxygen is an external paramagnetic influence and apparently does not affect the chlorin transition probabilities to the same degree as the copper which is incorporated directly into the molecule.

TABLE II

QUANTUM YIELDS—ZINC TETRAPHENYLCHLORIN

Run	Chlorin concn. $\times 10^5$	Quinone	Quinone concn.	Slope (M) $\times 10^9$	V	$k_1 \times 10^{22}$	D	$I_0 \times 10^{14}$	γ	f	γ'
57	1.25	1,4-Benzo-	4.38×10^{-4}	2.38	2.31	7.14	1.06	6.95	0.0048	0.422	0.0020
48	1.25	1,4-Benzo-	5.55×10^{-5}	1.48	2.42	6.82	0.70	4.58	.0047	.447	.0021
51	1.25	1,4-Benzo-	5.55×10^{-3}	1.75	2.39	6.90	1.47	9.64	.0026	.745	.0020
40	1.25	1,4-Benzo-	5.55×10^{-4}	1.64	2.32	7.11	0.82	5.38	.0043	.526	.0023
70	1.25	1,4-Benzo-	2.57×10^{-2}	1.20	2.28	7.23	1.25	8.20	.0020	...	.0020
32	1.68	9,10-Phenanthra-	5.38×10^{-4}	2.32	2.42	6.82	1.04	6.82	.0059	.549	.0033
58	1.25	9,10-Phenanthra-	5.96×10^{-5}	1.98	2.34	7.05	1.08	7.08	.0040	.788	.0032
46	1.25	9,10-Phenanthra-	2.98×10^{-3}	1.24	2.49	6.62	0.84	5.52	.0034	...	.0034

TABLE III

QUANTUM YIELDS—OXYGEN UPON ZINC AND MAGNESIUM TETRAPHENYLCHLORINS

Run	Chlorin	Chlorin concn. $\times 10^5$	Oxygen concn.[4]	Slope (M) $\times 10^9$	V	$k_1 \times 10^{22}$	D	$I_0 \times 10^{-14}$	γ
73	Zinc	1.25	7.28×10^{-3}	3.90	3.00	5.50	1.47	9.64	0.0074
67	Magnesium	0.551	7.28×10^{-3}	0.467	3.00	5.50	1.38	9.05	.00094

The spectra of the "bleached" products of zinc and magnesium chlorins, shown in Fig. 3, are markedly different. Even more surprising are the spectra of the metal-free products (Fig. 4) since, at this point, the compounds would have been identical provided that the hydrogen peroxide had attacked each of the original metallochlorins in the same manner. The obvious differences between the behavior of zinc and magnesium chlorins with oxygen suggests that the reaction may not be clean-cut but rather a compromise between several possibilities. Calvin and Dorough[2] have found that the "bleached" zinc chlorin product, when chromatographed on talc, yielded traces of metal-free chlorin and porphin as well as two unknown substances characterized by blue zones on the column.

Consistent with this is the observation that reaction rates and quantum yields toward a given oxidant change from one metallochlorin to another as illustrated in Table III of this paper and Table VI of the preceding paper.[1] Calvin and Dorough[2] showed that toward 1,2-naphthoquinone copper chlorin is only about one-hundredth as reactive as zinc chlorin. As would be expected, zinc chlorin solutions, in the presence of oxygen, are "bleached" within a few minutes by diffuse indoor light, whereas copper chlorin solutions under

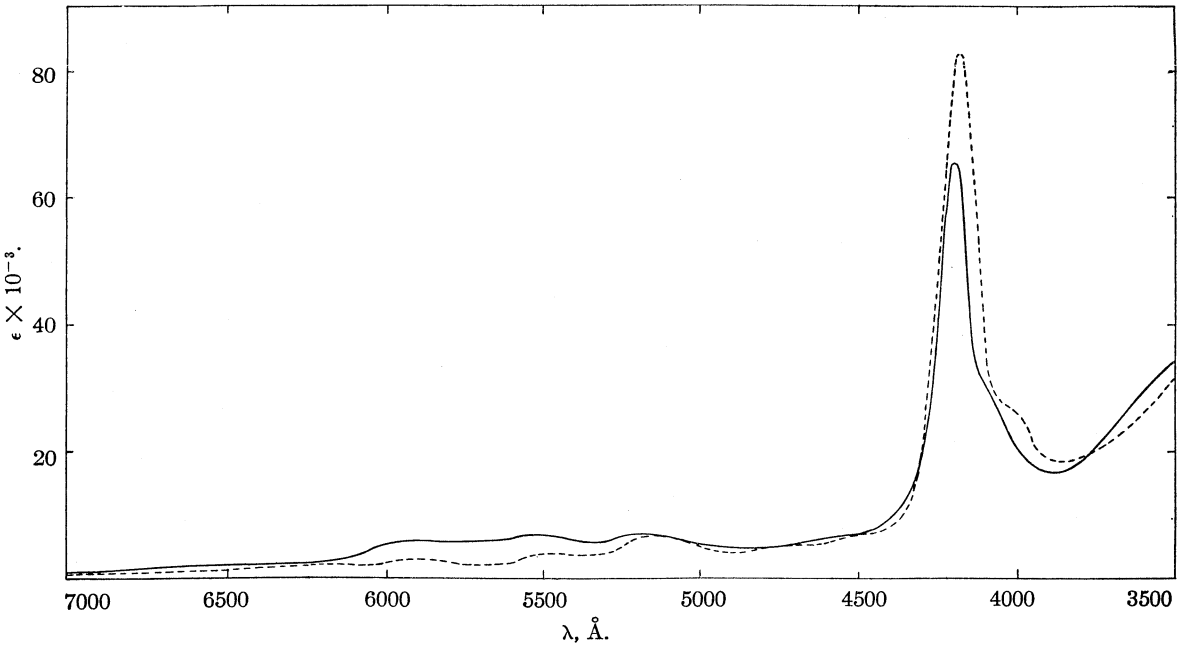

Fig. 4.—- - - -Magnesium tetraphenylchlorin-oxygen product (metal-free); — zinc tetraphenylchlorin in benzene.

(4) Solubility of oxygen in benzene at 19°: "International Critical Tables," 1st ed., 1928, Vol. III, pp. 261–283.

similar conditions are stable for many hours.

The absorption curves of the metallochlorin "bleached" products are qualitatively similar to the curves for irreversible "bleaching" of chlorophyll by oxygen in acetone, as reported by Aronoff and MacKinney.[5] Furthermore, in the same paper, these authors report a value of 5×10^{-4} for the quantum yield of irreversible "bleaching" of chlorophyll solutions in benzene. This is in order of magnitude agreement with our value of 9.4×10^{-4} for the quantum yield of the photo-oxidation of magnesium chlorin by oxygen.

(5) Aronoff and MacKinney, THIS JOURNAL, **65**, 956 (1943).

Summary

1. Zinc and magnesium tetraphenylchlorins may be photo-oxidized by molecular oxygen in a manner similar to ortho- and para-quinones.

2. Oxygen does not inhibit a chlorin–quinone reaction but merely reacts competitively with the quinone for the chlorin (at least for quinones of lower oxidation potential than oxygen).

3. A secondary reaction occurs between hydrogen peroxide and the porphin yielding a product similar to that obtained by "bleaching" chlorophyll in the presence of oxygen.

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[CONTRIBUTION FROM THE INSTITUTE FOR THE STUDY OF METALS, THE UNIVERSITY OF CHICAGO]

The Extraction of Gallium Chloride by Isopropyl Ether

BY NORMAN H. NACHTRIEB AND ROBERT E. FRYXELL

The distribution of gallium chloride between aqueous hydrochloric acid and diethyl ether has received the attention of several workers. Grahame and Seaborg[1] report that the distribution is independent of gallium concentration in the range 10^{-12} to 10^{-3} molar, but Swift[2] reports a relatively greater extraction for higher concentrations.

It is well known that the distribution of gold chloride[3,4] and ferric chloride[5,6,7,8] between aqueous hydrochloric acid and ethers is dependent on the concentration of the metal chloride. In a recent paper the present authors reported data for ferric chloride showing that this distribution (using isopropyl ether) follows the simple Nernst distribution law for sufficiently low ferric chloride concentrations.[7] It was suggested that the existence of polymers in the ether phase need not be postulated to explain the dependence of the distribution on iron at higher concentrations, but alternatively, the anomaly may be due to a self-promoted activity of ferric chloride in the aqueous phase.

This paper reports a similar study which has been made of the distribution of gallium chloride between aqueous hydrochloric acid and isopropyl ether.

Experimental

Preparation of Solutions.—For the majority of the experiments, radioactive Ga^{72} was used to facilitate analysis. The gallium was received as a mixture of oxide and nitrate.[9] A solution was prepared by dissolving 0.0559 g. of this material in 20.0 ml. of 7.30 molar hydrochloric acid, purified by extraction with two 20-ml. portions of isopropyl ether, and won back from the ether with water to provide a gallium tracer solution. This solution was diluted to 50.0 ml. It was assigned a concentration of 0.00594 *M*, based upon a gravimetric determination of the gallium in the oxide–nitrate mixture after its activity had decayed.

A stock solution of inactive gallium chloride was prepared as follows: 5.1457 g. of gallium metal (99.9%) was dissolved in hot aqua regia, evaporated to a sirupy consistency twice with 10-ml. portions of concentrated nitric acid, and finally taken to dryness. The residue was heated at *ca.* 260° until the nitrate was completely converted to oxide. An excess of concentrated hydrochloric acid (20.0 ml.) was added; warming effected complete solution. It was discovered that by warming and blowing air over the surface of this solution, a gel formed which would not redissolve on dilution. Apparently, this was a basic salt, since addition of a few ml. of hydrochloric acid caused solution. Aeration of the solution at room temperature was successful in removing the small excess of hydrochloric acid. Analysis of this solution after dilution to 75.0 ml. gave: $(Ga) = 0.8957\ M$, $(Cl^-) = 2.677\ M$.

The isopropyl ether was purified by shaking with alkaline potassium permanganate solution, drying over calcium chloride, and distilling. The fraction boiling in the range 66.5 to 67.5° at 747.1 mm. was collected.

Analytical Methods.—Measurement of the radioactivity of the samples served as a determination of relative concentrations of gallium. Aliquots of solutions were evaporated just to the point of dryness under an infrared lamp on 1″ copper disks having spun-up edges. Counting rates were determined with a thin-wall mica window Geiger–Müller tube in conjunction with a Higginbotham type scaler. Whenever possible, a total count of at least 5,000 was registered. The background of the counter was 28 counts/minute. The statistical error was probably lower than the errors due to self-absorption and to handling an isotope with a half life of only fourteen and one-tenth hours. The latter error was minimized by counting consecutively the copper disks corresponding to the ether and aqueous phases of a single extraction.

Gallium analyses listed in Table I and those noted in Table II were performed by the 8-hydroxyquinoline–potassium bromate titration method as described by Kolt-

(1) D. C. Grahame and G. T. Seaborg, THIS JOURNAL, **60**, 2524 (1938).

(2) E. H. Swift, *ibid.*, **46**, 2375 (1924).

(3) W. A. E. McBryde and J. H. Yoe, *Anal. Chem.*, **20**, 1094 (1948).

(4) F. Mylius and C. Hüttner, *Ber.*, **44**, 1315 (1911).

(5) R. W. Dodson, G. J. Forney and E. H. Swift, THIS JOURNAL, **58**, 2573 (1936).

(6) J. Axelrod and E. H. Swift, *ibid.*, **62**, 33 (1940).

(7) N. H. Nachtrieb and R. E. Fryxell, *ibid.*, **70**, 3552 (1948).

(8) C. H. Craft and G. R. Makepeace, *Ind. Eng. Chem., Anal. Ed.*, **17**, 206 (1945).

(9) Supplied by Isotopes Branch, United States Atomic Energy Commission, Oak Ridge, Tennessee.

hoff and Sandell.[10] This method was checked against the hydroxide precipitation method[11] and found to be good to 0.5% with 5–15 mg. of gallium. The method was also used to demonstrate that significant amounts of gallium were not lost in the evaporation of solutions on the copper counting disks.

Free acid was calculated from titrations with standard sodium hydroxide, allowing for the quantity of base consumed in the precipitation of gallium hydroxide. Brom cresol purple was the indicator used. The validity of this calculation is discussed later.

Determinations of chloride were made by the Fajans method on the solution remaining from the acidity determination. Dichlorofluorescein was the indicator used.

Extraction Procedure.—In an experiment similar to the one reported by Nachtrieb and Conway for ferric chloride,[12] extraction equilibrium was found to be established within six minutes. All extractions were carried out in 10-ml. glass-stoppered cylinders with 5.0 ml. of isopropyl ether and 5.0 ml. of aqueous solution of known gallium chloride and hydrochloric acid concentrations, except as noted. Cylinders were alternately thermostatted at 20.0 ± 0.1° and mixed by inversion for a total time of at least thirty minutes. The two phases were separated with pipets and transferred to stoppered test-tubes. Before the aliquots were taken for analysis, the tubes were centrifuged for several minutes to separate any small amount of the other phase.

The equilibrium concentrations of gallium in the aqueous and ether phases were calculated by solving sets of simultaneous equations of the type

$$a(\mathrm{Ga})_{aq} + b(\mathrm{Ga})_{eth} = c(\mathrm{Ga})_{initial} \quad (1)$$

$$\frac{(\mathrm{Ga})_{eth}}{(\mathrm{Ga})_{aq}} = \frac{\text{ether counting rate (counts/ml./min.)}}{\text{aqueous counting rate (counts/ml./min.)}} \quad (2)$$

where c is the initial aqueous volume and a and b are the final volumes of the aqueous and ether phases, respectively.

Discussion of Results

Empirical Formula of the Gallium Complex in the Ether Phase.—Analyses of a number of ether phases for gallium, chloride and ionizable hydrogen gave the results shown in Table I. The values given for hydrogen and chloride have been corrected for the solubility of hydrochloric acid in isopropyl ether as given by Nachtrieb and Conway.[12] The empirical formulas tabulated in the last column show that essentially equimolecular amounts of hydrochloric acid and gallium chloride are co-extracted from aqueous solutions initially less than 7 *M* hydrochloric acid. The fourth formula listed is far different from $HGaCl_4$. It may be that the solubility of hydrochloric acid in isopropyl ether is altered by the presence of the gallium complex and that the correction applied is too large. If so, the error is relatively larger for this particular sample, in which the total concentrations were quite low.

Extractions from 8 *M* hydrochloric acid gave $HCl:GaCl_3$ ratios significantly greater than unity. These formulas may correspond to conditions favoring the formation of complex molecules containing more than one HCl. Nevertheless, it seems clear that the empirical formula for the gallium complex is quite analogous to that determined for iron.[12]

All gallium analyses reported in Table I were made by the 8-hydroxyquinoline–potassium bromate method. It is interesting to note that the total cation concentration (hydrogen plus gallium) is usually 2–3% lower than the chloride concentration. This may represent an error in the calculation used in determining free acid, in which the assumption is made that gallium has consumed exactly three hydroxide ions at the brom cresol purple end-point. Potentiometric titrations were performed using a calomel–glass electrode system, but although the indicator end-point appeared slightly before the inflection in the potentiometric curve, the discrepancy was much less than the 2–3% error in the charge balance. The disagreement may be due to the occlusion of gallium salts within the gelatinous hydroxide or the precipitation of a basic gallium salt requiring less than three equivalents of hydroxide. A similar observation has been noted by Fricke and Meyring.[13]

TABLE I

ANALYSES OF ETHEREAL PHASES

[HCl]$_i$	[Ga]$_{eth}$	[Cl]$_{eth}$ (cor.)[a]	[H]$_{eth}$ (cor.)[a]		Empirical formula
3.00	0.0823	0.3342	0.0898		$H_{1.09}GaCl_{4.06}$
4.00	.4126	1.614	.3480		$H_{0.84}GaCl_{3.91}$
4.00	.0551	0.2162	.0475		$H_{0.86}GaCl_{3.93}$
4.00	.00402	.0127	.00141		$H_{0.35}GaCl_{3.17}$
5.00	1.210	5.114	1.354		$H_{1.12}GaCl_{4.23}$
5.00	0.4448	1.825	0.453		$H_{1.02}GaCl_{4.10}$
6.00	.5294	2.139	.5024		$H_{0.95}GaCl_{4.04}$
6.00	.1566	0.6348	.1529		$H_{0.98}GaCl_{4.05}$
6.00	.0532	.2151	.0505		$H_{0.95}GaCl_{4.04}$
7.00	1.484	6.140	1.553		$H_{1.05}GaCl_{4.14}$
7.00	1.097	4.847	1.423		$H_{1.31}GaCl_{4.42}$
7.00	0.3829	1.672	0.496		$H_{1.30}GaCl_{4.37}$
7.00	.3446	1.462	.420		$H_{1.22}GaCl_{4.24}$
8.00	1.080	4.782	1.430		$H_{1.33}GaCl_{4.43}$
8.00	1.298	5.529	1.530		$H_{1.18}GaCl_{4.25}$
8.00	0.3076	1.469	0.562		$H_{1.82}GaCl_{4.77}$
8.00	.4081	1.960	.689		$H_{1.69}GaCl_{4.80}$ (heavy ether)
8.00	.0397	0.2086	.0788	[b]	$H_{1.98}GaCl_{5.25}$ (light ether)
8.00	.4796	2.213	.740		$H_{1.54}GaCl_{4.61}$ (heavy ether)
8.00	.1391	0.576	.196	[b]	$H_{1.41}GaCl_{4.14}$ (light ether)
8.00	1.137	4.801	1.262		$H_{1.11}GaCl_{4.22}$ (heavy ether)[c]
8.00	0.546	2.298	0.673		$H_{1.23}GaCl_{4.21}$ (heavy ether)[c]
9.00	.580	2.543	.732		$H_{1.26}GaCl_{4.38}$

[a] Corrected for the solubility of hydrochloric acid in isopropyl ether. [b] Heavy and light phases from a single extraction. [c] The corresponding light phases not analyzed.

(10) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Company, New York, N. Y., revised edition, 1943, p. 638. Credit is due Dr. L. P. Pepkowitz for demonstrating that the method is applicable to gallium.

(11) W. F. Hillebrand and G. E. F. Lundell, "Applied Inorganic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1929, p. 388.

(12) N. H. Nachtrieb and J. G. Conway, THIS JOURNAL, **70**, 3547 (1948).

(13) R. Fricke and K. Meyring, *Z. anorg. Chem.*, **176**, 325 (1928.)

Variation of the Distribution Coefficient with Gallium Chloride Concentration.—Similar to the case of ferric chloride,[7] it can be shown that on the assumption of a polymerized gallium complex in the ether phase, the distribution expression would be

$$(Ga)_{n\ eth}/(Ga)^{n}_{aq} = K_{(H^+),(Cl^-)}\ \text{constant} \qquad (3)$$

under conditions of constant aqueous hydrogen and chloride ion activities. The stoichiometric gallium concentration as analytically determined will be proportional to the concentration of the ion species which takes part in the distribution equilibrium under these conditions. Equation (3) may be expressed in the form

$$\log (Ga)_{n\ eth} = \log K + n \log (Ga)_{aq} \qquad (4)$$

from which it appears that the association number n would be the slope of a plot of the logarithm of the ethereal gallium activity against the logarithm of the aqueous gallium activity for extractions performed under conditions of constant aqueous hydrogen and chloride activity and of varying total gallium concentration.

Table II gives the initial gallium chloride and hydrochloric acid concentrations, the initial and final phase volumes, the final gallium concentrations and the distribution ratios at various initial hydrochloric acid concentrations. Figure 1 is a plot of the data in Table II. These curves are similar to those obtained for ferric chloride.[7] At sufficiently low gallium concentrations the slope is unity, corresponding to the "ideal" behavior predicted by the simple Nernst distribution equation. With increasing gallium concentration the slope increases sharply, and for higher acidities passes through a maximum, then decreases, becoming less than unity. The decrease in slope at these high gallium concentrations may be due to several causes, such as (1) decrease in the aqueous hydrochloric acid concentration due to its extraction, and (2) the approach to saturation of the gallium complex in the ether phase (see below).

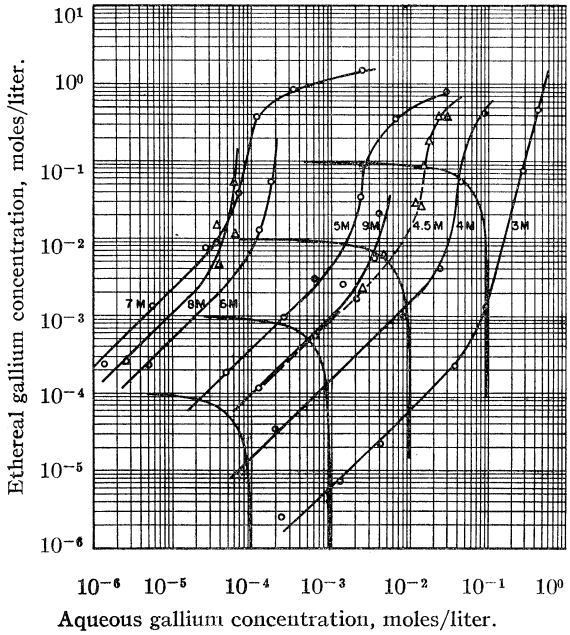

Fig. 1.—Variation of distribution with gallium concentration for several hydrochloric acid concentrations.

Variation of the Distribution Coefficient with Aqueous Hydrochloric Acid Concentration.—In Fig. 2 are plotted the distribution coefficients as a function of acidity for several initial gallium concentrations. These are taken from the intersections of the distribution curves with the rectangular hyperbolas (representing initial gallium concentrations) drawn in Fig. 1. The optimum acidity for efficient extraction is about 7.2 molar. It is evident that up to 0.01 molar, the distribution is essentially independent of gallium concentration, especially for the lower acidities. The salting-out effect, as postulated for the case of ferric chloride,[7] (if this be the cause of the changing slope in Fig. 1) becomes important above 0.01 molar gallium concentrations.

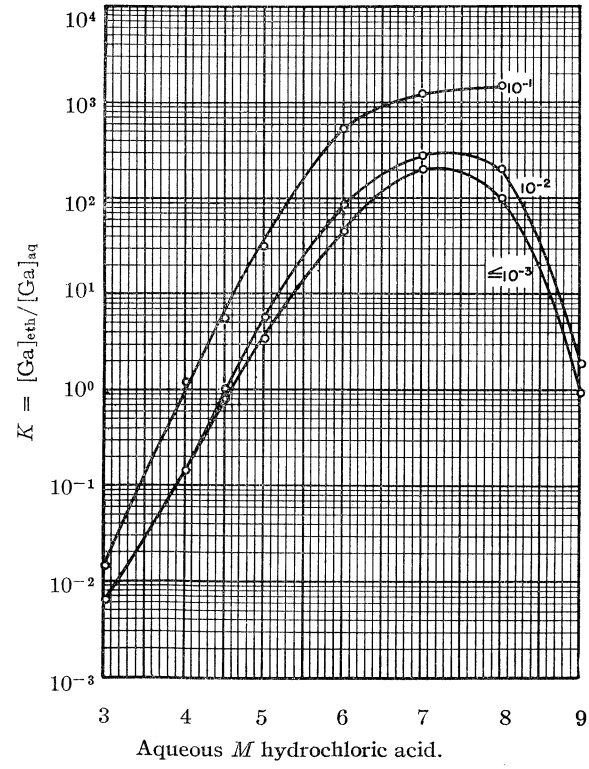

Fig. 2.—Variation of distribution coefficient with hydrochloric acid concentration for several initial gallium chloride concentrations.

Appearance of a Three Phase System.—For extractions made from 8.00 and 9.00 M hydrochloric acid, increase in the concentration of gallium chloride caused the separation of a

TABLE II

DISTRIBUTION OF GALLIUM CHLORIDE BETWEEN AQUEOUS HYDROCHLORIC ACID AND ISOPROPYL ETHER

				Volume, ml.				$K = \frac{[Ga]_{eth}}{[Ga]_{aq}}$
$[HCl]_i$[a]	$[Ga]_i$	$[Ga]_{aq}$	$[Ga]_{eth}$	Aqi	Ethi	Aqfinal	Ethfinal	
3.00	0.8981	0.4360	0.4774	5.00	5.00	4.60	5.21	1.095
3.00	.3597	.2864	.0760	5.00	5.00	4.98	4.92	0.265
3.00	.0920	.0896	.00126	5.00	5.00	5.06	4.88	.0141
3.00	.0373	.0355	.000218	5.00	5.00	5.21	4.92	.00613
3.00	.00924	.00907	5.75×10^{-5}	5.00	5.00	5.06	4.93	.00634
3.00	.00408	.00397	2.18×10^{-5}	5.00	5.00	5.10	4.85	.00548
3.00	.00119	.00116	7.12×10^{-6}	5.00	5.00	5.10	4.88	.00615
3.00	.000238	.000231	2.53×10^{-6}	5.00	5.00	5.08	4.92	.0109
4.00[b]	.5156	.0895	0.4126	5.00	5.00	4.68	5.12	4.61
4.00[b]	.1031	.0454	.0551	5.00	5.00	5.00	4.90	1.21
4.00[b]	.0309	.0243	.00402	50.00	50.00	50.5	49.5	0.165
4.00	.000238	2.01×10^{-4}	3.35×10^{-5}	5.00	5.00	5.10	4.90	.167
4.00[b]	.00937	0.00816	0.00101	100	100	101	99	.124
4.50	.4031	.0307	.3536	5.00	5.00	4.71		11.5
4.50	.4028	.0234	.3794	5.07	5.00			16.2
4.50	.2019	.0181	.1859	5.00	5.00	4.90		10.3
4.50	.1013	.0155	.0858	5.00	5.00	5.00		5.55
4.50	.0409	.0119	.0291	5.00	5.00	5.03		2.45
4.50	.0409	.0141	.0268	5.00	5.00			1.90
4.50	.0107	.00472	.00605	5.00	5.00	5.09		1.28
4.50	.00471	.00249	.00221	5.00	5.00	5.10		0.89
5.00	.8962	.0307	.7750	5.00	5.00	4.30	5.40	26.2
5.00	.3588	.00676	.3483	5.00	5.00	4.83	5.06	51.5
5.00	.0901	.00280	.0892	5.00	5.00	5.05	4.89	31.9
5.00	.0363	.00240	.0352	5.00	5.00	5.10	4.80	14.7
5.00	.00829	.00140	.00704	5.00	5.00	5.11	4.87	5.03
5.00	.00360	.000652	.00303	5.00	5.00	5.13	4.83	4.65
5.00	.00119	.000266	.000945	5.00	5.00	5.11	4.85	3.55
5.00	.000238	.0000506	.000191	5.00	5.00	5.16	4.83	3.78
6.00[b]	.05156	.000180	.0532	100.0	100.0	102	96	296
6.00[b]	.00111	.000126	.0125	225.0	25.0	231.6	16.8	99.5
6.00	.000238	4.96×10^{-6}	2.44×10^{-4}	5.00	5.00	5.18	4.77	49.1
7.00	1.3441	0.00262	1.460	5.00	5.00	3.95	5.60	556
7.00	0.8962	.000346	0.860	5.00	5.00	4.39	5.21	2490
7.00[b]	.3918	.000120	.383	12.5	12.5	12.3	12.3	3191
7.00	.3227	.000555	.336	5.00	5.00	5.00	4.80	605
7.00[b]	.2062	.000341	.825	40.0	10.0	39.7	9.5	2420
7.00	.0901	.000100	.0955	5.00	5.00	5.16	4.71	952
7.00	.0363	.0000700	.0394	5.00	5.00	5.25	4.63	560
7.00	.00829	3.67×10^{-5}	.00887	5.00	5.00	5.25	4.65	242
7.00	.00119	5.79×10^{-6}	.00128	5.00	5.00	5.26	4.63	221
7.00[b]	.000462	2.73×10^{-5}	.00763	450	50.0	471	29	279
7.00	.000238	1.36×10^{-6}	.000254	5.00	5.00	5.25	4.65	187

[a] i signifies initial concentrations and volumes. [b] Gallium analysis by 8-hydroxyquinoline method.

third liquid phase intermediate in density between the aqueous and ether phases, formed at the expense of the ether phase.[14] Near the lower gallium concentration limit of the three-phase region the volume of the intermediate ("heavy ether") phase is comparatively small, becomes larger at higher concentrations of gallium chloride, and at extremely high concentrations, the system again becomes two phase. Data obtained at 8.00 and 9.00 *M* hydrochloric acid are collected in Table III. The distribution coefficients at gallium concentrations below the three phase region are also plotted in Fig. 1. It is felt that the appearance of the third phase is related to the solubility of the gallium complex in isopropyl ether and, thus, the ether layer in the two phase system at very high gallium concentrations is considered "heavy." It is interesting to note that the ratio $(Ga)_{heavy\ ether}/(Ga)_{light\ ether}$ is relatively more constant than the other two possible distribution coefficients. This is reflected in the columns $(Ga)_{light\ ether}$ and $(Ga)_{heavy\ ether}$. However, with such a limited number of data, no conclusions can be drawn concerning the nature

(14) In the analogous system, ammonium chlorogallate in anhydrous diethyl ether, a second ether phase has been observed at high ammonium chlorogallate concentrations (H. Friedman, Dissertation, The University of Chicago, 1949).

TABLE III

DISTRIBUTION OF GALLIUM CHLORIDE BETWEEN AQUEOUS HYDROCHLORIC ACID AND ISOPROPYL ETHER

					Volume, ml.					K =		
[HCl]i	[Ga]i	[Ga]aq	[Ga]l.eth.	[Ga]heavy	Aqi	Ethi	Aqfinal	Ethfinal	Heavy ether	$\frac{[Ga]_{l.eth}}{[Ga]_{aq}}$	$\frac{[Ga]_{h.eth}}{[Ga]_{aq}}$	$\frac{[Ga]_{h.eth}}{[Ga]_{l.eth}}$
8.00	0.8962	0.000575		0.855	5.00	5.00	4.44	5.24			1487	
8.00	.9040	.00432		.860	5.00	5.00	4.42	5.23			199	
8.00	.9185	.00656		.874	5.00	5.00	4.40	5.22			133	
8.00	.2886	.000111		.318	5.00	5.00	5.26	4.55			2866	
8.00	.1882	.000879	0.0469	.419	5.00	5.00	5.40	2.43	1.97	53.4	476	8.93
8.00	.2021	.000672	.0699	.374	5.00	5.00	5.32	2.21	2.28	104	556	5.35
8.00	.0905	.0000983	.0585	.331	5.00	5.00	5.57	3.70	0.71	595	3370	5.66
8.00	.0954	.000316	.0619	.354	5.00	5.00	5.60	3.68	.70	196	1120	5.71
8.00	.0368	.000163	.0445		5.00	5.00	5.60	4.12	.10	272		
8.00	.00876	.0000604	.0103		5.00	5.00	5.69	4.23		170		
8.00	.00408	.0000385	.00469		5.00	5.00	5.60	4.30		122		
8.00[a]	.00111	5.88×10^{-5}	.0559		225	25.0	244	6.0		951		
8.00	.000238	2.72×10^{-6}	.000272		5.00	5.00	5.62	4.30		100		
8.00[a]	.000231	3.55×10^{-5}	.0148		450	50.0	490	6		417		
9.00	.6275	0.00187		.666	5.00	5.00	5.02	4.69			356	
9.00	.9175	.00255		.879	5.00	5.00	4.37	5.21			344	
9.00	.2062	.00204	.0302	.459	5.00	5.00	6.16	1.50	2.12	14.85	226	15.2
9.00	.2305	.0143	.0450	.421	5.00	5.00	6.27	0.91	2.43	3.14	29.4	9.4
9.00	.0901	.00297	.0227	.534	5.00	5.00	6.50	2.52	0.70	7.62	180	23.5
9.00	.0905	.0109	.0256	.498	5.00	5.00	6.79	2.35	.64	2.34	45.5	19.4
9.00	.0368	.00397	.0210	.561	5.00	5.00	6.70	2.96	.17	5.28	141	26.8
9.00	.00829	.00364	.00553		5.00	5.00	6.75	3.05		1.52		
9.00	.00360	.00140	.00268		5.00	5.00	6.57	3.28		1.91		
9.00	.00384	.00210	.00167		5.00	5.00	6.70	3.09		0.80		
9.00	.00119	.000635	.000548		5.00	5.00	6.80	2.96		0.86		
9.00	.000238	.000124	.000115		5.00	5.00	6.75	3.05		0.93		

[a] Gallium analysis by 8-hydroxyquinoline method.

and origin of the three phase system. For this purpose further investigation will be necessary. Measurement of densities, refractive indices and molecular weights would be highly desirable.

The dependence of the distribution coefficient on gallium concentration, the empirical formula of the gallium complex in the ether phase and the appearance of the third phase at high acid and gallium concentrations demonstrate a strong similarity of the gallium chloride and ferric chloride systems. (The third phase in the iron system has been reported by Dodson and coworkers[5].) It is unfortunate that the gallium solutions are not amenable to absorption spectrum measurements in the visual region. For $HFeCl_4$ in isopropyl ether, Beer's law conformity was observed for iron concentrations ranging from 0.01 to 0.4 molar.[12] By analogy, this lends support to the hypothesis that the anomalous distribution of gallium chloride between aqueous hydrochloric acid and isopropyl ether may be due to a salting-out effect and not necessarily to a polymerization of the gallium complex in the ether phase.

Acknowledgment.—It is a pleasure to acknowledge the assistance of Miss M. C. Bachelder who performed many of the gravimetric analyses, and of Mr. Lyle Raub, who helped in conducting the experiments with the radioactive isotope. The authors are also indebted to Dr. William L. Fink of the Aluminum Company of America for making available some of the gallium used in the investigation.

Summary

The distribution of gallium chloride between aqueous hydrochloric acid and isopropyl ether has been found to obey the simple Nernst partition law for low gallium concentrations. At concentrations of gallium exceeding 0.01 molar, the partition increases in favor of the ether phase. The empirical formula of the gallium complex in the ether phase is $HGaCl_4$, if extracted from an aqueous solution not exceeding 7 molar hydrochloric acid.

Under certain conditions, a third ether-rich phase has been observed.

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[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE]

Vapor Pressure of Titanium

BY JOHN M. BLOCHER, JR., AND I. E. CAMPBELL

In view of the current interest in the use of titanium metal at high temperatures, it is important that vapor-pressure data be made available. The vapor pressure of titanium has been determined over the range from 1500 to 1800°K., using the method of Langmuir.[1]

The vapor pressure (p) was calculated from the measured rate of evaporation *in vacuo* (m) of an electrically heated titanium wire by the well-known Knudsen equation

$$\alpha p = m(2\pi RT/M)^{1/2} \qquad (1)$$

where m is in grams per square centimeter per second, and M is the molecular weight in the vapor phase. The *accommodation coefficient* (α) was assumed to be unity as has been found generally to be the case for metals.[2]

Measurement of the weight per unit length of the wire before (w_0) and after (w) a run of t seconds duration leads to the rate of evaporation by the relationship[1]

$$m = \left(\frac{\rho}{\pi}\right)^{1/2} \frac{w_0^{1/2} - w^{1/2}}{t} \qquad (2)$$

where ρ is the density. These average m values may be checked by following the resistance of the wire during the run. If one plots the square root of the ratio of the resistance (R_0) of the wire at t = 0 (extrapolated) to the resistance at time t against t, one should obtain in the case of constant m, a straight line of slope x which leads to the rate of evaporation by the relationship[1]

$$m = (\rho w_0/\pi)^{1/2} x \qquad (3)$$

Experimental.—Titanium wire of 0.46-mm. diameter and of 99.7 to 99.9% purity was supplied by the U. S. Bureau of Mines. It was produced by the magnesium reduction of titanium tetrachloride.[3] Lengths of 8 to 9 cm. were mechanically cleaned and polished with fine emery paper. Contact with 1-mm. tungsten electrodes was made by placing the ends of the wire and of the electrodes into slotted copper blocks (0.95 × 0.95 × 1.6 cm.), and then crimping the assembly in a vise.

The filament assemblies were sealed in turn into a 1-liter Pyrex round-bottom flask, being oriented along the large diameter perpendicular to the axis of the neck. A plane Pyrex window was sealed into the neck of the flask through which the temperature measurements were made. In order to prevent clouding of the window between temperature readings by the condensed titanium, a magnetically operated shutter was provided between the window and the filament. The effectiveness of the shutter in preventing the progressive formation of appreciable optically absorbing film was evident from the constancy during each run of the product of the filament voltage and the cube-root of the current[1] together with the constancy of the observed optical temperature. The bulb was evacuated to 10^{-6} mm. of mercury by means of a vacuum system consisting of a Cenco-Hyvac mechanical pump followed by a single-stage mercury condensation pump and a liquid air-trap.

Prior to the run, the bulb was alternately outgassed by flaming, and flushed with pure dry helium. A glow discharge from a Tesla coil was played on the wire during the next to the last pump-down in an effort to clean off small particles of abrasive, etc.

A battery-stabilized direct-current supply was used to heat the filament wire, the resistance of which was derived from current and voltage. The heating current was determined by measuring with a potentiometer the voltage developed across a standard resistance in series with the filament. A voltage divider was provided to measure with the potentiometer, the voltage across the filament. Corrections were made for lead resistance determined at the end of the run by passing a current equal to the average of that used during the run through the lead assembly with the copper terminal blocks soldered together.

Filament temperatures were determined with a Leeds and Northrup optical pyrometer calibrated with window *in situ* against a N.B.S. standard tungsten-ribbon lamp. The observed temperatures were corrected for the emissivity of titanium.[4] It is fortunate that the heat conductivity of titanium is relatively low. This led to an observed constant temperature (±10°) over 95% of the length of the wire.

Approximately one-tenth of the filament was allowed to evaporate during each run. The rates of evaporation as determined by resistance change were quite constant throughout the runs, except for short periods at the start when the wire was becoming stabilized (evaporation of small magnesium content, transition from α- to β-titanium, etc.)

(1) I. Langmuir, *Phys. Rev.*, **2**, 329 (1913).

(2) H. L. Johnston and A. L. Marshall, THIS JOURNAL, **62**, 1382 (1940).

(3) R. S. Dean, J. R. Long, F. S. Wartman, E. L. Anderson and E. T. Hayes, *Trans. Am. Inst. Mining Met. Engrs., Inst. Metals Div.*, **166**, 369 (1946). The titanium powder produced by the reduction was compacted and then sintered *in vacuo* at 1000° for sixteen hours, volatilizing the impurities, hydrogen and magnesium. The remaining principal impurities are Fe <0.1%, Si <0.1% and O + N, <0.1%.

(4) Van Arkel, "Reine Metalle," J. Springer, Berlin, 1939, p. 187. The emissivity was checked in the neighborhood of 1400°K., $\epsilon_{0.655\mu}$ = 0.49 by temperature observations on the surface of and on a hole in an induction-heated titanium block. The results checked to within ±10° (the uncertainty in the reading of the temperature of the filament wire).

Data.—The experimental results are given in Table I. A "high-temperature density" of 4.35 (as compared to the room-temperature value of 4.5) was determined from the observed sag in in the filaments upon heating.[5] This value was used for ρ in Equations (2) and (3).

TABLE I

RATE OF EVAPORATION OF TITANIUM

Temp., °K.	Time of run, sec.	Rate of evaporation,[a] g./sq. cm./sec.	
1510	144,000	1.62×10^{-8}	1.80×10^{-8}
1613	39,300	1.60×10^{-7}	1.86×10^{-7}
1636	21,120	2.9×10^{-7}	3.1×10^{-7}
1727	4,800	1.33×10^{-6}	1.37×10^{-6}
1822	1,050	9.2×10^{-6}	8.9×10^{-6}

[a] The first value was determined by resistance change, the second by weight loss.

One run was made at each of the recorded temperatures.

Thermodynamic Treatment.—The validity of the data can best be tested by determining the constancy of ΔH_0^0 in the relationship

$$R \ln p \text{ (atm.)} = \left(\frac{F^0 - H_0^0}{T}\right)_{\text{solid}} - \left(\frac{F^0 - H_0^0}{T}\right)_{\text{vapor}} - \frac{\Delta H_0^0}{T} \quad (4)$$

The free-energy function of the solid is related to the heat capacity as

$$\left(\frac{F^0 - H_0^0}{T}\right)_{\text{solid}} = \frac{1}{T}\int_0^T C_p dT - \int_0^T C_p d \ln T \quad (5)$$

The free-energy functions of the vapor can be determined accurately from spectroscopic data.[6]

The C_p data for solid titanium of Kelley[7] in the low-temperature range, and of Jaeger and others[8] from 200° to 1200° were used in evaluating Equation (5). Free-energy functions for titanium vapor were evaluated using spectroscopic data from Landolt–Börnstein.[9]

The values of ΔH_0^0 of sublimation as calculated from Equation (4) using the vapor-pressure data are given in the fifth column of Table II. The average value of ΔH_0^0, 111,064 cal., added to the difference between $(H^0 - H_0^0)$ of solid and vapor leads to the heat of sublimation at 298.2°K., $\Delta H_{298.2}$ = 111,720 cal.

The fact that there is no apparent trend of ΔH_0^0 with temperature, and that the maximum deviation from the mean is only 578 cal. speaks well for the validity of the data.

Carpenter and Reavell[10] have recently determined the rate of evaporation of titanium using the present technique. In an advance announcement of their results, they give no data, but present the following equation for the rate of evaporation of titanium

$$\log mT^{1/2} = 7.70 - (2.07 \times 10^4/T) \quad (6)$$

The authors have calculated ΔH_0^0 at their own experimental temperatures using this equation. The resulting values given in the sixth column of Table II show a trend with temperature of roughly twice the maximum spread of the present data. Thus, Equation (6) is inconsistent with the C_p data. However, there is fair agreement with the C_p data and with the present vapor-pressure data at 1613 and 1636°K. The reason for the deviation at higher and lower temperatures may become apparent when the experimental data of Carpenter and Reavell are published.

TABLE II

ΔH_0^0 OF SUBLIMATION OF TITANIUM

T, °K.	$-\left(\frac{F^0 - H_0^0}{T}\right)_{\text{vapor}}$	$-\left(\frac{F^0 - H_0^0}{T}\right)_{\text{solid}}$	Vapor pressure,[a] atm.	ΔH_0^0,[a] cal.	ΔH_0^0 (C. and R.),[b] cal.
1510	46.282	12.26	2.05×10^{-9}	111,393	110,094
			2.28×10^{-9}	111,076	
1613	46.637	12.73	2.08×10^{-8}	111,394	110,926
			2.42×10^{-8}	110,894	
1636	46.713	12.84	3.8×10^{-8}	110,937	111,101
			4.1×10^{-8}	110,724	
1727	47.005	13.23	1.79×10^{-7}	111,633	111,892
			1.86×10^{-7}	111,512	
1822	47.294	13.61	1.28×10^{-6}	110,486	112,636
			1.24×10^{-6}	110,595	

Av. ΔH_0^0 = 111,064 ± 578 cal.

[a] The upper value was determined by resistance change, the lower by weight loss. [b] Calculated using Equation (6) of Carpenter and Reavell.

If the average value of ΔH_0^0 from the present work be substituted in Equation (4) together with a linear expansion of $(F^0 - H_0^0/T)_{\text{sublimation}}$ as a function of the absolute temperature, one arrives at the equation

$$\log p \text{ (atm.)} = 7.782 - (24{,}275/T) - 0.230 \times 10^{-3}T \quad (7)$$

which is believed to represent the vapor pressure of titanium to within 10% over the range 1200–2000°K. This equation together with the experimental data is plotted in Fig. 1. The points in the squares are those obtained from weight loss, and those in the small circles from resistance change. The large circles are centered midway between the weight-loss and resistance-change points, and have radii of 10°. The dashed curve is from Equation (6).

The data may be extrapolated to give an equation for the vapor pressure of liquid titanium. A reasonable entropy of fusion of 2.5 e. u. at the melting point, 2000°K.[11] is assumed together with a constant heat capacity for the liquid of 8.0 cal./mol./°. These values, when combined with ΔH_0^0

(5) Van Arkel, ref. 4, p. 185, gives 4.31 as the density of β-titanium at the transition temperature.

(6) W. F. Giauque, THIS JOURNAL, **52**, 4808 (1930).

(7) K. K. Kelley, *Ind. Eng. Chem.*, **36**, 865 (1944).

(8) F. M. Jaeger, E. Rosenbohm and R. Fonteyne, *Rec. trav. chim.*, **55**, 615 (1936).

(9) Landolt–Börnstein, "Tabellen," Pt. 3, III Suppl., p. 2346.

(10) L. G. Carpenter and F. R. Reavell, *Nature*, **163**, 527 (1949).

(11) Van Arkel, ref. 4, p. 186.

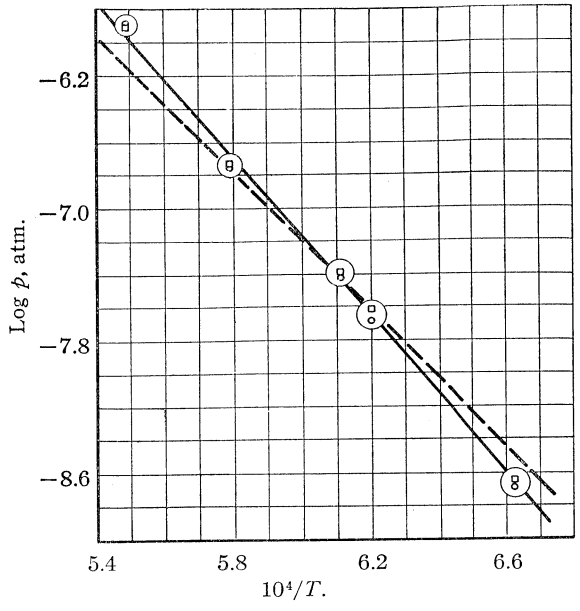


Fig. 1.—Vapor pressure of titanium: O, resistance change; □, weight loss; large circles, ±10° temperature. The full curve is that of Equation (7). The dashed curve is from Equation (6) of Carpenter and Reavell.

and the free-energy functions for titanium vapor as given by Latimer,[12] lead to vapor pressures which may be expressed to within 2.5% by the equation

$$\log p \text{ (atm.)} = 6.255 - (22{,}110/T)$$

The calculated boiling point is 3535°K.

It has been observed in this Laboratory that at the temperatures encountered in the present work, oxygen and nitrogen diffuse very rapidly into titanium, forming solid solutions. This fact greatly reduces the possibility of an error encountered with many metals using the Langmuir technique, *i. e.*, a lowering of the rate of evaporation by surface oxide or nitride films. The impurities in solid solution with the titanium used in the present work, a maximum of 0.005 mole-fraction, would reduce the vapor pressure of pure titanium, and might yield observed values roughly 99.5% of the true values. This difference is insignificant relative to experimental error.

Acknowledgment.—It is with gratitude that the authors acknowledge the financial aid of the Iodine Educational Bureau, Inc., in carrying out this work. The interest of Mr. A. C. Loonam[13] is gratefully acknowledged. His independent interpretation of the vapor-pressure data resulted in a ΔH_0^0 value but 160 cal. above that of the authors.

Summary

The vapor pressure of solid titanium has been determined in the range 1500–1800°K. by measuring the rates of evaporation of titanium wire using the Langmuir technique. The data fit the thermodynamic requirements quite well and yield heats of sublimation of 111,000 cal. at 0°K. and 111,700 at 298.2° K. The resulting equation for the vapor pressure of solid β-titanium, valid over the range 1200–2000°K., is $\log p$ (atm.) = $7.782 - (24{,}275/T) - 0.230 \times 10^{-3} T$.

The data may be extrapolated to yield an equation for the vapor pressure of the liquid: $\log p$ (atm.) = $6.255 - (22{,}110/T)$, leading to a normal boiling point of 3535°K.

The data agree over a limited range with the incomplete experimental results of Carpenter and Reavell. Their equation for the rate of evaporation of titanium has been shown to be inconsistent with other available thermodynamic data.

(12) Wendell M. Latimer, "Tables of Free-Energy Functions for Elements and Compounds in the Temperature Range 2000–5000°K." MDDC-1462, U. S. Atomic Energy Commission, Sept. 10, 1947, p. 4.

(13) Deutsch and Loonam, Consultants, 70 E. 45th Street, New York 17, N. Y.

COLUMBUS 1, OHIO RECEIVED JUNE 6, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY]

The State of Oxidation of S^{35} Formed by Neutron Irradiation of Potassium Chloride

BY W. S. KOSKI

When potassium chloride is irradiated with thermal neutrons the following is one of the reactions that takes place

$$Cl^{35} + n \longrightarrow S^{35} + H' + Q$$

The Q of this reaction as estimated from the masses is 0.63 mev. From simple considerations of conservation of energy and momentum, one can estimate the energy of the recoiling sulfur fragment as equal to 17.6 kev. Since it is believed[1,2] that ionization by a rapidly moving particle is probable only at velocities comparable to the effective velocities of free electrons, the recoiling sulfur fragment will produce no appreciable ionization by the process of electron ejection and capture. However, the irradiated chlorine is an ion in the crystal lattice, and the proton on leaving the compound nucleus will reduce the nuclear charge by +1 leaving the residual sulfur fragment with a double negative charge. This charge may be reduced by electron capture by the proton as it moves through the electronic field of the sulfur fragment. Such

(1) H. A. Bethe, *Rev. Mod. Phys.*, **9**, 262–265 (1937).

(2) J. Knipp and E. Teller, *Phys. Rev.*, **59**, 659 (1941).

considerations would lead one to believe that the sulfur activity should be present as sulfide ion or possible elementary sulfur. This seems to be contrary to observation,[3] since it has been reported that the sulfur activity appears in its highest state of oxidation rather than in its lowest. We thought it might be of interest to investigate this apparent contradiction, especially since this information was very pertinent to another problem that we have under investigation.

Experimental Details

Materials.—All of the chemicals used in this work were of a C. P. grade, and unless otherwise stated were used as commercially available with no further purification. The water that was used as a solvent was freshly distilled, having a specific conductance of $1-2 \times 10^{-6}$ mho. The alcohol was absolute and taken from a freshly opened container and no further attempts were made at purification.

Preparation of Carbonyl Sulfide.—The carbonyl sulfide that was used in this work was prepared[4] by the reaction of carbon monoxide with an excess of sulfur at 425° for sixteen hours. The carbon monoxide was prepared from oxalic and concentrated sulfuric acids. The water and carbon dioxide were removed with liquid nitrogen.

Separation of Carriers.—During the course of this work it was necessary to separate various combinations of carriers. Mixtures of sulfide and sulfate or sulfite and sulfate ions were separated by acidifying the solutions and distilling the resulting hydrogen sulfide or sulfur dioxide, and whenever necessary the gas samples were collected and oxidized with bromine and nitric[5] acid and precipitated as barium sulfate. Whenever mixtures of sulfide, sulfite and sulfate ions were used they were prepared just before use and always in alkaline solutions in order to avoid complications by reactions between sulfides and sulfites. In these cases the separations were performed by precipitating the sulfide by adding appropriately acidified copper chloride solution. The resulting copper sulfide was oxidized to the sulfate and the sulfate precipitated as barium sulfate. The sulfite ion was separated by distillation, collected, oxidized and precipitated as barium sulfate. In addition to using copper for the sulfide separation, lead acetate was used following the procedure of Bassett and Durrant,[6] thus enabling us to make the separation directly in the 2 *N* sodium hydroxide solution. The same results were obtained with both methods of separation.

Pre-irradiation Treatment of Potassium Chloride.[7]—In view of the nature of this experiment it was considered desirable to remove as much oxygen and water from the potassium chloride sample as possible. The potassium chloride was put into a quartz container and attached to a high vacuum system. The sample was then heated to a temperature of approximately 700° for sixty hours. The system was pumped on with an oil diffusion pump backed by a suitable mechanical pump, and at the conclusion of the heating treatment the pressure in the system with the heat on was better than 10^{-5} mm. The sample was permitted to cool, and then 15 cm. of purified carbon monoxide was admitted, the container was sealed and the sample was irradiated in the Oak Ridge pile.

Treatment of the Irradiated Samples.—The quartz vessel containing the irradiated potassium chloride sample was sealed on to a vacuum system. A portion of the carbon monoxide atmosphere in which the potassium chloride was bathed was put into a gas counter and tested for activity. The gas was radioactive but none of it was condensable in liquid nitrogen. A portion of this carbon monoxide was then mixed successively with sulfur dioxide, carbonyl sulfide and sulfur monochloride, and on separation of the condensable gases with liquid nitrogen only traces of activity were found in the condensed gases.

The potassium chloride container was then opened in a dry nitrogen atmosphere and some of the crystals were dissolved in water containing traces of carrier ions or, if necessary, in carrier-free alcohol. The various experiments discussed were performed with 5-cc. portions of these solutions.

Preparation of Radioactive Samples for Measurements.—All the sulfur samples that were measured for radioactivity were oxidized to the sulfate and precipitated as barium sulfate. The precipitates were then collected on one-inch filter papers in a Hirsch funnel, washed with water, acetone, dried, mounted and examined for activity with a Geiger–Müller counter. In all cases the amounts of sulfate present were adjusted so that all of the samples compared had the same amount of barium sulfate.

The activities of gaseous samples were measured by fitting a small gas cell over the mica window of the counter. This cell was pumped out, and then the gas to be tested was admitted and measured for activity.

Discussion of Results

Untreated Potassium Chloride Samples.—When a sample of potassium chloride which has had no outgassing treatment is irradiated with neutrons and then dissolved in a water solution containing sulfide, sulfite and sulfate ions as carriers, it is found that on separation of the carriers practically all of the activity is present as sulfate. This observation is in agreement with the results of Willard mentioned earlier.

One of the most obvious ways of oxidizing sulfur is by reaction with atmospheric oxygen. However, experience with reactions of macro amounts of sulfur and oxygen indicate that the tetravalent state of sulfur should be expected. This, however, is not a serious objection since the sulfur formed in the body of the crystal is in an unusual habitat, and it might well undergo oxidation to the hexavalent state through a heterogeneous catalytic process. Furthermore, the S^{35} at the moment of its creation is in a high state of electronic excitation and may well react with any oxygen present to form sulfur trioxide.

During the course of irradiation of the crystals elementary chlorine is formed and the sulfur fragments would be oxidized through the formation of such compounds as sulfur mono- and dichlorides. On hydrolysis, however, these compounds lead to sulfite rather than sulfate ions.

There is, of course, the possibility that some of the free chlorine formed during the irradiation may bring about oxidation of the sulfur when the sample is brought into solution. Experimental results that will be cited later indicate that very little of the oxidation is actually brought about by this mechanism.

If one tentatively takes air oxidation as the explanation for the presence of hexavalent sulfur it remains to be shown that potassium chloride

(3) John E. Willard, Conference on the Chemical Effects of Nuclear Transformations at Brookhaven National Laboratory, August 19, 20 (1948).

(4) G. N. Lewis and W. N. Lacey, THIS JOURNAL, **37**, 1976 (1915).

(5) Kolthoff and Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Company, 1937, New York, N. Y., p. 320.

(6) H. Bassett and R. G. Durrant, *J. Chem. Soc.*, 1401 (1927).

(7) This phase of the work was carried out at Brookhaven National Laboratory in collaboration with Dr. V. W. Cohen.

crystals can occlude reasonable amounts of foreign gaseous substances. Experimental studies[8] have shown that potassium, thallium and the halogens can be incorporated in alkali halide crystals. From such work it appears reasonable that the crystals in question can contain appreciable amounts of a gaseous substance such as air. The oxygen in a potassium chloride crystal may be present there as a result of two processes (1) diffusion and (2) incorporation in the crystal during the formation of the crystal from a solution. The latter is probably the most effective mechanism since diffusion of gases into solids is slow at ordinary temperatures; consequently only the surface layers would contain atmospheric oxygen which arrived through diffusion and absorption, whereas the body of the crystal would have oxygen which was probably introduced during crystal growth.

S^{35} from Outgassed Potassium Chloride.—In a number of experiments on a certain sample of outgassed and irradiated potassium chloride it was found that about 64% of the total sulfur activity present was in the hexavalent state and the remainder in a lower state. Essentially the same value was obtained even if the amounts of carriers were varied, indicating that there was no exchange between sulfide and sulfate or between sulfite and sulfate complicating the picture. This observation on the exchange is in agreement with the prior work of Voge and Libby.[9] It might be mentioned that different samples of potassium chloride varied widely as to per cent. activity present as sulfate. Some irradiated crystals have been obtained with as low as 15% of total activity present as sulfate. There are also indications that not even all of the individual crystals that have been irradiated simultaneously in the same container have the same per cent. total activity as sulfate. Only a few experiments have been done in this connection, but an indication has been obtained that the larger crystals have a much greater percentage of activity present as sulfate than the smaller crystals. This may not be too unexpected since a larger crystal would require more prolonged pumping and more severe outgassing conditions to remove its occluded oxygen.

Behavior of Trace Amounts of Sulfur Compounds in Solution.—It may be appropriate to comment at this point on the behavior of sulfur compounds in solution. If some potassium chloride crystals containing 63% of the activity as sulfate are put into ordinary distilled water from which no pains were taken to remove air and then carriers of sulfide and sulfate are added and separated, it is found that all of the activity appears as sulfate ion. If, on the other hand, the crystals are dissolved in a solution of sulfite and sulfate carriers and then some sulfide carrier is added, analysis shows that the activity is now 63% sulfate and 37% sulfite with the sulfide ions carrying no activity. Apparently the activity that was present as sulfide ions in trace amounts is rapidly oxidized to sulfite ion, and further rapid oxidation is prevented by the presence of macro amounts of sulfite carrier. As a result of a number of such experiments it was concluded that in general if the irradiated potassium chloride crystals were dissolved in distilled water from which air had not been removed the trace amount of radiosulfur is oxidized to the chemical form of the carrier having the lowest oxidation state. If no carrier or if only sulfate ion is present as a carrier the radiosulfur goes up to the hexavalent state. Water solutions of radiosulfur could be kept for hours without appreciable oxidation if care was taken to exclude atmospheric oxygen. This observation leads us to conclude that the free chlorine present in the crystal as a result of irradiation is not producing oxidation of the sulfur on solution of the crystal. It was found that if a potassium chloride crystal was dissolved in alcohol there was no oxidation even if the solution was kept for weeks. If a portion of the alcohol solution was put into distilled water containing dissolved air the sulfur compounds did oxidize with a half-time of about thirty minutes for 50% of the sulfide to be oxidized to sulfate. On the other hand, if the crystal was dissolved directly in a portion of the same water, the oxidation was complete in less than three minutes, indicating that in the presence of solid potassium chloride the oxidation is much faster and may be well a heterogeneous process on the surface of the crystal.

State of Oxidation of the Non-Sulfate Sulfur.—The results obtained for three samples of outgassed and neutron-irradiated potassium chloride crystals are summarized in Table I. These samples are not strictly comparable since sample number 2 was outgassed at a somewhat higher temperature than number 1 and sample number 3 was composed of very small crystals selected from sample number 2 after irradiation.

TABLE I

ACTIVITY IN CARRIERS

Carriers	Sample no.	Sulfide	Sulfite	Sulfate	Total activity	% activity as sulfate
Sulfide, sulfate	1	396	...	750	1160	64.6
Sulfite, sulfate	1	...	403	776	1194	64.9
Sulfide, sulfite, sulfate	1	430	36	755	1200	63
Sulfide, sulfate	2	780	...	465	1270	36.6
Sulfite, sulfate	2	...	630	430	1080	39.8
Sulfide, sulfate	3	602	...	121	758	16
Sulfite, sulfate	3	...	673	105	802	13

It is clear from these results which are representative of a number of such experiments that very little of the activity is present in the form of sulfite ion. It is felt that a safe upper limit is

(8) R. M. Barrer, "Diffusion in and through Solids," Cambridge University Press, 1941, p. 110.

(9) H. H. Voge and W. F. Libby, THIS JOURNAL, **59**, 2474 (1937).

5% and very probably the figure is lower than this. The small amount of activity present in the sulfite may actually be due to a slight solution of the copper sulfide in the acid that was present or there may be a small amount of reaction between sulfide and sulfite ions. In the case of precipitation of the sulfide in strongly alkaline solution, no reaction between sulfide and sulfite is to be expected but here also a small residual activity seemed to be present in the sulfite carrier, although there was some indication that it might be less than that found in the former case. Normally one would expect the oxidation of sulfur to stop at sulfur dioxide, but as has been already pointed out, the conditions under which the sulfur finds itself in the crystal are far from normal and apparently when oxidation does occur it goes up to the hexavalent state.

The small amount of activity present as sulfite has an additional significance. It means that no appreciable portion of the recoiling sulfur fragments formed in the nuclear reaction Cl^{35} (*n.p.*) S^{35} react chemically with chlorine to form such compounds as SCl_2, S_2Cl_2, etc., for such compounds on hydrolysis give sulfur dioxide. Likewise the absence of sulfite activity indicates the absence of thionates and polythionates.

These various results indicate that the non-sulfate sulfur is either in the form of elementary sulfur or sulfide ions. Attempts to distinguish between sulfur and sulfide ions were unsuccessful because of the rapid exchange that exists between these two states of sulfur in solution.

Heating irradiated potassium chloride crystals above the melting point in an atmosphere of carbon monoxide failed to produce any carbonyl sulfide. This observation would indicate that little or no free sulfur was present, but admittedly this evidence is not too good since under such drastic treatment and in such an unusual habitat free sulfur if present may well undergo some chemical transformation.

Acknowledgment.—The author wishes to express his appreciation to Professor R. D. Fowler for many illuminating discussions which were extremely helpful during the course of this investigation. It is also desired to acknowledge the coöperation of various members of the staff of the Brookhaven National Laboratory where the initial phase of this work was carried out.

Summary

The state of oxidation of S^{35} formed by neutron irradiation of potassium chloride depends on the pre-irradiation treatment of the crystals. If the crystals were carefully outgassed by heating and pumping the radioactive sulfur appeared in part either as sulfur or more probably as sulfide ion. If no precaution was taken to remove air from the crystals all of the S^{35} appeared in the hexavalent state. In all cases tested there was always some activity present as hexavalent sulfur and in the most favorable situation as little as 15% of the total sulfur activity was present in the highest oxidation state. It is concluded that atmospheric oxygen which is occluded in the crystal is responsible for the hexavalent state of the radio sulfur.

BALTIMORE, MARYLAND RECEIVED MAY 5, 1949

[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, AND BROOKHAVEN NATIONAL LABORATORY]

Infrared Spectra of Ortho-, Meta-, Para- and Omega-Monodeuterotoluenes in the 2–16 Micron Region[1a]

BY JOHN TURKEVICH,[1] HUGH A. MCKENZIE,[2] LEWIS FRIEDMAN AND ROBERT SPURR[3]

In connection with studies being carried out on the mechanism of exchange reaction between deuterium and aromatic compounds, it was found necessary to investigate the infrared spectrum of the monodeuterotoluenes. The present paper contains information on the preparation of these compounds and the infrared spectrum in the 2–16 micron region.

Preparation of the Compounds

The various monodeuterotoluenes were prepared by deuterolysis of the appropriate Grignard reagent. The latter was made using the procedure and apparatus of Weldon and Wilson.[4] After the formation of the ether solution of the Grignard reagent, it was connected to a vacuum system and most of the ether was distilled off. It was found preferable not to remove the ether completely since complete removal would make it extremely difficult to effect the reaction between the Grignard compound and the heavy water. The reaction flask was cooled in a Dry Ice–acetone-bath and the heavy water was added dropwise. The system was then allowed to warm up slowly overnight. The reaction mixture was shaken vigorously and then allowed to stand for at least twenty-four hours. The hydrocarbon and remaining ether were removed from the flask

(1) Consultant, Brookhaven National Laboratory.

(1a) Research carried out, in part, under the auspices of the Atomic Energy Commission.

(2) Visiting Fellow at Princeton University of the Australian Council for Scientific and Industrial Research.

(3) Visiting Assistant Professor, Princeton University.

(4) L. H. P. Weldon and C. L. Wilson, *J. Chem. Soc.*, 235 (1946).

by vacuum distillation to a trap cooled with liquid air. The contents of the trap were then redistilled to obtain a deuterotoluene fraction. The latter was redistilled to obtain a fraction boiling at 110°. The compounds were prepared and purified at the Frick Chemical Laboratory of Princeton University. The mass spectra of all the deutero compounds were examined by Dr. F. Mohler of the National Bureau of Standards. The results indicate that there is less than 0.2% of the dideuterium compound present in each sample and at most 5% of non-deuterated toluene. Further data on the purity will be relegated to the end of the paper.

Materials

o-**Toluidine** was purified by crystallization of the oxalate[5] and the fraction boiling at 182° in a 70-cm. column was collected.

o-**Bromotoluene** was prepared from the *o*-toluidine by the method of Bigelow.[6]

m-**Bromotoluene** was the Eastman Kodak Co. product. Examination of its infrared spectrum showed that it was free from the ortho, para or omega compound.

p-**Toluidine** was purified by crystallization of the hydrochloride.

p-**Bromotoluene** was obtained by diazotization of *p*-toluidine at 5–10°.[7] The product obtained boiled at 183°.

Benzyl chloride was the 181° fraction of the Paragon benzyl chloride.

Toluene was a special sample obtained from the U. S. Bureau of Standards.

Heavy water of 99.8% purity was obtained from the Atomic Energy Commission.

Results

The infrared spectra in the 2- to 16-micron region were obtained in 0.1-mm. thick rock salt cells on the Baird Associates Double Beam Recording Spectrophotometer[8] of the Chemistry Department of the Brookhaven National Laboratory. The results obtained for toluene, ortho-, meta-, para- and omega-monodeuterotoluene are presented in Table I and Figs. 1–5. The figures contain the absorption both of the pure compound and of a 10% solution in carbon tetrachloride. The data in the carbon tetrachloride solution are of doubtful value in regions of strong absorption of carbon tetrachloride, namely, 705–840 cm.$^{-1}$.

Data are also given on the spectrum of toluene obtained by the Naval Research Laboratory and published by the American Petroleum Institute under the serial number 308.

TABLE I

ABSORPTION BANDS OF VARIOUS TOLUENES

Toluene		Deuterotoluenes			
Present work	API 308	Ortho	Meta	Para	Omega
	3040	3040 S			3049 S
3000 VS[a]		2985 S	3010 S	2994 S	3000 S
				2959 S	2960 Sh
2915 VS	2924	2900 S	2907 S	2898 S	2890 S
	2874		2850 S		
2830 M		2830 S		2833 S	2830 S
					2790 M
2740 W	2740	2712 W	2732 W	2717 W	
					2670 W
2600 W	2590	2570 VW	2580 VW	2580 VW	
					2551 W
2535 W	2538				
2520					
	2410		2469 VW		
2380	2364				
2340 W	2336				
2300 W	2315	2315 W	2320 W		
	2283				
2230 VW	2263	2220 M	2252 M	2252 WM	2250 Sh
	2208			2230 M	2210 Sh
2180 VW	2188	2174 VW	2170 VW		
2150 VW	2164	2150 VW			2150 S
	2066		2060 W		
1985 Sh	1988				
1935 M	1941	1930 WM	1931 MW		1923 S
		1908 WM		1894 MW	
		1875 W	1875 WM		
1852 M	1855	1842 W	1855 WM	1845 W	1845 M
1795 M	1802	1800 WM	1900 M		1802 M
				1789 WM	1786 S
1739 M	1736	1718 W	1721 WM	1735 W	1724 W
	1698		1705 W		
1675 WM	1675				
1660 VW		1645 M		1675 WM	
1616 S	1605	1608 S	1616 S	1680 S	1613 S
1587 Sh	1575	1590 W			1565 M
	1527				
1497 S	1497	1504 Sh	1500 Sh	1510 W	
		1481 S	1486 S	1497 S	1499 S
1466 S	1460	1475 Sh	1475 Sh		
		1464 Sh	1462 S	1454 S	1458 S
			1420 W	1420 W	1440 W
1390 S	1379	1380 S	1386 S	1380 S	1386 MS
1339 W	1333		1350 W	1351 WM	1351 M
1316 WM	1314			1310 W	
	1282	1284 W	1295 WM		1285 S
					1277 S
1250 W	1250		1250 VW		
1217 WM	1211	1210 W	1209 WM	1206 W	1210 W
1181 M	1179	1176 WM	1170 M	1179 M	1180 M
1161 W	1156	1156 WM		1151 M	1150 M
		1126 M	1126 M	1126 M	1126 S
				1121 M	
1111 WM	1107	1110 W	1106 S	1111 S	
		1095 W			
1087 S		1085 WM	1085 S	1080 S	1080 S
1082 Sh	1081	1076 W	1076 W	1076 Sh	
1044 S	1042	1045 S	1050 S	1040 S	1045 W
1036 S	1030	1033 Sh		1029 S	1033 S
1005	1003			1013	
	982	985 WB	983 WB	983 W	987 M
	966				
		943 WM		944	
930	930				
		914 W	917 S	917 W	915 M
898 M	896	893 W	894 S	893 W	900 M
878 W	872	865 M	879 MS	863 M	
846 W	844	834 W	836 M	836 S	842 M
		798 WM	800 BS	803 M	807 M
788 WM	786	785} BS		785 M	
		765	763 WM		
730 S	728	725 S	725 S	726 S	
		716 S		710 S	715 S
695 S	694	695 S	695 S	693 S	694 S

[a] *Notation on intensity:* S, strong; M, medium; W, weak; VW, very weak; B, broad; Sh, shoulder.

(5) L. Vanino, "Handbuch der präparativen Chemie," Vol. 2, Ferd. Enke, Stuttgart, 1914, p. 438.

(6) Bigelow in "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 130.

(7) Bigelow, *ibid.*, p. 183.

(8) W. S. Baird, H. M. O'Bryan, C. Ogden and D. Lee, *J. Opt. Soc. Amer.*, **37**, 754 (1947).

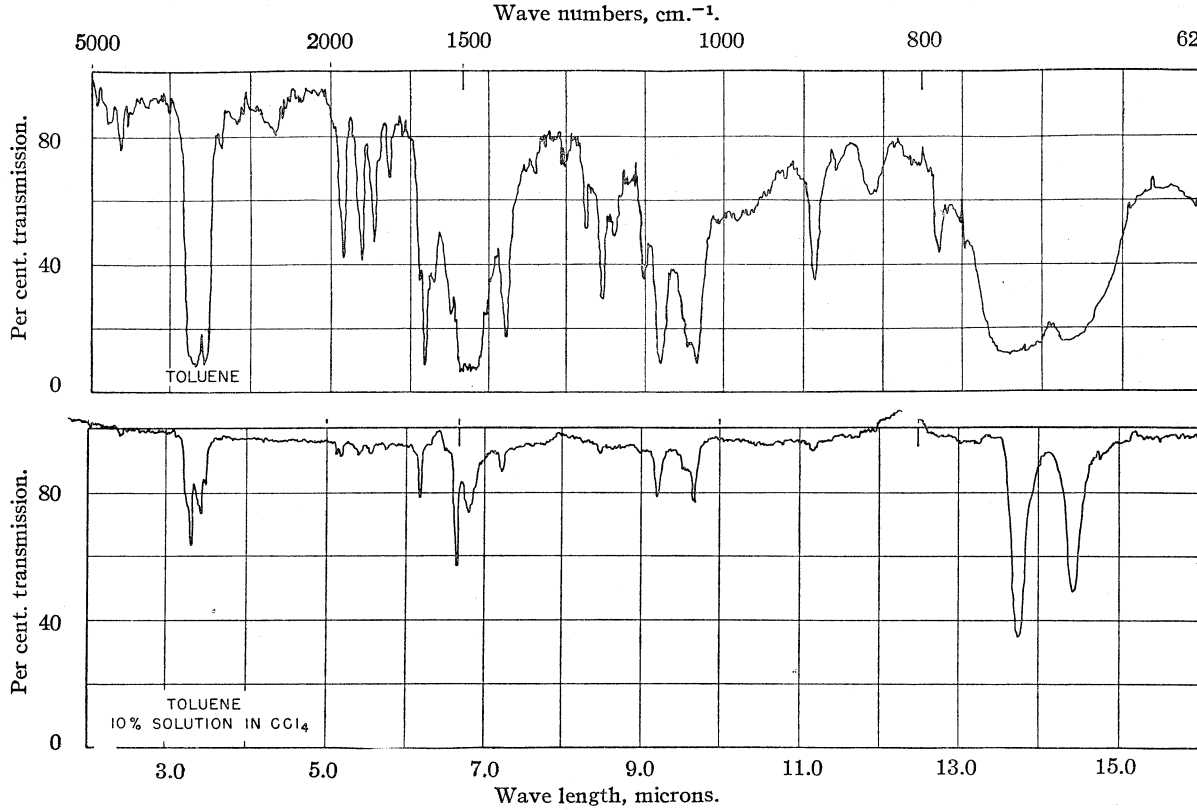


Fig. 1.—Infrared spectrum of toluene.

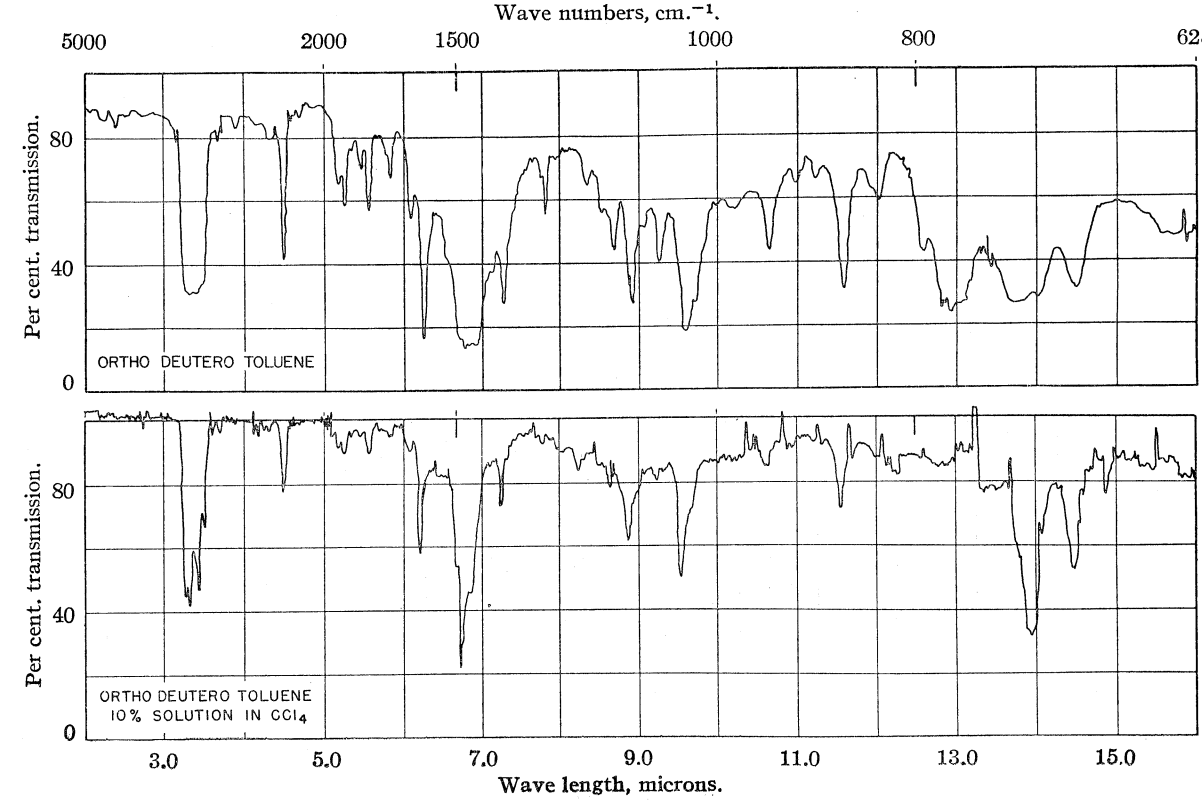


Fig. 2.—Infrared spectrum of *o*-deuterotoluene.

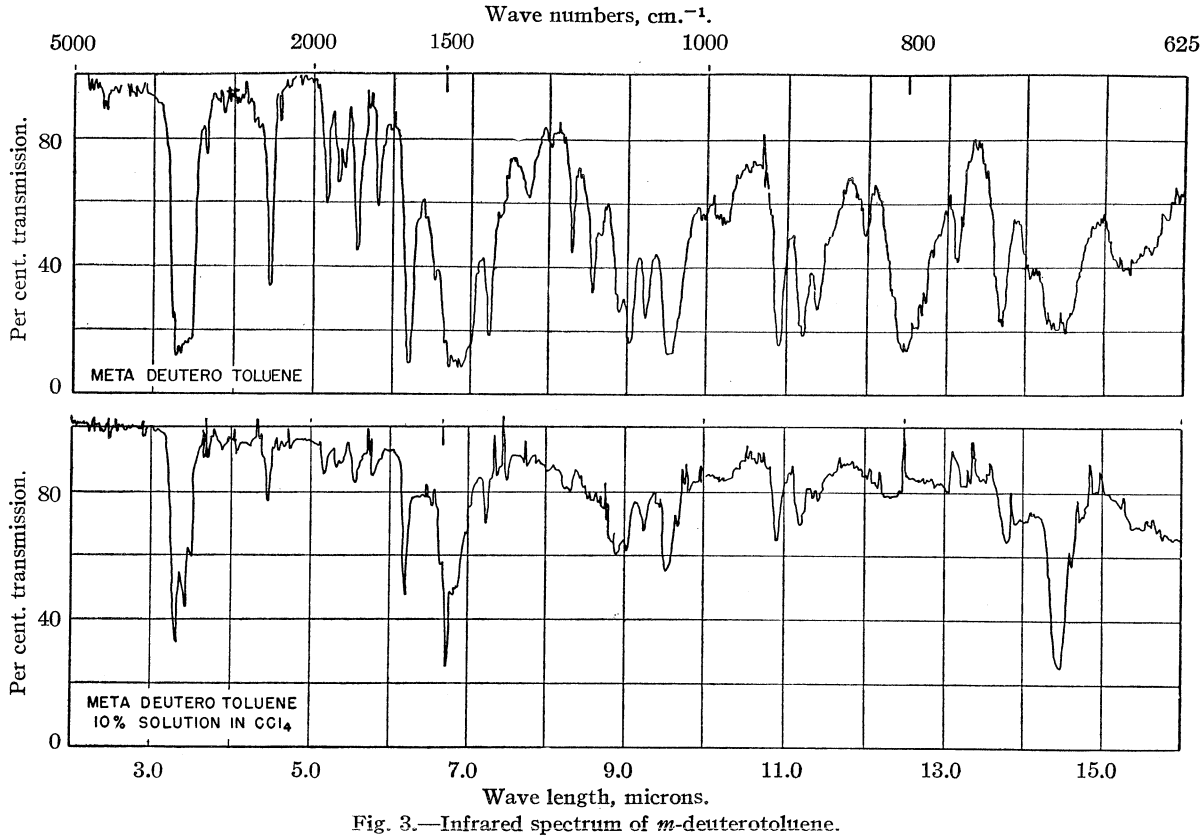


Fig. 3.—Infrared spectrum of *m*-deuterotoluene.

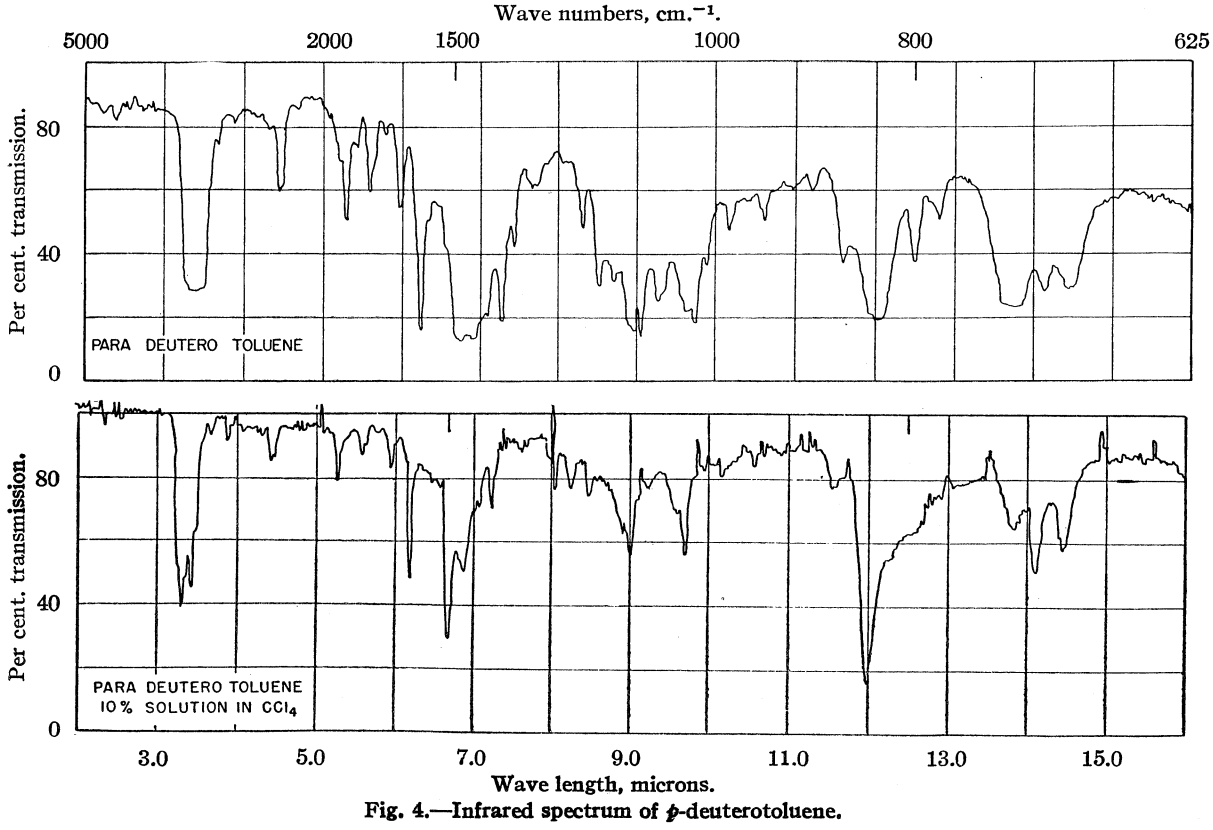


Fig. 4.—Infrared spectrum of *p*-deuterotoluene.

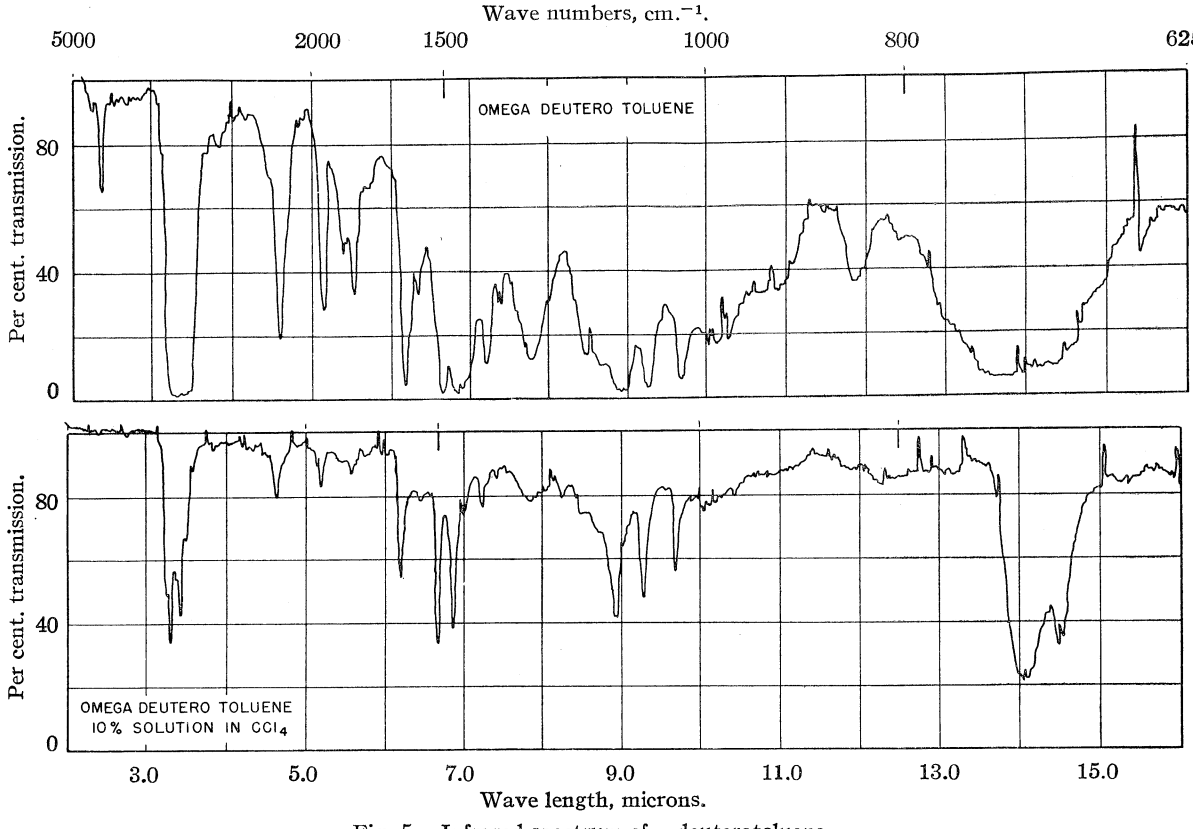


Fig. 5.—Infrared spectrum of ω-deuterotoluene.

Discussion

A complete discussion and interpretation of the results will be withheld until work is completed on spectra in the near infrared at high resolution using lithium fluoride optics, on the spectra in the 16- to 38-micron region using KBr and KRS 5 (thallium bromide–iodide) optics and on the Raman spectra. In the meantime, we wish to record the following observations.

The 4.6-micron region contains the bands due to the carbon–deuterium valence vibration. Non-deuterated toluene shows a very weak absorption in this region, undoubtedly due to an overtone or combination. When the deuterium atom is substituted in the ring the absorption band is at 2220–2252 cm.$^{-1}$, while when the deuterium atom is in the side chain the absorption is at 2150 cm.$^{-1}$. Thus it is easy to distinguish compounds containing deuterium in the ring from those containing deuterium in the side chain. Furthermore, the ortho-monodeutero compound absorbs at 2220 cm.$^{-1}$, the meta- at 2252 cm.$^{-1}$, and in the para compound the band is split in two at 2230 and 2252 cm.$^{-1}$. The per cent. of transmission of this carbon–deuterium stretching frequency is less in the meta compound than in the ortho compound and is least in the double peak of the para compound. All these bands are relatively sharp while that in the omega compound is rather broad and of the same intensity as that of the meta compound.

We would also like to discuss the purity of the compounds on the basis of the infrared data obtained. It is not possible to find a band that is characteristic of the non-deuterated toluene in this region of the infrared spectrum. The band at 730 cm.$^{-1}$ would satisfy this criterion were it not for the fact that the para compound has a broad band at 726 cm.$^{-1}$. The omega compound can be identified easily by the position of its carbon–deuterium stretching band at 2150 cm.$^{-1}$. The weakness of the absorption of other compounds in this region indicates the absence of the side-chain substituted deuterium in the ring-substituted deuterium compounds. The band at 1645 cm.$^{-1}$ can be used to establish the absence of the ortho compound in the meta, para and omega samples. The band at 879 cm.$^{-1}$ in the meta compound can be used to indicate the absence of this compound in the ortho, para and omega samples. The band at 1675 cm.$^{-1}$ is present in the para but not in the ortho, meta or omega samples. Thus the purity of the compounds is indicated within the accuracy of the infrared spectrometer.

Summary

The preparation of the ortho, meta, para and omega deuterotoluenes has been described and their infrared spectra from 2 to 16 microns presented.

RECEIVED JULY 9, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Reactions of Triphenylsilane and Triphenyltin Hydride

BY HENRY GILMAN AND H. W. MELVIN, JR.

Previous reports[1a,b] have shown that triethylsilane reacts with organolithium compounds in ether to form tetrasubstituted silanes and lithium hydride. We are now reporting that the reaction of triphenylsilane with phenylithium, methyllithium and *n*-butyllithium resulted in the formation of tetraphenylsilane, methyltriphenylsilane and *n*-butyltriphenylsilane, respectively, in good yields. These reactions may be formulated as

$$(C_6H_5)_3SiH + RLi \longrightarrow (C_6H_5)_3SiR + LiH$$

It is interesting to note that some tetraphenylsilane was formed in the reaction with *n*-butyllithium, possibly as a consequence of disproportionation,[2] even under these mild conditions. However, lithium *p*-thiocresoxide was without effect on triphenylsilane when these reactants were heated in ether.

The extent of the reaction between triphenylsilane and phenylmagnesium bromide appeared to be insignificant, for 90% of the silane was recovered. Since it has been shown that the reactivity of Grignard reagents is increased when dioxane is added to their solutions,[3] triphenylsilane was treated with a phenylmagnesium bromide solution containing this compound. Apparently reaction was inappreciable because triphenylsilane was recovered to the extent of 90%.

In extending the examination of the reaction of organolithium compounds to other similar hydrides of Group IV elements, it was found that triphenyltin hydride reacts with phenyllithium to form tetraphenyltin (90%) and lithium hydride.

Pape[4] obtained tetrapropylsilane as well as the expected tripropylsilane when trichlorosilane and dipropylzinc were heated in a sealed tube at 150° for six hours. He wrote an equation to account for the transformations

$$2SiHCl_3 + 4Zn(C_3H_7)_2 \longrightarrow SiH(C_3H_7)_3 + Si(C_3H_7)_4 + 3ZnCl_2 + Zn + C_3H_8$$

The formation of tetrapropylsilane along with free zinc and propane might be explained by a reducing action of the Si–H bond in tripropylsilane. It appears not unlikely, however, that the tetrapropylsilane may have been formed by a reaction similar to that described with RLi compounds. Organometallic compounds differ largely in rate of reaction rather than in kind of reaction,[5] and the forced conditions used by Pape may have been the determining factor in the results obtained by him. Inasmuch as Grignard reagents lie between organolithium and organozinc compounds in reactivity, it is probable that they also would react like organolithium compounds under appropriate conditions.

In order to determine whether triphenylsilane is a reducing agent, a solution of it in xylene was heated with acridine.[6] No products that might be formed by such a reduction were isolated.

It is highly probable that R_3GeH and R_3PbH[7] compounds would react like the corresponding silicon and tin compounds. However, triphenylmethane is known to react as follows with RLi compounds

$$(C_6H_5)_3CH + RLi \longrightarrow (C_6H_5)_3CLi + RH$$[8]

Experimental

Triphenylsilane.—This compound was prepared in essential accordance with the directions of Reynolds, Bigelow and Kraus.[9] Our yield was 88% in a preparation starting with 0.62 mole of trichlorosilane. Hydrolysis was effected by pouring the reaction mixture on cracked ice containing sulfuric acid. Inasmuch as this compound melted at 44–45° instead of 36–37°[9] after two recrystallizations from 95% ethanol, it was analyzed.

Anal. Calcd. for $C_{18}H_{16}Si$: Si, 10.77. Found: Si, 10.67, 10.72.

Triphenyltin Chloride.—Triphenyltin chloride was prepared by a modification[10] of the procedure of Kocheshkow, Nadi and Aleksandrow[11] from 55 g. (0.1785 mole) of tetraphenyltin and 11.2 g. (0.0429 mole) of stannic chloride. The yield of triphenyltin chloride, melting at 103–104°, was 47.2 g. (72%). Repeated recrystallization from petroleum ether (b. p. 77–115°) did not raise the melting point.

Triphenyltin Hydride.—Triphenyltin chloride instead of the bromide was used in the preparation of this compound.[12] From 20 g. (0.0518 mole) of triphenyltin chloride was obtained 1.5 g. (8.3%) of triphenoltin hydride. In a second run, using 17.8 g. (0.046 mole) of triphenyltin chloride, the yield was 6.8 g. (42%) of triphenyltin hydride. The compound was purified by distillation *in vacuo* in an apparatus previously swept with nitrogen. No percentage yield was reported by the earlier workers.[12]

(1) (a) Gilman and Massie, THIS JOURNAL, **68**, 1128 (1946); (b) Meals, *ibid.*, **68**, 1880 (1946); U. S. Patent 2,444,784, *C. A.*, **42**, 7317 (1948).

(2) Ladenberg, *Ann.*, **173**, 159 (1873); Calingaert, Soroos and Hnizda, THIS JOURNAL, **62**, 1107 (1940); Calingaert and Beatty, Chap. 24 in Gilman's "Organic Chemistry," 2nd. Edition, John Wiley and Sons, Inc., New York, N. Y., 1943.

(3) Bergman and Rosenthal, *J. prakt. Chem.*, [2] **135**, 267 (1932); Gilman and Gainer, THIS JOURNAL, **69**, 877 (1947).

(4) Pape, *Ber.*, **14**, 1873 (1881).

(5) For a discussion of relative reactivities of organometallic compounds, see Chap. 5 of Gilman, "Organic Chemistry," 2nd. Edition, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 518–524.

(6) J. L. Towle, in unpublished studies, has shown that thiols, under these conditions, will reduce acridine and related compounds. See, also, Gilman and Dickey, THIS JOURNAL, **52**, 4573 (1930).

(7) Compounds of the type R_4PbH have not been isolated. See Gilman and Bailie, *ibid.*, **61**, 731 (1939).

(8) Gilman and Young, *J. Org. Chem.*, **1**, 330 (1936).

(9) Reynolds, Bigelow and Kraus, THIS JOURNAL, **51**, 3070 (1929). See, also, Jenkins, Lavery, Guenther and Post, *J. Org. Chem.*, **13**, 862 (1948), for the most recent account of the preparation of R_4SiH types.

(10) The authors are grateful to C. E. Arntzen (Doctoral Dissertation, Iowa State College) for these directions.

(11) Kocheshkow, Nadi and Aleksandrow, *Ber.*, **67**, 1348 (1934).

(12) Chambers and Scherer, THIS JOURNAL, **48**, 1059 (1926).

Triphenylsilane and Phenyllithium.—To 26 g. (0.1 mole) of triphenylsilane dissolved in 50 ml. of ether was added 0.1 mole of phenyllithium in 107 ml. of ether with the immediate formation of a white precipitate. At the end of the addition Color Test I[13] was negative. A portion of the precipitate was removed and analyzed as described under "Identification of Lithium Hydride." Subsequent to hydrolysis and recrystallization from benzene, there was obtained 30.3 g. (90%) of tetraphenylsilane, m. p. 230–232°.

Anal. Calcd. for $C_{24}H_{20}Si$: Si, 8.33. Found: Si, 8.3, 8.3.

Triphenylsilane and Methyllithium.—Triphenylsilane (0.044 mole) and 0.044 mole of methyllithium were interacted as described above. After working up the reaction mixture in the customary manner and recrystallizing the product from ethanol, 11.6 g. (93%) of methyltriphenylsilane, m. p. 66–67°,[14] was obtained. This product was identified by the method of mixed melting points.

Triphenylsilane and *n*-Butyllithium.—To 0.05 mole of triphenylsilane dissolved in 25 ml. of ether was added 0.045 mole of *n*-butyllithium in 70 ml. of ether. Color Test I[13] was negative after one-half hour. After hydrolysis, the hydrolysate was extracted with hot benzene. The benzene layer was separated, dried and the solvent removed by distillation. The residue, a gummy material, was extracted with 95% ethanol and the solid remaining was shown to be tetraphenylsilane (10.7% of the product). From the ethanol was obtained 10 g. (63.5%) of *n*-butyltriphenylsilane melting at 86°. Disproportionation[2] has been reported to occur among silicon compounds, and this phenomenon might account for the formation of tetraphenylsilane.

Anal. Calcd. for $C_{22}H_{19}Si$: Si, 8.86. Found: Si, 8.67, 8.72.

Triphenylsilane and Phenylmagnesium Bromide.—Three experiments in which triphenylsilane was treated with phenylmagnesium bromide were carried out. In the first, 0.023 mole of phenylmagnesium bromide and 0.031 mole of triphenylsilane were refluxed in ether for twenty-four hours. In the second, 0.0154 mole of triphenylsilane in 15 ml. of ether was treated with 0.012 mole of phenylmagnesium bromide in 10 ml. of ether. Most of the ether was removed by distillation and replaced with 20 ml. of dry xylene in which the reactants were refluxed for twenty-four hours. In the third, a mixture of 0.022 mole of phenylmagnesium bromide containing 3 ml. of dioxane and 0.019 mole of triphenylsilane was stirred at room temperature for twenty-four hours. In each case, Color Test I[13] was positive at the end of the reaction time. The quantities of triphenylsilane recovered were 7.4 g. (92.5%), 3.5 g. (88%) and 4.5 g. (90%), respectively.

Triphenyltin Hydride and Phenyllithium.—In the first of two runs of this reaction, 0.0043 mole of triphenyltin hydride was treated with 0.0044 mole of phenyllithium, a precipitate being formed at once. Then 0.0044 mole of benzyl chloride was added to react with any triphenyltinlithium that might have formed. On hydrolysis an ether-insoluble solid separated. This was collected on a filter, washed with five 5-ml. portions of ether and dried over sulfuric acid in a vacuum desiccator. The yield of tetraphenyltin melting at 228–230° (mixed m. p., 228–230°) was 1.7 g. (91%). In the second run, using 0.0117 mole of triphenyltin hydride, 0.0119 mole of phenyllithium and 0.0119 mole of benzyl chloride, a portion of the solid formed was analyzed as described under "Identification of Lithium Hydride." Subsequent to working up the mixture, the yield of tetraphenyltin was 4.5 g. (90%).

Identification of Lithium Hydride.—When triphenylsilane and triphenyltin hydride, respectively, were treated with phenyllithium, a white precipitate immediately formed. In each case the solid was allowed to settle and the ether decanted in a nitrogen atmosphere. The residue was then centrifuged for one and one-half hours and the supernatant ether was decanted. The solid was twice washed with anhydrous ether, centrifuged, and the ether decanted. The residual solvent was removed by heating the solid on a steam-bath *in vacuo*. The combined ether washings completely distilled at 36–38°, indicating the absence of benzene.

A sample of the dried precipitate was hydrolyzed, the solution was titrated for total alkalinity, and the solid residue was recovered. From 1.4300 g. of the solid formed in the reaction between triphenylsilane and phenyllithium was obtained 1.3968 g. of residue, identified as tetraphenylsilane. The total alkali, 0.00415 mole, was in agreement with the loss in weight of the sample (0.0332 g.) when this was calculated as lithium hydride (0.00418 mole). On hydrolysis of 0.2895 g. of the precipitate formed in the reaction between triphenyltin hydride and phenyllithium, 0.2842 g. of solid residue, identified as tetraphenyltin, was recovered. The total alkali (0.00067 mole) again checked with the loss in weight of the sample (0.0053 g.) when this was calculated as lithium hydride (0.00067 mole).

Triphenylsilane with Acridine, and with Lithium *p*-Thiocresoxide.—Twenty-six grams (0.11 mole) of triphenylsilane and 4.8 g. (0.027 mole) of acridine were dissolved in 80 ml. of dry xylene under nitrogen connected to a trap,[15] and the solution refluxed for thirty hours. On cooling, a solid was formed. This was dissolved in acetone and treated with ethanolic hydrogen chloride to precipitate acridine hydrochloride which, in turn, was treated with 10% sodium hydroxide to liberate the base. The base was recrystallized from ethanol, and 4.7 g. (98%) of acridine, melting at 106°, was recovered. No depression occurred when a mixed melting point determination with an authentic specimen was made. From the acetone solution 24.7 g. (95%) of triphenylsilane was obtained.

Lithium *p*-thiocresoxide was prepared from 5 g. (0.04 mole) of *p*-thiocresol in 20 ml. of ether and 0.036 mole of phenyllithium in ether. Color Test I[13] was negative at the end of the addition, and a solid separated. Then was added 7.8 g. (0.03 mole) of triphenylsilane dissolved in 25 ml. of ether. The mixture was refluxed, by external heating, for twenty-four hours with stirring. After working up the mixture, 7.5 g. (95%) of triphenylsilane was recovered. From the aqueous layer, 4.4 g. (88%) of *p*-thiocresol (mixed m. p.) was obtained.

Summary

The reaction between triphenylsilane and some organolithium compounds has been investigated, and it has been shown that the reaction which takes place is

$$(C_6H_5)_3SiH + RLi \longrightarrow (C_6H_5)_3SiR + LiH$$

A similar reaction occurs with triphenyltin hydride. Under corresponding conditions, phenylmagnesium bromide seems to be without effect in this type of reaction with triphenylsilane.

Disproportionation appears to occur in the reaction between triphenylsilane and *n*-butyllithium, inasmuch as some tetraphenylsilane was obtained in addition to the expected *n*-butyltriphenylsilane.

Triphenylsilane did not reduce acridine, nor did it react with lithium *p*-thiocresoxide.

AMES, IOWA RECEIVED APRIL 4, 1949

(13) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

(14) Marsden and Kipping, *J. Chem. Soc.*, **93**, 198 (1908).

(15) Gilman and Hewlett, *Rec. trav. chim.*, **48**, 1124 (1929).

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICS, UNIVERSITY OF MICHIGAN]

Macromolecular Weights Determined by Direct Particle Counting. I. The Weight of the Bushy Stunt Virus Particle[1]

BY ROBLEY C. WILLIAMS AND ROBERT C. BACKUS

Introduction

The weights of macromolecules and particles of colloidal dimensions can be determined by a variety of methods: diffusion, osmotic pressure, sedimentation velocity, sedimentation equilibrium, X-ray patterns,[2] light scattering,[3] ultramicroscopy[4] and by direct electron microscopy. Each of these methods has advantages and limitations, and each is particularly applicable only over a certain range of sizes. In the application of any of the methods a determination must be made, either directly or indirectly, of one of two sets of quantities: (1) the volumes and densities of the macromolecular particles, or (2) the number of particles in a known volume of solution and the dry weight of the particles in an aliquot of that volume.

In a general way one would expect that the most reliable method would be the one which most directly determines the quantities involved in the definition of molecular weight: the mass in grams per mole of one molecular species. Any notably indirect method is subject to the assumptions involved in the derivation of the working formulas, and to the reliability of the chain of relations existing between the directly observable quantities and the weight of a gram-molecule. Thus, for example, in the sedimentation equilibrium method, what is directly measured is the space gradient of the index of refraction, or the opacity of the solution in the centrifuge cell. But in order to compute the molecular weight of the solute one must know the variation of the refractive index, or opacity, with concentration of solute, the partial specific volume of the solute while undergoing sedimentation, the density of the solution, the angular velocity of the centrifuge, and, additionally, one must sediment for a sufficient length of time to know that he has achieved equilibrium. Further, one must have reason to believe that the solute molecules do not interact, and that no electrical field gradients are set up by the concentration gradient, a condition best satisfied by the use of a dilute solution, but contrary to the *observational* requirement that a fairly concentrated solution be used.

On the other hand, the limitations on the two direct types of determinations are severe. Accurate measurement of particle size by electron microscopy is limited to particles larger than about $M = 10 \times 10^6$. The possible shrinkage effects of severe desiccation in the microscope make for uncertainty, and, of course, the density of the particle must be known. Determinations of M by ultramicroscopy are severely limited by the fact that, as seen in scattered light, all particles look approximately alike. Hence, one must have an external check on the homogeneity of the specimen. Further, the counting of particles in a suspension is difficult and uncertain, and is restricted to those particles whose size and index of refraction are great enough to allow them to be individually counted. The last restriction has effectively prevented the use of ultramicroscopy in accurately determining the weights of protein macromolecules.

The Method of Direct Particle Counting by Electron Microscopy

A direct method of determining weights of macromolecules has been developed which preserves the theoretical simplicity of ultramicroscopy and removes many of its limitations. The number of macromolecules or particles in a known volume of suspension is counted in the electron microscope and the dry weight of the particles in an aliquot of the known volume is measured. The lower limit of size of molecules is that which is barely countable (*ca.* $M = 70{,}000$), while the electron microscope itself furnishes a fairly reliable estimate of the homogeneity of the particles. The fundamental sources of error are four only: the evaluation of the volume of solution whose particles are being counted, the counts themselves, the degree of homogeneity of the material and the determination of the dry weights. These sources of error will be discussed in detail later. The use of the method of direct particle counts is illustrated in this contribution by a determination of the particle weight of the bushy stunt virus. This virus is chosen because it can be readily grown and highly purified; its particles are exquisitely uniform in size, are easily countable in electron micrographs, and the weight of the virus particles has been previously measured in several laboratories. This particle will hereafter be referred to as the BSV particle.

Experimental

The BSV Preparations.—The BSV particles[5] were obtained from *Datura metaloides* that had been infected with the bushy stunt virus, and were purified by differential centrifugation in a manner similar to that described by

(1) This research has been supported in large part by a grant from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

(2) These five methods are reviewed in Cohn and Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943.

(3) Reviewed by Oster, *Chem. Rev.*, **43**, 319 (1948).

(4) Burton, "The Physical Properties of Colloidal Solutions," 3rd ed., Green and Co., New York, 1938.

(5) We are indebted to Mr. Russell Steere for furnishing us with ample quantities of plant juice containing the virus particles.

Stanley.[6] The leaves were frozen for several days, chopped while frozen and the cold juice pressed out through cheese cloth. The juice was then clarified at 4500 r.p.m. in an angle-head centrifuge and the clarified liquid filtered through a thin layer of Celite. The filtered juice was allowed to stand at 4° overnight and decanted into the ultracentrifuge tubes for an acceleration to 50,000 g., followed by immediate deceleration. The clarified juice was then spun at 50,000 g. for seventy-five minutes in a 10° Grebmeier rotor and the supernatant liquid discarded. The pellet was resuspended in fresh double distilled water and clarified at 4500 r.p.m. A sufficient aliquot of the resuspended, clarified pellet so obtained, designated P_1, was set aside for analysis.

The remainder of P_1 was carried through another high-speed sedimentation, resuspension and low-speed clarification cycle. The ultracentrifuge supernatant P_{2s}, as well as the second reworked pellet P_2, was now saved. The cycle was repeated until samples of P_1, P_2, P_3, P_4, as well as the corresponding supernatant suspensions, P_{2s}, P_{3s}, P_{4s} were obtained. Subsequent to the supernatant plant juice first discarded only undissolved material was discarded, and all resuspension volumes were precisely determined. The cycling was completed in seventy-two hours, with the temperature of the suspensions kept near 4° in order to minimize bacterial contamination.

Counting the BSV Particles.—The number of BSV particles per ml. of the seven suspensions obtained as above can be counted in the electron microscope if all of them in a known volume of diluted suspension can be surely observed. It has been found that an adaptation of a spraying technique is suitable for this purpose. (The details of the spraying method employed and an estimate of its reliability will be published elsewhere.[6a]) The BSV-particle suspension was diluted to an appropriate concentration and quantitatively mixed[7] with an aqueous suspension of Dow Latex polystyrene particles[8] *containing a known number of latex particles per ml.* The mixed suspension was then sprayed directly upon collodion-coated microscope screens to form small, approximately circular patterns containing both the latex and the BSV particles. The patterns varied in diameter from about 5 to 30μ and the dilutions were so adjusted that the average pattern contained about 50 latex particles and 100 BSV particles. The numbers of both the latex and BSV particles were counted, thus establishing the number of BSV particles per ml. The droplet patterns were shadow-cast and photographed at a magnification of about 4000×. Enough pictures were obtained to provide about 1000 latex particles for comparison with the number of BSV particles in each suspension.

Calibration of the Latex Particles.—There are several possible ways of determining the number of latex particles per ml., but only one way appeared to be immediately available to us. This consisted of the determination of (a) the volume average of the latex spheres, (b) the density of dry latex and (c) the dry weight of the latex particles in a known volume of a suspension to be used as the standard. The first two measurements yield the weight average of the particles, and this combined with the dry weight gives the number of latex spheres per ml. in the standard suspension.

The method of determining the average diameter of the latex particles has been reported.[8] From the value of the average diameter and an auxiliary curve of size dispersion (see below) the average volume of the particles was computed. The density was measured by immersing chips of thoroughly dried material in aqueous copper sulfate solutions of known densities.

The Dry Weight of the BSV Suspensions.—Small amounts (approx. 10 mg.) of the resuspended and clarified pellets of BSV were placed in weighing bottles and dried to constant weight over P_2O_5 *in vacuo*. The usual precautions were taken to avoid absorption of moisture while weighing. The dried material was further treated to six hours at 95° in P_2O_5-dried air in a vacuum-type desiccator. The desiccator was then evacuated to an air pressure of 100 μ while still hot, and allowed to cool while evacuated for thirty hours. The dry weights were then redetermined.

Tests for Homogeneity.—Inasmuch as the total weight of the dried material containing the BSV particles is measured, the effect of any non-volatile impurity, not counted as BSV particles, will be to increase the apparent particle weight. A search for impurities of this nature was made in a direct way (microscopically) and in an indirect way (spectrophotometrically): (1) It was found that the electron micrographs could be used as sensitive indicators of impurities. Spray droplets of fairly concentrated BSV particle suspensions, without the addition of latex, were photographed and carefully examined for what would appear to be material other than the BSV particles. The average micrograph of a droplet contained about 2000 BSV particles and all of any existing non-volatile impurity. Bacterial contamination was quantitatively assessed by examining several hundred droplet patterns. Areas of the microscope screens sufficiently large to contain an estimated 5 million BSV particles were scrutinized directly for bacteria as their images were moved across the fluorescent screen of the microscope. (2) The optical density of the BSV suspensions was measured through wave length 2600 Å., the peak of the absorption band of nucleic acid. Suspensions were diluted to contain approximately equal numbers of BSV particles per ml., and the ultraviolet absorption calculated in terms of BSV particles/ml. and also in mg. dry weight/ml. This measurement, like all others, does not give an absolute measure of purity, but rather an indication of relative purity.

Results

The Standard Polystyrene Latex Suspensions.—The average diameter of the polystyrene particles was taken[8] to be 2590 ± 25 Å. Recalculation with the aid of the distribution curve shown in Fig. 1, results in a diameter of 2600 Å. for the particle of average volume. The dry density of the latex was found to be 1.052 ± 0.001 g./cc., and the dry weight of 4.00 ml. of the standard sus-

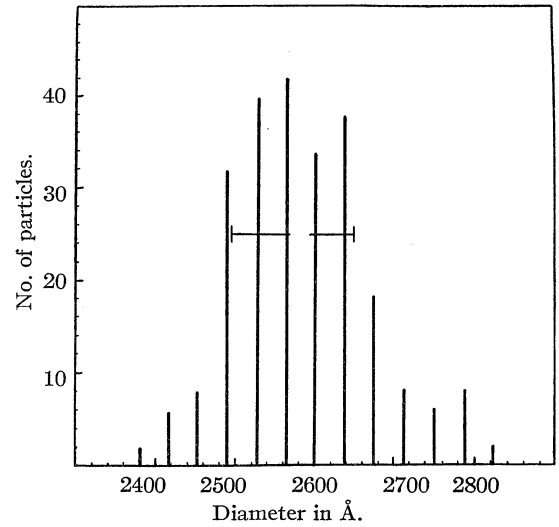


Fig. 1.—Dispersion curve of the diameters of 225 particles of Dow polystyrene latex. Horizontal line shows that 70% of the particles fall within a diameter range of ±3%.

(6) Stanley, *J. Biol. Chem.*, **135**, 437 (1940).

(6a) Scheduled for *J. Applied Phys.*, January, 1950.

(7) Chamot and Mason, "Handbook of Chemical Microscopy," Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1938, p. 441.

(8) Backus and Williams, *J. Applied Phys.*, **20**, 224 (1949).

TABLE I

DATA FOR THE DETERMINATION OF THE WEIGHT OF THE BSV PARTICLE BY COUNTS

Pellet	Total no. of PSL[a] counted	Ratio[b] of BSV/PSL	Dil. of BSV as sprayed[c]	No. of BSV/ml. in spray ($\times 10^{-10}$)	No. of BSV/ml. as weighed ($\times 10^{-14}$)	Dry wt. of BSV susp. (mg./ml.[d])	Wt. of one BSV particle (gm. $\times 10^{17}$)	(mol. wt. units $\times 10^{-8}$)
P_1	970	1.74	8000	7.76	6.21	10.8	1.74	10.4
P_2	1032	1.56	6000	6.96	4.18	7.30	1.74	10.4
P_3	1175	1.66	8000	7.41	5.93	9.00	1.52	9.2
P_4	1095	2.72	2000	12.1	2.42	3.90	1.61	9.6

[a] PSL = polystyrene latex particles. [b] Ratio of numbers of BSV particles to PSL particles as sprayed. [c] Dilution compared to the suspension as weighed. [d] Total weights were from 7.40 to 15.2 mg. No measurable difference between heated dried and unheated dried samples.

pension was found to be 69.2 ± 0.05 mg. The standard suspension was diluted 40-fold for spraying, and the dilution for each set of BSV particle counts was separately pipetted. Simple calculations show that the number of latex particles per ml. as sprayed was 4.46×10^{10}.

The Counts, Weights, and Particle Weights of BSV Particles.—In Table I are shown the results of the counts, dry weights, and particle weights obtained from the preparations P_1, P_2, P_3 and P_4.

Ultraviolet Absorption.—The data and results of the measurement of optical density at 2600 Å. are shown in Table II.

TABLE II

ULTRAVIOLET ABSORPTION OF BSV PREPARATIONS

Pellet or supn.	No. of BSV/ml.[a] ($\times 10^{-13}$)	Opt. dens.[b] (D) at 2600 Å.	(D) per BSV/ml. ($\times 10^{-13}$)	Dry wt.,[c] (mg./ml.)	(D) for a 0.1% susp.
P_1	1.03	0.87	0.85	0.018	4.8
P_2	1.29	1.01	.78	.023	4.4
P_{2s}	1.29	1.37	1.06		
P_3	1.17	0.97	0.83	.018	5.4
P_{3s}	1.28	1.05	.82		
P_4	1.28	1.09	.85	.021	5.2
P_{4s}	1.28	1.17	.91		

[a] Calculated from counts and known dilutions. [b] For an absorption cell 1 cm. thick. [c] Dry weight per ml. for a suspension of concentration shown in col. 2. Data available only for pellets.

TABLE III

INTERNAL CHECK ON BSV PARTICLE COUNTS AND DILUTIONS

Pell. or supn. fluid	Vol. in ml. which resus.[a]	Vol. in ml. in subseq. peleting	No. of BSV/ml. ($\times 10^{-14}$)	No. of BSV in volumes indic. in: Col. 2 ($\times 10^{-15}$)	Col. 3 ($\times 10^{-15}$)	Appar. loss of BSV[b] in: (%)	(mg.)
P_1		8.8	6.21		5.47	9	7.8
P_{2s}	14.4		0.55	0.79			
P_2	10.0	8.0	4.18	4.18	3.34	5	1.7
P_{3s}	14.4		0.52	0.75			
P_3	4.10	2.5	5.87	2.41	1.47	5	1.4
P_{4s}	14.4		0.29	0.42			
P_4	4.00		2.42	0.97			

[a] Volume to which pellet was resuspended; supernatant volume left unchanged. [b] Difference in % between numbers of BSV particles in P_n(col. 6) and $[P_{n+1} + P_{(n+1)s}]$ (col. 5).

Internal Check on BSV Particle Counts and Dilution Factors.—The data provide a convenient internal check on the precision of the counts and of the dilutions. Inasmuch as the solid material in each resuspended and clarified pellet, plus its supernatant, derives from the solid material in the preceding resuspended and clarified pellet (less the known amount removed for analysis), the accuracy of the counting and dilution can be checked by simple subtraction. Thus, for example, P_1 was resuspended in 10 ml. of distilled water and 1.2 ml. removed for assay. The remaining 8.8 ml. were used in the formation of P_2 and P_{2s}. The total number of BSV particles found in the resuspended and clarified P_2 plus P_{2s} should equal that found in the 8.8 ml. of P_1. Table III gives the data and the results of the internal checks.

Discussion

Precision of the Particle Weight Determination.—The evaluation of the number of latex particles per unit volume depends upon two kinds of measurements: the average volume of the latex spheres, and the density of the dried latex. Calculation of average volume is based upon a determination of average diameter and shape discussed elsewhere.[8] Other determinations of average diameter have been privately communicated to us from six different laboratories, and the extremes of average diameter have been 2560 ± 30 and 2610 ± 30 Å. Since the spread in seven independent measurements, by wholly independent methods, is about 2%, it is felt that our adopted value of 2590 Å. is probably reliable to 1%. The average volume can be calculated only after a dispersion curve of relative diameters is obtained. Figure 1 shows a distribution of diameters obtained for 225 particles. When the latex material is handled properly in the microscope, so as to avoid undue heating by the electron beam, its uniformity in size is quite satisfactory. Some small error of finite sampling is introduced, however, by the failure of the latices to be of perfectly uniform diameter. Since small errors in diameter are multiplied by a factor of three when translated to error in volume, a generous estimate of the limit of uncertainty of the volume-average of the latex spheres might accordingly be estimated at 5%.

The density of the dried latex can easily be

measured to an accuracy far greater than 1%. The uncertainty here is whether or not the density of an individual particle is the same as that obtained for the dried chips. The latex dilutions were made with a precision far exceeding 1% and the weight of the dried sample was enough (69.2 mg.) to assure a high precision in weighing. It is concluded that the uncertainty in the figure for the number of latex particles per ml. is about the same as the major uncertainty indicated above (5%) in the volume of a single particle. This estimated 5% uncertainty in the average mass of the latex particles is troublesome in that it enters systematically into all of our determinations of particle weights. However, other methods of measuring either the mass of the particles or the number per ml. are available (by sedimentation velocities in media of different densities, and by light-scattering) and any subsequent refinement in these determinations can be applied directly as a correction to the calculated values of weights determined by this method.

Drying and Weighing the Virus-Containing Material.—Although the BSV suspensions have been dried and weighed in an accepted manner there is still the likelihood that some water has been weighed along with the protein. The error in the weight determination alone has been estimated by repeated weighings, and the standard deviation is about 0.5%. But the unanswerable question as to whether the results represent the anhydrous macromolecular weight of the virus is precisely the same question that plagues any determination of molecular weight of proteins, since *all* methods involve at some stage either a determination of density or of dry weight. It can only be said that our results represent the weight of the BSV particle under conditions of drying involving heating to 95° and prolonged exposure *in vacuo* to phosphorus pentoxide.

The Tests for Purity and Homogeneity of the BSV-Containing Material.—As Pirie[9] and others have adequately discussed, there is no single criterion of purity of a protein preparation, nor does the sum of all criteria offer any proof of purity. Indeed, the concept of purity has meaning only as related to the experimental methods used for detecting impurities.

Electron microscopy coupled with our technique of specimen preparation has been relied upon heavily for indications of impurity in our BSV preparations. The electron microscope has formerly been little used with any confidence for this purpose, owing to the difficulty of defining fields representative of the original suspension, but by spraying droplets containing the purified BSV particles, one obtains a representative field in each drop pattern. Droplets of suspensions of all seven pellets and supernatants have been sprayed in sufficiently concentrated form to result in about 2000 BSV particles per drop pattern, and micrographs of these have been carefully examined. In the case of P_1 and to a less extent in P_2, P_{2s} and P_{4s}, there was some very small-sized material present. Pellets P_3 and P_4 had no detectable inhomogeneous material, although an amount as great as 1% of the total would have been readily observable. (A high-quality, uranium-shadowed micrograph will show the presence of objects as small as 30 Å. in mean diameter, or 1/1000 the volume of a BSV particle.) There are, however, three kinds of impurities essentially undetectable by electron microscopy alone: particles too small to be detectable and which do not form observable aggregates upon drying, material of about the same size and shape as the BSV particles, and material of great size but rarely present. Although there is no way to detect the presence of the first impurity by electron microscopy, it is believed that the great dilutions involved in four cycles of centrifugation would have reduced the concentration of the first impurity to a negligible amount. The second type of impurity will cause little error in our determination of particle weight since it will be counted and weighed along with the BSV particles. The third type, typically to be found as bacteria, could cause serious error, since a medium-sized bacterium is equal in weight to about 20,000 BSV particles. No bacterial material, nor any material of comparable size, was found in a search embracing fields containing about 5 million BSV particles, and the conclusion is that the error in weight due to contamination by particles of relatively great size is less than 1%.

The evidence from the light absorption at 2600 Å., combined with the molecular weight determinations, is indicative of relative purity if we assume that non-BSV proteins contain little, if any, nucleic acid. As Tables I and II show, the nucleic acid absorption per BSV particle is approximately constant in all pelleted material, and even in all supernatant liquids except the first one, P_{2s}. The absorption per unit weight concentration is found to increase significantly for the most completely washed pellets, P_3 and P_4, while the calculated particle weights are smallest for these pellets. This relation is best explained by assuming that in the first two pellets there was some non-BSV material present which added to the dry weights but not to the ultraviolet absorption.

It is to be noted that analytical centrifugation and electrophoresis have not been used as criteria of purity of our preparations. The reason for this deliberate omission is that both of these methods are sensitive only to rather special kinds of impurities: those which are present in sufficient concentration and are sufficiently homogeneous (either with respect to sedimentation velocity or in net ampholytic charge-density) to create detectable skewness in a concentration gradient. Gross amounts of impurities of miscellaneous sedimentation and/or electrophoretic velocities can be in the solutions and remain undetectable by these methods.

(9) Pirie, *Biol. Rev., Cambridge Phil. Soc.*, **15**, 377 (1940).

Precision of the Counts.—The error of counting can be statistically analyzed for the size of the most probable error. Computations of standard deviation have been made for all counts and have fallen between 2 and 4%. From statistical theory it is known that the standard deviation in ascertaining the number ratio of 1000 pairs of particles, if mixing is perfect, should be about $1/\sqrt{1000}$, or 3% (*i. e.*, if the counts show this standard deviation, the mixing would be defined as perfect). There is the possibility of a systematic error in the distribution of particles in the drop patterns; some, for example, may become dislodged from the substrate film before shadowing. This possibility has been checked by running a dilution curve of BSV particles *vs.* latex particles over a 5 × 2-fold series of dilutions. These results will be published in detail later, but they can be summarized briefly by saying that the dilution factors calculated from pipetting are checked to within 4% by the counts.

The internal consistency of dilutions and counts, Table III, is a further check against a systematic error. Some loss is to be expected in going from one pellet to the next pellet and supernatant. Some of the loss will be in the clarification sediment, roughly estimated to be 1 mg. in $P_1 \rightarrow P_2 + P_{2s}$, and to be negligible for the later pellets. In resuspending each pellet, however, care was taken not to include any material clearly outside the pellet and clinging to the side of the ultracentrifuge tube. In the $P_1 \rightarrow P_2 + P_{2s}$ cycle an observable quantity was found here and might amount to 2 or 3 mg. Allowance for these obvious losses reduces the per cent. loss in the $P_1 \rightarrow P_2 + P_{2s}$ operation to about 6%. It is felt that since this over-all check on counts and dilutions does not indicate a discrepancy greater than 6% in any of the three cycles, only the statistically predictable small random errors are present. This conclusion is particularly evident when it is noted from the last two paragraphs that both ratios and sums are internally consistent.

Summary of Estimated Errors and Results.—The errors detailed above, if added unfavorably, would result in an upper limit of error of an individual determination of particle weight of about 10%. The question now arises of how best to average the values of the particle weights obtained from the four pellets. An arithmetic mean would decrease the probability of an accidental error strongly affecting the result, but would neglect the evidences for increased purity in the last two pellets. In view of the strength of this evidence, *the most probable value of the dry weight of the bushy stunt virus particle obtained by the method of direct particle counts is* $9.4 \pm 0.7 \times 10^6$ *in molecular weight units.*

Conclusions Regarding the Method.—The method of measuring macromolecular weights by direct counting has the primary advantage of simplicity and directness. It serves as a proper check on molecular weights obtained by centrifugation owing to its freedom from the complications and assumptions involved in sedimentation studies. Its largest uncertainty at present, at least in the case of the highly-purifiable BSV particles, is the calibration of the concentration of the latex particles. The counts of the particles can be made to within any predetermined accuracy with sufficient patience and, indeed, if all the counts discussed here had been made on a suspension of only one pellet, the standard deviation of counting would have been reduced to about 1%. The drying, weighing, and assessing of impurities are measurements that are common to all determinations of large molecular weights, although the methods of measurement vary. In particular, sedimentation velocity provides a sensitive and convenient way of detecting and measuring one component of a paucidisperse system. Even here, however, polydispersity or undetected impurities will cause trouble, since they affect the precision of the auxiliary diffusion constant.

A particularly inviting aspect of the method of direct particle counts is that the suspensions can be sprayed and counted at astonishingly low concentrations. All other methods of measuring macromolecular weights become observationally more precise as the concentration of solute is increased, but since side effects, such as aggregation, always enter at high concentrations, it is common practice to extrapolate experimental results to infinite dilution. With the particle count method the solute is best sprayed at concentrations less than 1 mg. per liter or 0.0001%, compared with the usual sedimentation concentration of 0.4%. At a dilution of 1 mg. per liter, each BSV particle is allotted an average solvent volume of 10 μ^3, or 100,000 times the volume of the particle. The droplets lose water by evaporation in their flight from the spray gun to the microscope screen, but their particle content is determined by the concentration in the droplet at the moment it becomes a discrete entity in the spray.

There are three limitations on the method: (1) the ubiquitous problem of purity, already discussed; (2) the lower limit of size of particles which are countable in the electron microscope, estimated at present to be at about $M = 70{,}000$ and (3) the necessity of suspending the particles in a medium which is wholly volatile.

Comparison with Other Determinations of the Weight of the Bushy Stunt Virus Particle.—A review of the determinations of the weight of the BSV particle, up to 1943, has been given by Lauffer,[10] and values obtained by sedimentation equilibrium, sedimentation velocity and diffusion and by X-ray patterns are critically examined. More recently Oster[11] has given a preliminary value of the molecular weight from light-scattering measurements. The four different kinds of deter-

(10) In "Colloid Chemistry," Vol. V, Reinhold Publ. Corp., New York, N. Y., 1944, pp. 801–805.

(11) Oster, *Science*, **103**, 306 (1946).

minations have yielded four rather divergent results for the anhydrous particle weight.

Sedimentation equilibrium	7.6×10^6
Sedimentation velocity and diffusion	10.6×10^6
X-Ray analysis	13.0×10^6
Light scattering	9.0×10^6

It is seen that the method of direct particle counts provides a mean value (9.4×10^6) not outside the limits of previous determinations.

Summary

1. A method of determining the particle weights of macromolecules suspended in a volatile medium is described. The method is called that of "direct particle counts," and consists essentially of counting, on electron micrographs, the numbers of macromolecules per unit volume of solution, and of obtaining the dry weight of an aliquot of the unit volume. Representative specimen fields are obtained by a spray method.

2. Dow latex particles of polystyrene are used as reference particles to determine the volumes of the spray droplets, which also contain the macromolecules.

3. The dry weight of centrifugally purified particles of the bushy stunt virus has been determined, and is found to be $9.4 \pm 0.7 \times 10^6$ in molecular weight units.

4. Discussions of sources of error are given, and it is concluded that the primary source of error is in the determination of the weight concentration of the latex particles in the spray droplets.

5. Evidence bearing on the purity of the bushy stunt virus preparations is discussed, and it is concluded that the particle weights of the material in the two most highly purified pellets are the most reliable.

ANN ARBOR, MICH. RECEIVED JUNE 9, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Configurational Correlation of (*levo*)-Glyceraldehyde with (*dextro*)-Lactic Acid by a New Chemical Method[1]

BY M. L. WOLFROM, R. U. LEMIEUX,[2] S. M. OLIN[2] AND D. I. WEISBLAT

Freudenberg[3] converted (*dextro*)-glyceric acid to (*dextro*)-lactic acid by methods which did not sever any of the bonds directly attached to the rotational center. (*levo*)-Glyceric acid was obtained by the oxidation of D-(*dextro*)-glyceraldehyde by Wohl and Schellenberg.[4] These data effect a configurational correlation between D-(*dextro*)-glyceraldehyde and (*levo*)-lactic acid and establish the designation D-(*levo*)-lactic acid. We report herein a confirmation of this correlation by a chemical method similar in principle to that employed in correlating L-(*levo*)-glyceraldehyde with L-(*dextro*)-alanine.[5]

Tetraacetyl-2-methyl-D-glucose diethyl thioacetal (I) was reductively desulfurized to yield tetraacetyl-2-methyl-1-desoxy-D-glucitol (II). Deacetylation of II produced 2-methyl-1-desoxy-D-glucitol (III) which on periodate cleavage with subsequent oxidation yielded an O-methyllactic acid (IV) that was isolated as its chromatographically purified *p*-phenylphenacyl ester[6] of m. p. 74–75° and $[\alpha]^{23}D$ −16.5° (*c* 2, benzene). This derivative was found to be identical with that obtained on the methylation of the *p*-phenylphenacyl ester of L-(*dextro*)-lactic acid (V), thus effecting a configurational correlation between L-glyceraldehyde and L-(*dextro*)-lactic acid. Carbon two in I is originally D_g, wherein the subscript[7] denotes the reference standard glyceraldehyde, but this carbon becomes L_g in the product of periodate cleavage in which the aldehyde group of D-glucose has been reduced to the hydrocarbon stage. These operations effectively produce an interchange of groups on this rotatory center with a consequent reversal of configuration.

Incidental to the above transformations, we describe herein the crystalline tetraacetyl-2-methyl *aldehydo*-D-glucose obtained by demercaptalation of I according to general technics previously described.[8,9]

Experimental[10]

Tetraacetyl-2-methyl-D-glucose Diethyl Thioacetal (I).[11]—2-Methyl-D-glucose diethyl thioacetal[12] (20 g.) was acetylated by overnight treatment at room temperature with acetic anydride (150 ml.) and pyridine (75 ml.). Crystalline material of fair purity was obtained on pouring the reaction mixture into 3 liters of ice and water; yield 27 g. Pure material was obtained on further crystalliza-

(1) This correlation was reported in *Abstracts Papers Am. Chem. Soc.*, **113**, 13Q (1948).

(2) Bristol Laboratories Research Associate (R. U. L.) and Research Fellow (S. M. O.) of The Ohio State University Research Foundation (Project 224).

(3) K. Freudenberg, *Ber.*, **47**, 2027 (1914).

(4) A. Wohl and R. Schellenberg, *Ber.*, **55**, 1404 (1922).

(5) M. L. Wolfrom, R. U. Lemiux and S. M. Olin, THIS JOURNAL, **71**, 2870 (1949).

(6) Following the general procedure of J. G. Kirchner, A. N. Prater and A. J. Haagen-Smit, *Ind. Eng. Chem., Anal. Ed.*, **18**, 31 (1946) recommended for the separation of fatty acids.

(7) E. J. Crane, *Chem. Eng. News*, **25**, 1364 (1947).

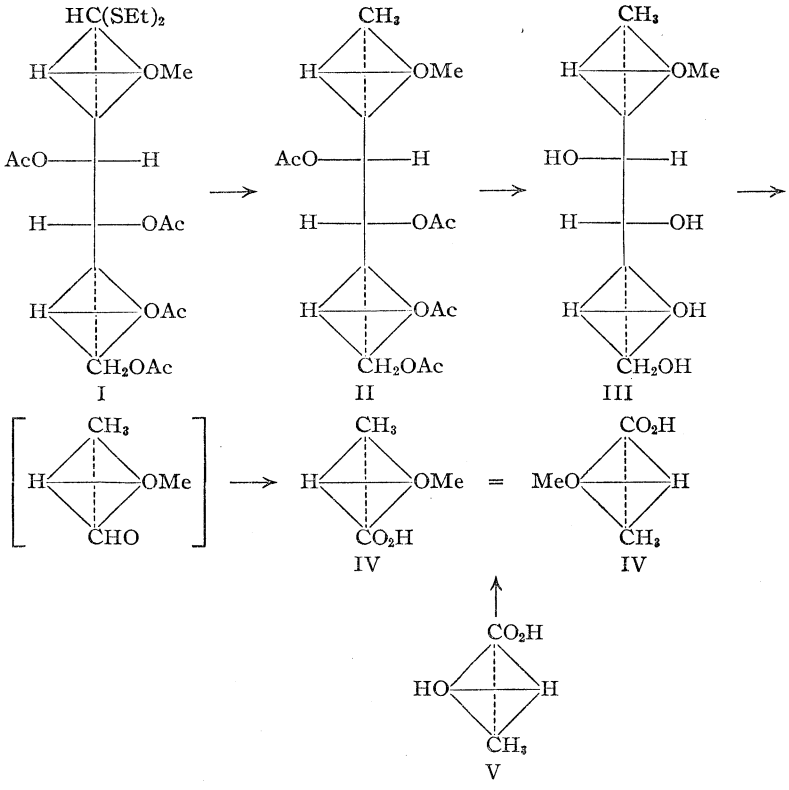
(8) M. L. Wolfrom, THIS JOURNAL, **51**, 2188 (1929).

(9) M. L. Wolfrom, M. Konigsberg and D. I. Weisblat, *ibid.*, **61**, 574 (1939).

(10) Unless otherwise noted, all experimental work was performed by Mr. S. M. Olin.

(11) Experimental work by D. I. Weisblat.

(12) T. Lieser and E. Leckzyck, *Ann.*, **511**, 137 (1934).



tion from methanol–water; yield 25 g., m. p. 45–46°, $[\alpha]^{24}D$ +40° (*c* 3, abs. $CHCl_3$), diamond-shaped plates. The substance was readily soluble in alcohol, ether and chloroform and was insoluble in water and petroleum ether.

Anal. Calcd. for $C_{11}H_{20}O_5S_2(CH_3CO)_4$: C, 48.70; H, 6.88; CH_3CO, 8.54 ml. 0.1 *N* NaOH per 100 mg. Found: C, 48.58; H, 6.70; CH_3CO, 8.93 ml.

Tetraacetyl-2-methyl-*aldehydo*-D-glucose.[11]—To 12.6 g. of tetraacetyl-2-methyl-D-glucose diethyl thioacetal dissolved in 45 ml. of acetone was added 25 g. of finely powdered cadmium carbonate and 5 ml. of water. To this was added with vigorous mechanical stirring, 25 g. of mercuric chloride dissolved in 40 ml. of acetone. Stirring was maintained for twenty hours at room temperature and then the reaction mixture was heated rapidly to boiling and gently refluxed for thirty minutes. The mixture was filtered into a flask containing cadmium carbonate (10 g.) and the residue was washed with acetone. The filtrate and washings were concentrated to dryness at 35° under reduced pressure in the presence of cadmium carbonate. The residue was extracted with three 100-ml. portions of warm chloroform (U. S. P.) and the extract was washed successively with water, 10% aqueous potassium iodide, and water until halide-free. The sirup obtained on solvent removal from the dried (decolorizing carbon) extract was crystallized from 25 ml. of ether; yield 6.3 g. (70%), m. p. 87–89°. Pure material was obtained on further crystallization from acetone–ether–petroleum ether (2:1:3); m. p. 89–90°, $[\alpha]^{24}D$ +24° (*c* 3, abs. $CHCl_3$), $[\alpha]^{25}D$ +7.5° (extrapolated) → +31° (1.5 hr., *c* 3, methanol). The substance crystallized as elongated prisms that reduced Fehling solution. It was readily soluble in ether, alcohol, chloroform, acetone and hot water; it was insoluble in petroleum ether and cold water.

Anal. Calcd. for $C_7H_{10}O_6(CH_3CO)_4$: C, 49.72; H, 6.12; CH_3CO, 11.04 ml. 0.1 *N* NaOH per 100 mg. Found: C, 49.78; H, 6.03; CH_3CO, 11.08 ml.

Tetraacetyl-2-methyl-1-desoxy-D-glucitol (II).—Raney nickel (25 g.) and tetraacetyl-2-methyl-D-glucose diethyl thioacetal (5 g.) was refluxed in 70% aqueous ethanol (110 ml.). After five hours no ethanethiol odor could be detected on acidification of the warm alcoholic solution and the reaction was assumed to be complete. The catalyst was removed by centrifugation and washed with 95% ethanol. The centrifugate and washings were combined, treated with activated carbon and filtered through a bed of Celite.[13] The sirup obtained on solvent removal under reduced pressure was crystallized from ethanol–water at 15°; yield 3.7 g. (92%), m. p. 62–65°, $[\alpha]^{23}D$ +39° (*c* 2, $CHCl_3$). Further crystallization enhanced the melting point to 67–68°.

Anal. Calcd. for $C_{15}H_{24}O_9$: C, 51.72; H, 6.93. Found: C, 51.92; H, 6.99.

2-Methyl-1-desoxy-D-glucitol (III).—Tetraacetyl-2-methyl-1-desoxy-D-glucitol (2.85 g.) was dissolved in anhydrous methanol (125 ml.) and a rapid stream of anhydrous ammonia was passed into the solution for fifteen minutes at 0°. The mixture was maintained at 25° for two hours and evaporated to dryness at reduced pressure. The crystalline residue was dissolved in warm methanol and crystallization was effected at 15°; yield 1.33 g. (2 crops, 92%), m. p. 133–134°, $[\alpha]^{23}D$ +21.5° (*c* 3, water). Further crystallization from methanol did not alter these constants.

Anal. Calcd. for $C_7H_{16}O_5$: C, 46.65; H, 8.95. Found: C, 46.70; H, 9.23.

***p*-Phenylphenacyl Ester of O-Methyl-L-lactic Acid (IV) from 2-Methyl-1-desoxy-D-glucitol (III).**—A solution of 1.18 g. of 2-methyl-1-desoxy-D-glucitol in 20 ml. of water was treated at 25° for sixty minutes with 25 ml. of *N* periodic acid. The solution was then made just alkaline to phenolphthalein with aqueous barium hydroxide. The filtered solution was kept overnight with strontium carbonate (10 g.) and bromine (5 g., shaken until dissolved). The filtered solution was then acidified with 2.5 *N* hydrochloric acid (2.5 ml.) and extracted with ether for seventy-two hours in a continuous extractor containing barium carbonate and 25 ml. of water in its distillation flask. The ether was then distilled from the suspension, which was then heated on a boiling water-bath for two hours. Barium carbonate was removed by filtration and the aqueous filtrate was concentrated to dryness under reduced pressure. The residual barium salt was dissolved in 4 ml. of water, acidified with 0.5 ml. of 6 *N* hydrochloric acid and refluxed for sixty minutes with 12 ml. of a solution of 0.6 g. of *p*-phenylphenacyl bromide in 12 ml. of 95% ethanol. Crystalline material separated on pouring the cooled solution into 20 ml. of water; yield 0.8 g.

An amount of 0.5 g. of the above material was dissolved in 25 ml. of benzene and added at the top of a 200 × 55 mm. (diam.) column of precipitated silicic acid[14] (160 g.) and developed with 1 liter of 2:2 benzene:petroleum ether (b. p. 85–100°, volume ratio). Two zones, at 16–17 mm. and 20–21 mm. from the top, were detected on the extruded column by ultraviolet light. Crystalline material was obtained from the acetone eluate of the sectioned top zone; yield 0.4 g., m. p. 72–74°, $[\alpha]^{22}D$ −16.0° (*c* 2, benzene). Pure material was obtained on recrystallization from ethanol–water; m. p. 74–75° unchanged on admixture with the product obtained from O-methyl-L-lactic acid as described below; $[\alpha]^{23}D$ −16.5° (*c* 2, benzene).

(13) No. 535, Johns–Manville, New York, N. Y., a siliceous filter aid.

(14) Mallinckrodt Chemical Works, St. Louis, Missouri.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.40; H, 6.03.

p-Phenylphenacyl O-Methyl-L-lactate from L-(*dextro*)-Lactic Acid (V).—An authentic sample of L-(*dextro*)-lactic acid[15] was converted to the *p*-phenylphenacyl ester (m. p. 139–140°[16]) and 0.76 g. of this ester, 7.5 g. of silver oxide and 20 ml. of methyl iodide were shaken mechanically at room temperature for four hours. The silver salts were removed by filtration and washed with warm methanol. The filtrate and washings were concentrated to a crystalline residue under reduced pressure; yield 0.70 g., m. p. 70–73°, $[\alpha]^{22}D$ −15.5° (*c* 3, benzene). Recrystallization from ethanol–water yielded pure material with constants unaltered by further crystallization or by chromatographic purification effected as described above; yield 0.54 g., m. p. 74–75°, $[\alpha]^{22}D$ −16.2° (*c* 3, benzene).

(15) A product of high purity made by the fermentation of carbohydrate material and for which we are indebted to the Clinton Industries, Inc., Clinton, Iowa.

(16) N. L. Drake and J. Bronitsky, THIS JOURNAL, **52**, 3715 (1930), record 145° as the melting point of the *p*-phenylphenacyl ester of lactic acid (presumably D,L).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.49; H, 6.06.

Summary

1. Reductive desulfurization of tetraacetyl-2-methyl-D-glucose diethyl thioacetal (I) yielded tetraacetyl-2-methyl-1-desoxy-D-glucitol (II) which on deacetylation (III) and periodate cleavage with subsequent oxidation produced an O-methyllactic acid (IV) whose *p*-phenylphenacyl ester was identical with that obtained by esterification and methylation of L-(*dextro*)-lactic acid (V). This effects a direct chemical correlation of L-(*levo*)-glyceraldehyde with L-(*dextro*)-lactic acid.

2. Tetraacetyl-2-methyl-*aldehydo*-D-glucose is described.

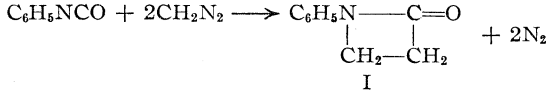
COLUMBUS, OHIO RECEIVED MAY 31, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Reaction of Diazomethane with Isocyanates and Isothiocyanates

BY JOHN C. SHEEHAN AND PATRICK T. IZZO[1]

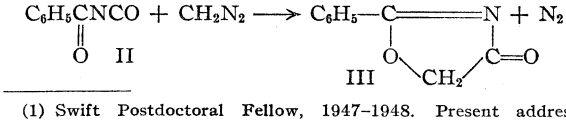
In a recent communication from this Laboratory the action of diazomethane on phenyl isocyanate was reported.[2] In a reaction analogous to the formation of cyclobutanone from ketene and diazomethane, the β-lactam of N-phenyl-β-alanine is formed.



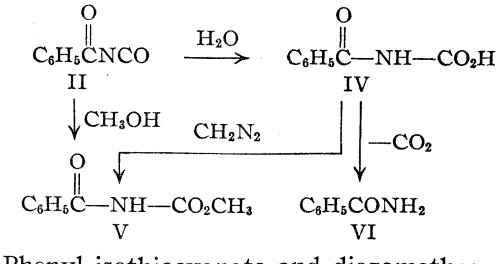
The preparation of this same β-lactam, 1-phenyl-2-azetidinone (I), by cyclization of an ester of N-phenyl-β-alanine with a Grignard reagent has since been described.[3] Phenyl isocyanate and diazomethane were reported by v. Pechmann[4] to yield an oily product which was not further characterized.

With *p*-bromophenyl isocyanate a β-lactam also is obtained. Under similar conditions no β-lactam was isolated from the treatment with diazomethane of α-naphthyl, *p*-nitrophenyl, benzyl and benzoyl isocyanates, or methyl and phenyl isothiocyanates.

Benzoyl isocyanate (II) reacted very rapidly at ice-bath temperature to give, in 68–70% yield, 2-phenyl-4-oxazolone (III). Unlike the formation of the β-lactam in the case of phenyl isocyanate, benzoyl isocyanate added only one methylene group, bridging its two reactive carbonyl groups.



The structure of 2-phenyl-4-oxazolone was proved by cleavage with boiling water. Hydrolysis took place at the carbon–nitrogen double bond, forming benzoylglycolic acid amide, which was identified by comparison with an authentic sample.[5] About 10–15% of the total reaction products was found to be N-benzoyl methyl carbamate (V), which was also obtained by interaction of methanol and benzoyl isocyanate. Absorption of a small amount of moisture during the addition of diazomethane to benzoyl isocyanate would explain the formation of this compound. A portion of the unstable N-benzoylcarbamic acid (IV) formed by the addition of water to the isocyanate presumably was methylated by diazomethane, and thus its decarboxylation to benzamide (VI) was prevented. However, some decomposition to VI apparently took place as benzamide was found in small amounts among the reaction products.



Phenyl isothiocyanate and diazomethane have been reported by v. Pechmann[4] to form an equimolar adduct, m. p. 172.5°, in unspecified yield. We obtained the addition product in 60% yield,

(1) Swift Postdoctoral Fellow, 1947–1948. Present address: American Cyanamid Company, Linden, New Jersey.

(2) J. Sheehan and P. Izzo, THIS JOURNAL, **70**, 1985 (1948).

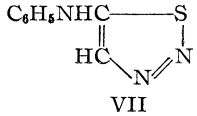
(3) Clarke, Johnson and Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 977.

(4) H. v. Pechmann, *Ber.*, **28**, 861 (1895).

(5) Aloy and Ch. Rabaut, *Bull. soc. chim.*, **13**, 458 (1913).

m. p. 179–180°, with decomposition. The addition was first assumed by v. Pechmann to have taken place in either of two ways to the nitrogen–carbon double bond of phenyl isothiocyanate. Failure to convert the supposed thiocarbonyl group to a carbonyl by treatment with mercuric oxide (confirmed by us) later led v. Pechmann[6] to formulate the reaction as proceeding by addition of diazomethane across the thiocarbonyl group of phenyl isothiocyanate to produce a sulfur-containing ring.

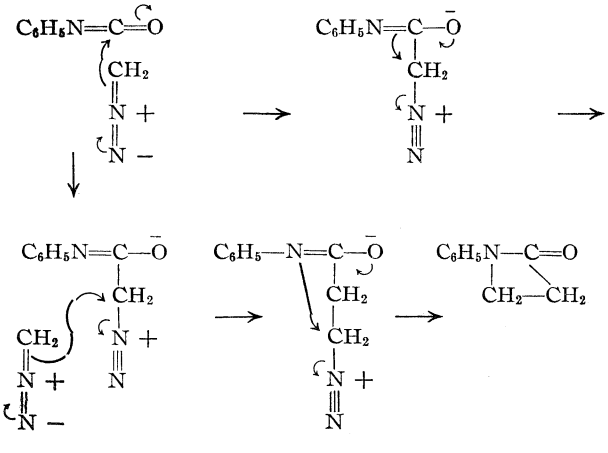
Of the two possible formulas v. Pechmann favored 5-anilino-1,2,3-thiadiazole (VII) or the tautomeric 5-phenylimino-1,2,3-thiadiazoline.



VII

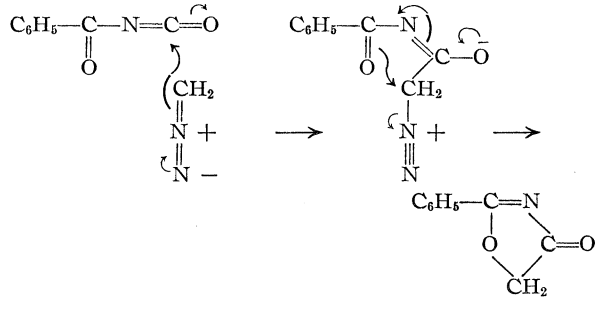
Our degradation studies confirm this structure. Hydrolysis with 10% sodium hydroxide produced a soluble sodium salt, but no sulfide ion was liberated. Reflux with 20% sulfuric acid yielded hydrogen sulfide and aniline (identified by the benzenesulfonamide and the phenylthiourea), but the adduct was essentially resistant to prolonged heating in boiling water. No methylaniline was found and no formaldehyde could be detected by the sensitive dimedon method. These results tend to rule out any structures having a thiocarbonyl group or a methylene unattached to carbon.

Although diazomethane reacts with phenyl isocyanate, benzoyl isocyanate and phenyl isothiocyanate to give three distinctly different types of products, related electronic interpretations can be made. The formation of a β-lactam may be explained by the successive addition of two methylene groups to the polarized carbonyl double bond of phenyl isocyanate.

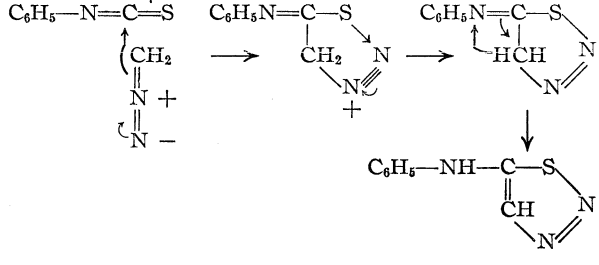


Apparently the addition of one methylene group leads to an electronic structure which is either unable to form a stable three-membered ring (an α-lactam), or such a substance may actually be formed but combines immediately with another molecule of diazomethane to enlarge the ring to the more stable four-membered ring (a β-lactam).

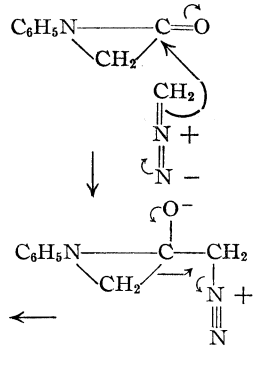
An electronic representation of the reaction with benzoyl isocyanate is similar. However, the presence of a neighboring carbonyl group changes the course of the reaction after the addition of one methylene group. The intermediate is so constituted that a stable five-membered oxazoline ring is preferentially formed, and the addition of a second methylene group does not take place.



The formulation of the phenyl isothiocyanate–diazomethane addition product as 5-anilino-1,2,3-thiadiazole receives further support from the following electronic interpretation of the addition mechanism.



In this case also structural differences in the isocyanate alter the course of the reaction. A molecule of diazomethane adds to the thiocarbonyl group, but the nucleophilicity of the neighboring sulfur atom makes possible ring closure to a stable five-membered ring at a faster rate than nitrogen is eliminated.



In each of the three cases the methylene portion of diazomethane first adds to the polarized carbonyl bond of the isocyanate (or isothiocyanate); the subsequent sequence of reactions is determined by structural characteristics of the particular isocyanate or isothiocyanate.

Diazomethane reacted vigorously with α-naphthyl, *p*-nitrophenyl and benzyl isocyanates,

(6) H. v. Pechmann and A. Nold, *Ber.*, **29**, 2588–2593 (1896).

but no well-defined monomeric products were isolated. Methyl isothiocyanate and diazomethane did not react appreciably at room temperature in ether; both starting materials were recovered in good yield.

Experimental[7]

β-Lactam of N-(*p*-Bromophenyl)-β-alanine.—Two grams (0.01 mole) of *p*-bromophenyl isocyanate was dissolved in 25 ml. of anhydrous ether and 35 ml. of a 0.49 *M* sodium-dried ether solution of diazomethane was added in small portions with shaking. A reaction set in immediately with brisk evolution of nitrogen and simultaneous precipitation of an amorphous, orange powder. After allowing the mixture to stand overnight, the clear ethereal solution was separated from the solid by decantation. The solid weighed 0.5 g. and gave positive tests for halogen.

The ether solution was evaporated to dryness, leaving 1.5 g. of a soft, brown semi-solid. This material was triturated with anhydrous acetone, which dissolved the larger part but left undissolved a white, pulverulent substance insoluble in the common organic solvents. This material was not further investigated.

The acetone solution was evaporated to dryness at reduced pressure and the brown, viscous residue was subjected to a slow evaporative distillation. A colorless, crystalline product (0.25 g., m. p. 110–118°) sublimed at 120–130° and 0.05 mm. After one recrystallization from benzene–ligroin, glistening platelets were obtained which melted at 126–127°.

Anal. Calcd. for C_9H_8ONBr: C, 47.82; H, 3.56; N, 6.19. Found: C, 47.86; H, 3.68; N, 6.28.

The compound hydrolyzed with dilute sodium hydroxide, but the hydrolysis did not proceed as readily as in the case of the simpler unhalogenated β-lactam, already reported.

2-Phenyl-4-oxazolone.—To a solution of 3.12 g. (0.021 mole) of benzoyl isocyanate[8] in 10 ml. of absolute ether, was added slowly from a buret a 0.23 *N* sodium-dried ethereal solution of diazomethane. Since the reaction was extremely vigorous, care was necessary to prevent violent bubbling and ejection of the reaction mixture from the flask. The diazomethane reacted instantaneously with the isocyanate without any discoloration of the solution and with simultaneous deposition of the colorless, crystalline oxazolone. The isocyanate solution could be "titrated" with the diazomethane to the appearance of the yellow color. The color did not appear until 88 ml. of the diazomethane solution had been added. The theoretical amount required on the basis of mole-for-mole reaction is 90 ml. Ten milliliters of diazomethane solution was added in excess and the reaction mixture was allowed to stand for one hour at room temperature and then overnight at 0–5°.

The colorless, crystalline mass was separated from the solution by filtration. This material weighed 2.30 g. (68%) and melted at 154–156°. Recrystallization from benzene lowered the m. p. to 150–152° dec.

Anal. Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.37; N, 8.68; mol. wt., 161.2. Found: C, 67.14; H, 4.35; N, 8.36; mol. wt., 185 (Rast, using camphor as a solvent).

Hydrolysis of 2-Phenyl-4-oxazolone.—To 0.5 g. of the oxazolone was added 40 ml. of water and the mixture was refluxed for two and one-half hours. Solution took place immediately upon warming; no ammonia was evolved. The cooled, clear solution was evaporated to dryness at reduced pressure, leaving a colorless oil which soon crystallized (m. p. 60–80°). After two recrystallizations from hot water, the compound melted constantly at 121–122° (0.23 g.). This product was insoluble in sodium bicarbonate solution and dissolved very slowly in hot 10% sodium hydroxide with evolution of ammonia. The melting points of mixtures with benzoic acid and benzamide showed a depression, but the melting point of a mixture with an authentic sample[5] of benzoyl glycolic acid amide (m. p. 120–121°) showed no depression.

Anal. Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82; mol. wt., 179.2. Found: C, 60.12; H, 5.29; N, 8.09; mol. wt., 190 (Rast, using camphor as a solvent).

N-Benzoyl Methyl Carbamate.—On standing in the cold, a second crop of crystals (0.6 g., m. p. 110–118°) separated from the concentrated ethereal mother liquor from the 2-phenyl-4-oxazolone preparation. After two recrystallizations from benzene, this compound melted constantly at 118–119°. The analytical data indicated an hydrolysis product of 2-phenyl-4-oxazolone. The melting point of a mixture with benzoyl glycolic acid amide was depressed.

Anal. Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.47; H, 5.27; N, 7.90.

N-Benzoyl methyl carbamate was prepared from benzoyl isocyanate and absolute methanol in anhydrous ether. After two recrystallizations from ethanol, the compound melted constantly at 118.6–120°. The melting point of a mixture with the above compound showed no depression.

The ethereal mother liquor was evaporated to dryness, leaving a brown, oily residue (0.35 g.) which crystallized on standing. Evaporative distillation of this material gave a good recovery of colorless crystals, m. p. 80–90°. Two recrystallizations from benzene gave a compound melting constantly at 127–128°. The melting point of a mixture with benzamide showed no depression.

5-Anilino-1,2,3-thiadiazole.—To 2.70 g. (0.02 mole) of phenyl isothiocyanate in 10 ml. of absolute ether was added 35 ml. of cold 0.65 *M* sodium-dried ethereal solution of diazomethane. Evolution of nitrogen did not immediately set in, but soon the solution turned deep amber and a crystalline product began to precipitate. After allowing the mixture to stand at room temperature for one hour, during which time a substantial amount of nitrogen was evolved, the reaction was stored overnight at 0–5°. The tan crystals were separated by filtration (1.7 g.) and the mother liquor was concentrated to about one-half its volume and allowed to stand in the cold for a few hours, giving a second crop of crystals (0.4 g.). The total yield of crystalline compound amounted to 2.1 g. (60%). This crude material turned to a black mass at 120° and decomposed at 168°. For purification, the crystals were first quickly triturated with cold acetone, which dissolved most of the dark-colored impurities. The solid residue was dissolved in hot absolute alcohol and decolorized (Norit). The compound crystallized in long, nearly colorless needles. A further recrystallization yielded a product with a faintly yellow cast, which darkened slightly at 170° and melted with decomposition at 179–180° (reported,[4] m. p. 172.5°).

Anal. Calcd. for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.71; mol. wt., 177.2. Found: C, 54.55; H, 4.12; N, 24.10; mol. wt., 205.3 (Rast, using camphor as a solvent).

The adduct was hydrolyzed by boiling with 20% sulfuric acid. After basification, a small amount of an amine was isolated by ether extraction. This was identified as aniline by the preparation of two derivatives and comparison with authentic samples: the benzenesulfonamide, m. p. 109–111°, and the phenyl thiourea, m. p. 152–153°. No formaldehyde could be detected (dimedon).

A portion (0.25 g.) of 5-anilino-1,2,3-thiadiazole was refluxed for three and one-half hours with 20 ml. of 10% sodium hydroxide solution. The compound dissolved completely as the solution warmed. The resulting water-clear solution was tested frequently with lead acetate paper; all tests were negative.

Summary

Diazomethane has been found to undergo three entirely different types of reaction with various

(7) All melting points are corrected.

(8) O. Billeter, *Ber.*, **36**, 3218 (1903).

isocyanates and isothiocyanates. Phenyl isocyanate and *p*-bromophenyl isocyanate interact with diazomethane in cold ethereal solution to form the β-lactams of N-phenyl-β-alanine and N-(*p*-bromophenyl)-β-alanine.

Benzoyl isocyanate reacts vigorously with diazomethane to give in 68–70% yield 2-phenyl-4-oxazolone. With phenyl isothiocyanate, diazomethane forms a crystalline equimolar addition product, 5-anilino-1,2,3-thiadiazole. An electronic interpretation of the reactions is presented.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Metalation of Some Sulfur-Containing Organic Compounds[1a]

BY HENRY GILMAN AND F. J. WEBB[1b]

Methyl phenyl sulfide was shown to undergo exclusive lateral metalation[2] with *n*-butyllithium in diethyl ether.

$$C_6H_5SCH_3 + n\text{-BuLi} \xrightarrow[HOH]{CO_2} C_6H_5SCH_2COOH$$

Under corresponding conditions nuclear metalation[3] is effected with both diethylbarium and diethylstrontium to give metalation products which yield on carbonation, *o*-methylmercaptobenzoic acid. Metalations of methyl phenyl sulfide with other reagents are now reported. To determine the generality of the lateral metalation with *n*-butyllithium, a number of aryl methyl sulfides and higher-alkyl aryl sulfides were studied.

lithium in ether, *n*-butyllithium in petroleum ether (b. p. 28–38°) and phenylsodium in benzene gave lateral metalation (Table I). The rate of reaction was especially slow in petroleum ether. Lateral metalation also occurred with *n*-butyllithium at 150° in the absence of solvent. Under corresponding conditions at 150–155°, *n*-butylmagnesium bromide gave a nuclear metalation since *o*-methylmercaptobenzoic acid was isolated subsequent to carbonation. Thus, ortho-nuclear substitution was effected by metalating agents of the Group II metals, magnesium, barium[3] and strontium[3] but lateral metalation by the metalating agents of the Group I metals, lithium and sodium. Anisole also gives ortho-

TABLE I

METALATION OF METHYL PHENYL SULFIDE

Metalating agent[a]	Time, hr.	Temp., °C.	Solvent	Acid[b] yield, %	Thiophenol yield, %	Recovered sulfide, %
Sodium	18	25–28	Ether	3.9	20.9	52.4
Sodium	18	25–28	Benzene	Trace[c]	Trace[c]	87.5
Mercuric acetate	9.5	95–100		36.6[d]		
n-Butylmagnesium	2	135–140	None[e]	42.0[f]	Trace[c]	63.0
bromide	5	150–155	None	0.2[g]		67.0
Methyllithium	20	34	Ether	0.12		84.0
n-Butyllithium	20	28–38	Pet. ether	Trace[c]		91.5
n-Butyllithium	168	28–38	Pet. ether	3.6	2.27	31.7
n-Butyllithium	3	130–150	None	Trace[c]	22.7	29.0
n-Butyllithium	1	To 150[h]	None	21.2	10.0	52.2
Phenyllithium	16	34	Ether	9.2		37.0
Phenylsodium	5	Room	Benzene	8.9		44.4
Phenylcalcium	46	34	Ether	[i]		78.5
iodide	3.5	150–160	None	[i]	13.0	58.8

[a] The mole ratio of metalating agent to sulfide was 1:1. [b] Phenylmercaptoacetic acid was isolated unless otherwise specified. The yield was calculated on sulfide introduced. [c] Traces were not identified. [d] The product was *p*-acetoxymercuriphenyl methyl sulfide. [e] The ether was distilled, prior to addition of the sulfide, until the desired temperature was reached, as measured by a thermometer in the liquid. [f] Valeric acid only was isolated. [g] The product was *o*-methylmercaptobenzoic acid. [h] The sulfide was added to the cooled residue, after distillation of the ether. The mixture was heated to 150° during thirty minutes and cooled during the next thirty minutes. [i] Benzoic acid only was isolated.

Metalation of Methyl Phenyl Sulfide.—The position substituted was conditioned by the metalating agent employed rather than by solvent or temperature. Methyl- and phenyl-nuclear metalation with Grignard reagents.[4] Phenylcalcium iodide failed to metalate methyl phenyl sulfide in ether or at 150–160° in the absence of solvent. This reagent did not metalate phenyl sulfide[5] but did metalate dibenzothiophene in the 3-position.[6] Mercuric acetate gave

(1a) Paper LXVI in the Series: "The Relative Reactivities of Organometallic Compounds"; the preceding paper with Gainer is in THIS JOURNAL, **71**, 2327 (1949).

(1b) Present address: Firestone Tire and Rubber Co., Akron, Ohio.

(2) Gilman and Webb, THIS JOURNAL, **62**, 987 (1940).

(3) Gilman, Haubein, O'Donnell and Woods, *ibid.*, **67**, 922 (1945).

(4) Challenger and Miller, *J. Chem. Soc.*, 894 (1938).

(5) Gilman and Bebb, THIS JOURNAL, **61**, 109 (1939).

(6) Gilman, Jacoby and Pacevitz, *J. Org. Chem.*, **3**, 120 (1938).

the *p*-acetoxymercuri- compound with methyl phenyl sulfide. The para substitution was proved by comparison of the bromomercuri- compound prepared from the acetoxymercuri- derivative and sodium bromide with that obtained from *p*-methylmercaptophenylmagnesium bromide and mercuric bromide. This orientation appears to be general for alkyl aryl and aryl ether types as both anisole[7] and phenyl sulfide[8] undergo *p*-mercuration.

Metalation of Other Aryl Methyl Sulfides.—*n*-Butyllithium in diethyl ether gave exclusive lateral metalation with each of the aryl methyl sulfides investigated as evidenced by the isolation of the corresponding arylmercaptoacetic acid on carbonation and hydrolysis (Table II). Identifications were completed by mixed melting point determinations with authentic specimens. Arrangement of the aryl radicals in order of decreasing yield of metalation product gives the series: phenyl-, *p*-tolyl-, α-naphthyl- > *p*-dimethylaminophenyl- > β-naphthyl- > *p*-chlorophenyl-.

TABLE II

METALATION OF ARYL METHYL SULFIDES BY *n*-BUTYLLITHIUM

Aryl group[a]	Time, hr.	Acid,[b] yield, %	Recovered sulfide, %
p-Tolyl	16	38.2	51.0
p-Chlorophenyl	5	5.8[c]	[d]
p-Dimethylaminophenyl	19	22.4[e]	52.1
p-Dimethylaminophenyl	19	15.1	43.1
α-Naphthyl	5	35.4	[d]
β-Naphthyl	20	11.7	85.0

[a] The mole ratio of metalating agent to sulfide was 1:1. The reactions were performed in refluxing ether solution. [b] The corresponding arylmercaptoacetic acid was isolated in each case and identified by a mixed melting point determination with an authentic specimen. The yields, based on sulfide introduced, are for pure acid or acid melting within 1–2° of the pure compound, unless otherwise noted. In check runs the yields differ by less than 10%. The reaction time beyond about five hours is not critical since the yields of phenylmercaptoacetic acid from methyl phenyl sulfide were 43.5 and 35.2% in fifteen hours and 37.6 and 39.7% in five and four and one-half hours, respectively. [c] The crude acid melted at 99–100° or at 105° after two recrystallizations from petroleum ether (b. p. 60–68°). [d] The neutral fraction was not investigated. [e] The crude acid melted at 75–80° and at 85–86° after two recrystallizations from benzene.

Higher-Alkyl Aryl Sulfides.—In marked contrast to the *methyl* aryl sulfides, the sulfides having higher-alkyl groups gave only *ortho* nuclear metalation, the corresponding *o*-alkylmercaptobenzoic acid being isolated (Table III). This orientation corresponds to that given by the oxygen ether types previously examined.[9] In general, the lateral metalations proceeded to a greater extent than the nuclear metalations. Ethyl phenyl sulfide was not metalated by phenylcalcium iodide on refluxing in ether solution for sixty hours. Traces of sulfur-containing acids other than the metalation acid were obtained from isopropyl and *n*-butyl phenyl sulfides with *n*-butyllithium. These melted at 154–156° and 79–80°, respectively, but were not identified.

TABLE III

METALATION OF HIGHER-ALKYL ARYL SULFIDES BY *n*-BUTYLLITHIUM

Sulfide[a]	Time, hr.	Metalation[b] acid, %	Benzoic[c] acid, %	Recovered sulfide, %
Ethyl phenyl	15	7.7	[d]	51.5
	15	5.4	3.3	59.4
n-Propyl phenyl	20	6.9	3.4	54.5
Isopropyl phenyl[e]	20	9.0	0	65.0
	20	11.0	0	67.8[f]
n-Butyl phenyl	19[g]	6.2	4.1	57.0
	19[g]	4.9	4.5	63.0
	18	6.4	1.2	64.0
Cyclohexyl phenyl	48	11.4[h]	(10 mg.)	58.4
	24	8.5[h]	0	60.5
Ethyl β-naphthyl	20	20.4[i]		37.3

[a] The mole ratio of sulfide to metalating agent was 1:1. The reactions were performed in refluxing ether solution. [b] The corresponding *o*-alkylmercaptobenzoic acid was isolated and identified by comparison with an authentic specimen, except in the last reaction. The yields are for pure acid based on sulfide introduced, unless otherwise noted. [c] The crude benzoic acid melted in the range 117–119°. [d] A small quantity (0.6 g.) of a crude acid isolated in this experiment probably contained benzoic acid. [e] The acid melted at 116–117° from petroleum ether (b. p. 60–68°) and was identified by comparison with a specimen from methyl thiosalicylate and isopropyl bromide in alcoholic potassium hydroxide. *Anal.* Calcd. for $C_{10}H_{13}O_2S$: S, 16.33. Found: S, 16.53. [f] The neutral fraction gave, from a one-tenth mole run, 1.25 g. of an unidentified oil, b. p. 174–176° (5–6 mm.), in addition to the recovered sulfide, b. p. 97–98° (20 mm.). [g] The *n*-butyllithium solutions used in these two experiments were filtered free of coarse particles but contained some finely-divided solid. All other *n*-butyllithium solutions were filtered entirely free of solid. [h] The acid melted at 85–86° from petroleum ether (b. p. 60–68°) and was identified by a mixed melting point determination with a specimen from thiosalicylic acid and bromocyclohexane in alcoholic potassium hydroxide. *Anal.* Calcd. for $C_{13}H_{16}O_2S$: S, 13.56. Found: S, 13.71. The yield was based on material melting in the range 75–80°. [i] The yield was based on crude acid melting at 130–135°. Two recrystallizations from benzene raised the melting point to 157–158° where it remained unaltered after recrystallization from aqueous acetic acid. The acid was not identified. It contained sulfur but the neutral equivalent did not agree with the theoretical value for a monocarboxyethyl naphthyl sulfide.

Diphenyl Disulfide.—With *n*-butyllithium in ether there was obtained 4.3% of crude *o,o'*-dicarboxydiphenyl disulfide, 31.4% of *n*-butyl phenyl sulfide and 17.9% of recovered diphenyl disulfide. The same acid was isolated in a previously reported reaction with thiophenol.[10]

***p*-Bromophenyl Methyl Sulfide.**—In contrast to *p*-bromoanisole which is metalated by *n*-butyl-[11] and methyllithium[12] to give 5-bromo-2-methoxy-

(7) Dimroth, *Ber.*, **35**, 2867 (1902).
(8) Sachs and Ott, *ibid.*, **59**, 171 (1926).
(9) Ref. 5; see also later papers in this series.
(10) Gilman, Arntzen and Webb, *J. Org. Chem.*, **10**, 374 (1945).
(11) Gilman, Langham and Jacoby, THIS JOURNAL, **61**, 106 (1939).
(12) Langham, Brewster and Gilman, *ibid.*, **63**, 545 (1941).

benzoic acid, *p*-bromophenyl methyl sulfide gave interconversion with *n*-butyllithium and chiefly coupling with methyllithium, the reaction products being, respectively, *p*-methylmercaptobenzoic acid and methyl *p*-tolyl sulfide. *p*-Bromophenyl methyl sulfide failed to form an organolithium compound in ether and was quantitatively recovered.

Methyl Phenyl Selenide.—Like phenyl selenide,[5] methyl phenyl selenide was cleaved by *n*-butyllithium in refluxing ether. On carbonation, 28.4% of benzoic acid and 25.6% of *n*-butyl methyl selenide were obtained. Amylsodium in petroleum ether (b. p. 28–38°) gave a 25% yield of benzoic acid after four hours at room temperature. Only a trace of acidic material was isolated on carbonating a mixture of methyl phenyl selenide and sodium sand in petroleum ether (b. p. 28–38°) after four hours of stirring at room temperature.

Cleavage Reactions.—No appreciable cleavage occurred when the aryl methyl sulfides were refluxed with *n*-butyllithium in diethyl ether for periods of time up to twenty hours. Noticeable cleavage resulted from more strenuous conditions of time and temperature. In each case the *methyl* group was eliminated with the formation of thiophenol. Refluxing of methyl phenyl sulfide with *n*-butyllithium in petroleum ether (b. p. 28–38°) for one hundred and sixty-eight hours gave 2.27% of thiophenol. Increased yields of thiophenol (10–22.7%) were obtained from methyl phenyl sulfide and *n*-butyllithium and phenylcalcium iodide at temperatures up to 160° in the absence of solvent. On carbonating a mixture of sodium sand and methyl phenyl sulfide which had been stirred eighteen hours at room temperature, there was isolated 20.9% of thiophenol and 3.5% of phenylmercaptoacetic acid. It is possible that the metalating agent was methylsodium.

$$C_6H_5SCH_3 + 2Na \longrightarrow C_6H_5SNa + CH_3Na$$

Ethyl, *n*-propyl, *n*-butyl and cyclohexyl phenyl sulfides, unlike the aryl methyl sulfides, were cleaved by *n*-butyllithium in refluxing ether with elimination of the *alkylmercapto* group and formation of benzoic acid in addition to the metalation acid. No thiophenol was found. The alkylmercapto residue was isolated only from the reaction of *n*-butyllithium with *n*-butyl phenyl sulfide which gave 6.5% of *o*-(*n*-butylmercapto)-benzoic acid, 1.2% of benzoic acid and 1.0% of butyl mercaptan (as the lead salt).[13] An exception was the reaction of isopropyl phenyl sulfide with *n*-butyllithium from which no benzoic acid was isolated in spite of a careful search. *n*-Butyl phenyl sulfide was cleaved in two ways by lithium metal in refluxing ether to yield on carbonation 11.9% of benzoic acid, 20.5% of thiophenol, 0.24% of *o*-(*n*-butylmercapto)-benzoic acid and 18.1% of recovered *n*-butyl phenyl sulfide. A trace of an acid melting at 270°, after recrystallization from ethanol, was also found but was not identified. The formation of *o*-(*n*-butylmercapto)-benzoic acid was probably due to a metalation by phenyllithium formed in the cleavage reaction. The formation of a trace of benzoic acid has been observed in the reaction of phenyl *n*-tetradecyl sulfide with *n*-butyllithium.[14]

(13) Wertheim, THIS JOURNAL, **51**, 3661 (1929).

Experimental

Sulfides.—The methyl and ethyl sulfides were generally prepared from the corresponding sulfate and aryl mercaptan in aqueous alkali. *n*-Propyl, isopropyl, *n*-butyl and cyclohexyl phenyl sulfides were prepared from the corresponding halide and thiophenol in alcoholic potassium hydroxide solution.[15] The boiling points and refractive indices agreed with the reported values.

General Procedure.—The metalations were performed according to procedures reported earlier.[16] The organolithium, -calcium and -magnesium reagents were filtered free of solid before use. The metalation reactions were worked up, following carbonation on Dry Ice, by acidification of the mixture and extraction with ether. The ether layer was successively extracted with 8% sodium bicarbonate solution and 10–20% potassium hydroxide solution. The neutral fraction was recovered from the ether layer after drying over anhydrous sodium sulfate. The two aqueous extracts were acidified and the precipitates recovered by filtration or extraction. Benzoic acid was separated from the metalation acid by fractional crystallization from petroleum ether (b. p. 60–68°) or was isolated by ether extraction of the filtrate from the acidified bicarbonate extract.

Diphenyl Disulfide.—A solution of *n*-butyllithium prepared from 0.2 mole of *n*-butyl bromide and 0.4 g. atom of lithium in 200 ml. of ether, was treated with 10.9 g. (0.05 mole) of diphenyl disulfide, refluxed for twenty hours and carbonated on Dry Ice. In the usual manner there was isolated 0.65 g. of crude *o,o'*-dicarboxydiphenyl disulfide. The pure white compound was obtained after several recrystallizations from ethanol and acetic acid–water mixtures; m. p. 302–305° (microscope stage).

Anal. Calcd. for $C_{14}H_{10}O_4S_2$: neut. equiv., 153. Found: neut. equiv., 156.

The methyl ester, prepared from the acid and diazomethane, melted at 131–132° after one recrystallization from ethanol.[17]

Distillation of the neutral fraction gave 5.2 g. (31.4%) of *n*-butyl phenyl sulfide; b. p. 96–98° (4 mm.), $n^{20}D$ 1.5458.[16] The distillation residue was recrystallized from ethanol to yield 1.95 g. (17.9%) of diphenyl disulfide identified by a mixed melting point determination.

***p*-Acetoxymercuriphenyl Methyl Sulfide.**—A mixture of 12.4 g. (0.1 mole) of methyl phenyl sulfide and 15.0 g. (0.05 mole) of mercuric acetate was stirred and heated on a steam-bath for nine and one-half hours and allowed to stand overnight. The white solid which formed was recrystallized from ethanol to give 6.7 g. of *p*-acetoxymercuriphenyl methyl sulfide; m. p. 183–184°, yield 36.6%. The constant melting point from ethanol was 184°.

Anal. Calcd. for $C_9H_{10}O_2SHg$: Hg, 52.40. Found: Hg, 52.84, 52.78.

***p*-Bromomercuriphenyl Methyl Sulfide.**—To an ethanol solution of 1.0 g. (0.0027 mole) of *p*-acetoxymercuriphenyl methyl sulfide was added 0.32 g. (0.0027 mole) of potassium bromide in 100 ml. of aqueous ethanol. The resulting precipitate weighed 0.93 g. (85.5%) and was purified by Soxhlet extraction with chloroform; m. p. 268–269°.

(14) F. W. Hoyt, Doctoral Dissertation, Iowa State College.

(15) Ipatieff, Pines and Friedman, THIS JOURNAL, **60**, 2731 (1938); Gilman and Heck, *ibid.*, **50**, 2223 (1928).

(16) See references 2, 3, 5 and 6.

(17) List and Stein, *Ber.*, **31**, 1670 (1898), report a melting point of 130.5° and Gattermann, *ibid.*, **32**, 1151 (1899), gives a melting point of 134°.

A mixed melting point determination with a specimen prepared from *p*-methylmercaptophenylmagnesium bromide and mercuric bromide showed no depression.

Anal. Calcd. for C_7H_7SHgBr: Hg, 49.68. Found: Hg, 49.64.

p-Dimethylaminophenyl Methyl Sulfide.[18]—To a solution of 5.1 g. (0.22 g. atom) of sodium in 100 ml. of liquid ammonia was added slowly, with stirring, 33.4 g. (0.1 mole) of bis-(*p*-dimethylaminophenyl) disulfide (prepared from the Grignard reagent and sulfur). A further small quantity of the disulfide was added to discharge the blue color, the solution being pink at the end. Dropwise addition of 28.4 g. (0.2 mole) of methyl iodide in 30 ml. of ether resulted in the formation of a white precipitate. After the ammonia had evaporated the residue was partitioned between water and ether. Evaporation of the dried ether layer followed by distillation gave 26.4 g. (79%) of *p*-dimethylaminophenyl methyl sulfide, b. p. 159–160° (20 mm.).

p-Dimethylaminophenylmercaptoacetic Acid.—To 1.67 g. (0.005 mole) of bis-(*p*-dimethylaminophenyl) disulfide in 75 ml. of liquid ammonia was added 0.23 g. (0.01 g. atom) of sodium followed by 0.95 g. (0.005 mole) of chloroacetic acid in 50 ml. of liquid ammonia. The ammonia was allowed to evaporate and the pink solid residue neutralized and extracted with ether. Evaporation of the dried ether solution gave the required acid, m. p. 85°, after recrystallization from benzene. The mixed melting point determination with the acid obtained by metalating *p*-dimethylaminophenyl methyl sulfide showed no lowering.

Anal. Calcd. for $C_{10}H_{13}O_2NS$: N, 6.63. Found: N, 6.66.

Methyl Phenyl Sulfide and Sodium.—A mixture of 12.4 g. (0.1 mole) of methyl phenyl sulfide and 2.5 g. (0.11 g. atom) of sodium sand in 75 ml. of diethyl ether was stirred for eighteen hours at room temperature (25–28°) prior to carbonation on Dry Ice. The reaction was worked up in the usual way to give 0.40 g. of phenylmercaptoacetic acid by precipitation and 0.25 g. of the same acid by extraction of the filtrate; m. p. 61–63°, yield 3.9%. By extraction with potassium hydroxide solution there was isolated 2.3 g. (20.9%) of thiophenol; b. p. 84–85° (50 mm.), $n^{23.5}D$ 1.5850. The recovered methyl phenyl sulfide amounted to 6.5 g. or 52.4%.

***n*-Butyl Phenyl Sulfide and Lithium.**—To a suspension of 1.38 g. (0.2 g. atom) of lithium cut in small pieces (1–2-mm. square) in 50 ml. of ether was added 16.6 g. (0.1 mole) of *n*-butyl phenyl sulfide in 25 ml. of ether. The mixture was stirred at room temperature for seven hours and then refluxed for thirty-six hours before carbonation on Dry Ice. Acidification of the bicarbonate extract gave 2.7 g. of acidic material, melting at 90–100°. Extraction with petroleum ether (b. p. 60–68°) separated an insoluble substance (unidentified) weighing 0.03 g. and melting at 270° after recrystallization from ethanol-water. The petroleum ether-soluble portion was fractionally crystallized to give 1.3 g. (10.6%) of benzoic acid and 0.05 g. (0.24%) of *o*-(*n*-butylmercapto)-benzoic acid both of which were identified by mixed melting point determinations. An additional 0.15 g. (1.3%) of benzoic acid was isolated by ether extraction of the original aqueous filtrate. The potassium hydroxide extract on acidification and distillation yielded 2.25 g. (20.5%) of thiophenol. Three grams (18.1%) of the starting material was recovered.

***p*-Bromophenyl Methyl Sulfide and Methyllithium.**—A solution of methyllithium, prepared from 14.2 g. (0.1 mole) of methyl iodide and 1.38 g. (0.2 g. atom) of lithium in 100 ml. of ether, was filtered, concentrated and treated with 10.2 g. (0.05 mole) of *p*-bromophenyl methyl sulfide in 20 ml. of ether. The total volume was 85 ml. After fifteen minutes, a 5-ml. aliquot was removed and carbonated. The remainder was refluxed for twenty-two hours before carbonation. Both portions were worked up in the same manner. The aliquot yielded only a trace of acidic material which was insufficient for investigation and 83.3% of recovered *p*-bromophenyl methyl sulfide. The main portion gave 5–10 mg. of *p*-methylmercaptobenzoic acid identified by a mixed melting point determination. Three fractions were obtained on distillation of the neutral fraction: (1) methyl phenyl sulfide (10.3%) boiling range, 80–87° (18 mm.); (2) methyl *p*-tolyl sulfide (14.1%) boiling range 96–100° (18 mm.); and (3) *p*-bromophenyl methyl sulfide, (5.9%) boiling range 115–120° (10 mm.). Each of the three fractions was identified by hydrogen peroxide oxidation to the corresponding sulfone and determination of the mixed melting point with an authentic specimen.

***p*-Bromophenyl Methyl Sulfide and *n*-Butyllithium.**—To the filtered solution of *n*-butyllithium prepared from 6.85 g. (0.05 mole) of *n*-butyl bromide and 0.70 g. (0.1 g. atom) of lithium in 100 ml. of ether, was added rapidly with stirring 5.08 g. (0.025 mole) of *p*-bromophenyl methyl sulfide in 50 ml. of ether. After fifteen minutes at room temperature, a 50-ml. aliquot was removed and carbonated on Dry Ice. By means of the usual procedures, there was isolated 1.23 g. (88%) of *p*-methylmercaptobenzoic acid[19]; m. p. 189.5–190°. The remainder of the reaction mixture was refluxed for seventeen hours before carbonation. There was isolated 6.1% of *p*-methylmercaptobenzoic acid and 18.3% of recovered sulfide.

Methyl Phenyl Selenide and *n*-Butyllithium.—Methyl phenyl selenide[20] was prepared from selenophenol and dimethyl sulfate in 80% yield; b. p. 89–90° (15 mm.), $n^{25}D$ 1.6060.

To the filtered solution of *n*-butyllithium prepared from 13.7 g. (0.1 mole) of *n*-butyl bromide and 1.40 g. (0.2 g. atom) of lithium in 100 ml. of ether was added 8.35 g. (0.05 mole) of methyl phenyl selenide in 25 ml. of ether. The solution was stirred for one-half hour at room temperature, refluxed for nineteen hours, carbonated on Dry Ice and worked up in the usual way. There was isolated 28.4% of benzoic acid, 25.6% of *n*-butyl phenyl selenide and 13.8% of recovered methyl phenyl selenide. The liquids were identified by boiling point and refractive index. When the reflux period was shortened to four hours, 21% of benzoic acid was obtained.

Methyl Phenyl Selenide and *n*-Amylsodium.—The metalating agent was prepared[21] at ice-bath temperature from 10.6 g. (0.1 mole) of *n*-amyl chloride and 5.7 g. (0.25 g. atom) of sodium in 100 ml. of petroleum ether (b. p. 28–38°). Without removing the ice-bath, 8.35 g. (0.05 mole) of methyl phenyl selenide was added rapidly. No change was observed for about fifteen minutes, when the mixture changed from a black to a gray color and refluxed for a few minutes. When the refluxing ceased, the ice-bath was removed and the stirring continued for four hours at room temperature. The thick brown mixture was carbonated as usual. The mixture was worked up by means of the customary procedures to yield 1.92 g. (31.8%) of crude benzoic acid, m. p. 117–119°. In an attempt to crystallize the acid from water, 0.15 g. remained undissolved and was removed by filtration. The filtrate deposited 1.5 g. of benzoic acid; m. p. 120–121°, yield 25%. The insoluble material was organic in nature but did not melt at 280°. It was not identified.

Since the amylsodium in the foregoing experiment contained excess sodium metal, it seemed advisable to test the action of sodium on methyl phenyl selenide. Accordingly, a mixture of 3.4 g. (0.02 mole) of methyl phenyl selenide and 1.05 g. (0.045 g. atom) of sodium sand in petroleum ether (b. p. 28–38°) was stirred for four hours and carbonated by Dry Ice. Only a trace of a red oil was isolated by acidification of the bicarbonate extract.

Sulfones.—Attempts were made to metalate methyl and ethyl phenyl sulfones, phenyl sulfone and dibenzothio-

(18) Zincke and Jörg, *Ber.*, **42**, 3374 (1909), prepared this compound by another method.

(19) Zincke and Jörg, *Ber.*, **43**, 3448 (1910).

(20) Baker and Moffitt, *J. Chem. Soc.*, 1722 (1930).

(21) Gilman and Pacevitz, THIS JOURNAL, **62**, 1301 (1940).

phene-5-dioxide. As expected from the known reactions of sulfones with Grignard reagents,[22] bicarbonate-soluble products were isolated in each case but only from methyl phenyl sulfone was the product identified. Here, *n*-butyllithium gave 47% of benzenesulfonylacetic acid and 45.5% of the sulfone was recovered. Ethyl phenyl sulfone reacted vigorously with ethylmagnesium bromide to yield on carbonation an acidic gum which was not identified. There was also separated a trace of an unidentified bicarbonate-insoluble but potassium hydroxide-soluble crystalline solid, m. p. 156°. The starting material was recovered to the extent of 61%. An unidentified acidic oil was also obtained from ethyl phenyl sulfone and *n*-butyllithium. This substance turned black on standing. Diphenyl sulfone reacted vigorously with *n*-butyllithium to give in low yield an acid melting at 200° after darkening from 120°. Attempts to purify this substance by recrystallization from a variety of solvents were unsuccessful.

(22) Ziegler and Connor, *ibid.*, **62**, 2596 (1940); Kohler and Tishler, *ibid.*, **57**, 217 (1935); Kohler and Potter, *ibid.*, **57**, 1316 (1935); **58**, 2166 (1936); Kohler and Larsen, *ibid.*, **57**, 1448 (1935); **58**, 1518 (1936).

An acidic gum was obtained from dibenzothiophene-5-dioxide and *n*-butyllithium following carbonation. All efforts to crystallize the product were unsuccessful.

Summary

1. Methyl aryl sulfides, in general, undergo lateral metalation with metalating agents of the Group I metals.

2. Methyl phenyl sulfide is metalated in the nucleus by *n*-butylmagnesium bromide.

3. Ethyl phenyl, *n*-propyl phenyl, isopropyl phenyl and *n*-butyl phenyl sulfides give *ortho*-nuclear metalation with *n*-butyllithium in diethyl ether.

4. Some cleavage reactions of alkyl phenyl sulfides with lithium and sodium metals and with *n*-butylmagnesium bromide and *n*-butyllithium have been examined.

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[CONTRIBUTION FROM THE GEORGE M. MOFFETT RESEARCH LABORATORIES, CORN PRODUCTS REFINING COMPANY]

Properties of the Fractions and Linear Subfractions from Various Starches

BY SYLVIA LANSKY, MARY KOOI AND THOMAS JOHN SCHOCH

There have been no critical standards by which to evaluate the purity and extent of degradation of the fractions from various starches. As a consequence, doubts frequently arise regarding the quality of the parent starch, the possibility of hydrolytic degradation during fractionation, and the purity of the final fractions. The present investigations were initiated primarily to isolate the linear and branched components of various common starches by optimum fractionation techniques, and to establish precise standards of purity and degree of degradation on the basis of iodine affinity and intrinsic viscosity. As this work progressed, the substantial differences between the linear fractions from the various starches required further elucidation from a molecular standpoint. This led to the development of a technique for separating the total linear material into a graded series of subfractions by partial precipitation methods. Various reducing value determinations for aldehydic end-groups have been investigated as a means for comparing the relative molecular size of the linear fractions and subfractions. These physical and chemical criteria have likewise had application in estimating the degree of hydrolysis of various modified starches and in elucidating the mechanism of β-amylase action on the starch fractions. Through the kindness of A. L. Potter and W. Z. Hassid, osmotic molecular weights and non-aldehydic end-group assays (by periodate oxidation) have been reported on many of the identical fractions here described.[1]

In the present paper, the linear and branched starch components are designated as the A-fraction and the B-fraction, respectively, in conformance with previously established definitions.[2]

Source of Starches.—Various samples of commercial corn starch were selected over a period of four years, choosing those lots which possessed the highest "hot paste viscosity." The wheat starch was an experimental batch produced at the Northern Regional Research Laboratory by sulfur dioxide steeping. Tapioca starches included samples from Brazil (kindly supplied by Mr. George Caesar of Stein, Hall and Company) and from the Dominican Republic, in each case selected by reason of high paste viscosity. Limited data are likewise available on the A-fraction from pre-war Javanese tapioca. Potato starches were of Maine and Idaho origin, from the New England Starch Company and Idaho Potato Starch Company, respectively. Data are also included on the B-fraction from pre-war German potato starch. Since commercial sago starch is frequently bleached with oxidizing agents, a sample of virgin unmodified sago flour was secured through the courtesy of Dr. C. G. Caldwell of the National Starch Company. This was suspended in methanol and screened through silk bolting cloth, then repeatedly sedimented in methanol and finally in distilled water. This treatment served to remove all foreign material and most of the pigment. Easter lily starch was furnished by Dr. R. M. Hixon of Iowa State College. The corn, wheat, sago and lily starches were defatted by five two-hour digestions under reflux with boiling 85% methanol, filtering and washing with 85% methanol after each digestion. In later studies, raw corn starch (non-defatted) was fractionated directly.

Fractionation Methods.—In all cases, primary separation was effected by selective precipitation with Pentasol (commercial mixture of amyl alcohols marketed by Sharples Solvents). Where the starch was dissolved by autoclaving, defatted starch was employed and the system was buffered at *p*H 6.2–6.3 prior to autoclaving by the addition of 40 ml. of 20% phosphate solution (16.4% with respect

(1) Potter and Hassid, THIS JOURNAL, **70**, 3488, 3774 (1948).

(2) Schoch in "Advances in Carbohydrate Chemistry," edited by Pigman and Wolfrom, Vol. I, Academic Press, New York, N. Y., 1945, pp. 247–277.

to anhydrous KH_2PO_4 and 3.6% to anhydrous K_2HPO_4) per 450-g. batch of starch in 15 l. of water. A number of starches were fractionated without autoclaving; in these cases, raw starch may be employed directly without preliminary defatting. In a 5-gal. Pyrex bottle equipped with mechanical stirrer and reflux condenser and heated in a suitable boiling water-bath, 300 g. of the starch was gelatinized in a boiling mixture of one liter of Pentasol and 15 l. of distilled water containing 50 ml. of the above phosphate buffer. The mixture was gently refluxed for three to four hours at 92° with continuous agitation, then cooled overnight with stirring and finally refrigerated for twenty-four hours. The A-fraction complex crystallized as rounded spherules; centrifugation at 50,000 r. p. m. in the Sharples continuous supercentrifuge gave a dense well-packed deposit, with no evidence of slimy material. This mode of fractionation is preferred over previous methods, since it avoids both the defatting operation and the possible hydrolytic degradation during autoclaving.

To isolate the B-fraction, the supernatant solution from the centrifuge was treated with one-third its volume of methanol, the mixture vigorously stirred for several minutes, then refrigerated overnight.[3] The B-fraction precipitated quantitatively as a soft curd which was removed and dehydrated by grinding for two or three minutes in a Waring Blendor with fresh methanol.

Two methods were employed for recrystallization of the A-fraction. By the earlier method,[2] the crude moist A-fraction was dissolved in boiling water in the presence of excess *n*-butyl alcohol to give a 1% solution (on dry substance basis). This was supercentrifuged to remove extraneous impurities, cooled and refrigerated to crystallize the A-fraction. Two such recrystallizations sufficed to raise the iodine affinity of the product to a maximum value. Since it became evident that this technique caused some subfractionation, a later method employed Pentasol as the recrystallizing agent. The crude moist A-fraction was dissolved in hot water (95–100°) with vigorous agitation, to give a solution of 0.2% concentration (dry substance basis). The hot solution was passed through the Sharples supercentrifuge, giving only a small amount of dark brown sediment in the lower part of the rotor. An excessive amount of white or light colored material indicates incomplete solution of the A-fraction, due to too low a temperature or to inadequate stirring during solution of the crude material. Any such undissolved residue can usually be recovered by dissolving in boiling water and recentrifuging. The total centrifugate was reheated to 90–95°, 5–6% by volume of Pentasol added, the mixture cooled overnight with continuous agitation, then refrigerated twenty-four hours and centrifuged. When crystallized at 0.2% concentration, the A-fraction separated as well-defined rosettes which gave a dense deposit in the centrifuge rotor. Attempts to recrystallize 1% solutions with Pentasol gave soft, bulky and even "sloppy" deposits. As many as seven recrystallizations with Pentasol were employed in an effort to attain maximum iodine affinity. While no attempt was made in these studies to control *p*H during recrystallization, it might be advisable to add a small amount of phosphate buffer.

The A-fraction was dehydrated by suspending in 10 volumes of *n*-butyl alcohol, stirring for several hours and filtering. This treatment was repeated several times and the product finally dried *in vacuo* at 70°. This method of drying avoids retrogradation, and the dried A-fraction is completely soluble in boiling water. Yields of A-fraction were not determined except in the case of certain modified starches.

Subfractionation of A-Fraction.—A number of methods have been investigated for the separation of A-fraction into a graded series of subfractions of different chain lengths. Selective retrogradation and partial precipitation with methanol were ineffectual. By far the best procedure involved partial precipitation with minimal amounts of the higher alcohols. While cyclohexanol has been used in some of these studies, *n*-octyl alcohol is preferred by reason of its lower solubility in water and more precise control of subfractionation. It should be noted that these agents precipitate the A-fraction at temperatures substantially above the levels of *n*-butyl alcohol or Pentasol precipitation.

The following procedure is cited as an example of optimum subfractionation technique (Run 17). One hundred g. of potato A-fraction (Batch P-7/9-A, twice recrystallized with Pentasol) was dissolved in 10 l. of boiling water and passed through the supercentrifuge or filtered through Pyrex glass wool to remove any slight trace of insoluble material. The clarified solution was reheated to 80–85°, 1.5 ml. of *n*-octyl alcohol added dropwise with agitation, and the mixture allowed to cool spontaneously with continuous stirring. Turbidity developed when the temperature dropped to 72°, and crystalline precipitation occurred in the range from 70 to 62°, as indicated by a "watered-silk" appearance on stirring. The mixture was allowed to cool overnight with stirring, then passed through the Sharples supercentrifuge at a rate of 200 ml. per minute, using the smallest injector nozzle. The first subfraction (designated as 17-a, to indicate Run 17, first subfraction) was removed from the rotor, dehydrated by successive digestions in *n*-butyl alcohol, filtered and dried to constant weight in the vacuum oven at 70°. The centrifugate was reheated to 80–85°, 1.0 ml. of octyl alcohol added and the mixture similarly cooled with stirring. After removal of the second subfraction (17-b), the third, fourth and fifth subfractions were similarly precipitated by the addition of 1.0-ml. portions of octyl alcohol. The sixth and last portion was precipitated with excess octyl alcohol. Mechanical losses of linear material during these successive centrifugings may total 10–15%. Consequently, weight distribution of the subfractions was calculated on the basis of total recovered material.

Hydrolysis Studies.—It was also of interest to determine the characteristics of linear and branched molecules smaller than those in the native starch. For this purpose, granular corn starch was hydrolyzed to various levels by treatment with dilute acid at a temperature below the gelatinization point, in much the same fashion as for the commercial production of "thin-boiling" starches. Suspensions of raw corn starch (40% on weight basis) in 0.075 *N* hydrochloric acid were digested in a constant temperature bath at 50° for five, sixteen, twenty-six and forty hours. The converted starches were neutralized to *p*H 6.0 with sodium carbonate, filtered, washed and air-dried. Similar conversions were run in 0.3 *N* hydrochloric acid for two, seven and sixteen hours at 50°. The acid-modified starches were subsequently fractionated by Pentasol precipitation and the linear fractions recrystallized twice with Pentasol.

Iodine Affinity.—The potentiometric titration method of Bates, French and Rundle[4] has been modified for routine evaluation of iodine affinity. A bright platinum electrode was employed in conjunction with a low resistance calomel electrode (Leeds and Northrop No. 1199–11 electrode, or Coleman No. 3-070 electrode with saturated potassium chloride junction). Potentials may be determined with an ordinary *p*H meter adaptable to millivolt readings, though use of a Leeds and Northrop Type K bridge and No. 2420-C galvanometer provides much simpler and more precise operation. To calibrate the electrode system, 373 mg. of potassium chloride and 830 mg. of potassium iodide were dissolved in 100 ml. of water and titrated with standard iodine solution between e. m. f. limits of 230–280 millivolts, the solution being stirred mechanically during the titration. The standard iodine solution was 0.05 *N* with respect to potassium iodide, 0.05 *N* to potassium chloride, and contained exactly 0.200 mg. of iodine per ml.; this was most conveniently prepared just prior to use by tenfold dilution of a stock iodine solution, the latter being standardized against arsenious oxide. Since the solution and iodine reagent were both 0.05 *N* with respect to potassium chloride and potassium iodide, there was no change in salt concentration during

(3) Schoch and French, *Cereal Chem.*, **24**, 231 (1947).

(4) Bates, French and Rundle, THIS JOURNAL, **65**, 142 (1943).

the titration. From the plotted curve of this titration, a calibration chart was prepared giving the total milligrams of free iodine in solution for each half-millivolt reading from 230–280 mv.

Before evaluation of iodine affinity, all starchy materials were Soxhlet-extracted for twenty-four hours with ethyl alcohol, to remove residual fractionating agents or natural lipids which repress the iodine affinity. The sample was then dried and pulverized to pass a 40-mesh screen. To prepare unmodified granular starches for analysis, the starch was gelatinized in boiling water to give a 1% paste, this was disintegrated by five minutes agitation in the Waring Blendor and the starch substance flocculated by the addition of excess methanol. Modified or so-called "thin-boiling" starches do not require pregelatinization. An appropriate sample (*i.e.*, approximately 40 mg. of A-fraction, 100 mg. of whole starch, or 200 mg. of B-fraction) was transferred to a dry 250-ml. beaker. Five ml. of 1 *N* potassium hydroxide solution was added by pipet and the sample dispersed in the alkali by trituration with a stirring rod, with care to avoid the formation of difficultly soluble lumps. The mixture was allowed to stand with occasional stirring for one hour, or until a perfectly clear solution was obtained. It was then neutralized to methyl orange with 0.5 *N* hydrochloric acid, 10 ml. of 0.5 *N* potassium iodide added and the solution diluted to 100 ml. (*i.e.*, by addition of 75 ml. of water). With some B-fractions, the sample did not dissolve to give the requisite crystal-clear solution in the alkali. In such cases, the mixture was neutralized and gently heated to assist solution.

Except for the presence of starchy substance, this solution was identical with that employed for the calibration. It was titrated potentiometrically in the same manner. After each addition of iodine, the solution was allowed to equilibrate for two minutes before determining the e. m. f.

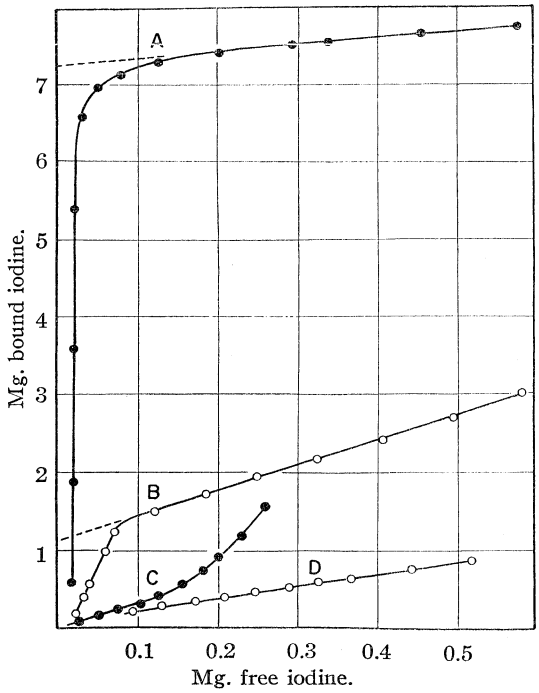

Fig. 1.—Method of plotting potentiometric evaluation of iodine affinity, showing titrations of (A) 38.4 mg. of corn A-fraction, (B) 182 mg. of corn B-fraction, (C) 193 mg. of tapioca B-fraction, and (D) 190 mg. of soluble "phytoglycogen" from Golden Bantam sweet corn. High quality waxy maize starch yields a curve identical with (C); the shape of the latter cannot be explained.

For each point of the titration, the free iodine in solution was calculated for the corresponding e. m. f. of the calibration chart, and this amount was deducted from the total iodine added at that point (*i.e.*, ml. of iodine added × 0.200 mg.) to give the bound iodine. Free iodine was then plotted against bound iodine as shown in Fig. 1. The upper linear portion of this curve was extrapolated to the zero axis (a mode of plotting suggested by Dr. Dexter French) and this amount of bound iodine taken as the iodine affinity of the sample. Results were converted to dry basis by separate moisture determination on the sample (*viz.*, four hours *in vacuo* at 70°). In the titration of A-fractions and normal starches, it is only necessary to obtain some 5 or 6 readings between 250–280 mv., omitting the lower ascending portion of the curve. With B-fractions or waxy starches, readings should be taken between 230–270 mv. Two or more determinations have been run on all samples here reported; average deviation from the mean is ±0.08% iodine affinity.

Intrinsic Viscosity.—The primary difficulty in evaluation of starch viscosity is the choice of solvent. The viscosity of solutions in such basic media as anhydrous ethylenediamine or aqueous potassium hydroxide shows a progressive decrease over a period of days, probably due to slow oxidative degradation of the polysaccharide. This is particularly objectionable when ethylenediamine is employed as solvent for the B-fraction, since one to three days are required to effect a homogeneous solution. Use of chloral hydrate or 30% ammonium thiocyanate solution avoids this drift in viscosity, but these agents do not dissolve the A-fraction, particularly when retrograded. One normal potassium hydroxide solution was finally selected because of its ease of preparation and standardization. Also, since its solubilizing action is much more rapid than ethylenediamine, degradation may be kept to a minimum. The intrinsic viscosity can be determined within two hours; hence no precautions are exercised to exclude oxygen or carbon dioxide.

The A-fraction (either retrograded or non-retrograded) dissolves readily and completely in 1 *N* potassium hydroxide solution. The B-fraction does not dissolve completely in either 1 or 5 *N* alkali, seemingly due to persistent aggregation effects.[3] However, the following procedure overcomes aggregation and is recommended for either fraction. An amount of the fraction equivalent to 2.00 g. on dry basis was quantitatively sifted into 200–300 ml. of cold water in a 600-ml. beaker, stirring vigorously with a glass propeller-type agitator to avoid formation of lumps. The suspension was heated in a boiling water-bath for thirty minutes, then allowed to cool to room temperature, stirring being continued throughout the heating and cooling periods. To prevent formation of insoluble skins by evaporation, the beaker was covered with a perforated watchglass during the heating and cooling operations. When cold, 100 ml. of 5 *N* potassium hydroxide solution was added by pipet and stirring continued for ten to fifteen minutes, usually producing a perfectly clear solution, entirely devoid of gel particles. The alkaline solution was rinsed into a 500-ml. volumetric flask and diluted to volume with distilled water, to give an 0.4% solution of the starch fraction in 1 *N* potassium hydroxide. This was filtered through a loose plug of Pyrex glass wool in a funnel stem, to remove any trace of fiber or insoluble material which might impede capillary flow. Accurate dilutions were made to some five or six concentrations between 0.1–0.4%, using 1 *N* potassium hydroxide solution for dilution. Viscosity was determined at each concentration with an Ostwald–Cannon–Fenske No. 100 pipet, maintained in a thermostated water-bath at 35.0°. Flow time at each concentration was determined to a precision of ±0.1 second or better (average deviation from mean), filling the viscometer at least twice and running at least three flow times for each filling. Specific viscosity was determined with reference to 1 *N* potassium hydroxide, and intrinsic viscosity was evaluated by plotting the function (η_{sp}/concn.) against concentration and extrapolating to zero concentration. Both the 1 and 5 *N* potassium hydroxide solutions must be adjusted within 1% of the

stipulated values (*i.e.*, 0.99–1.01, 4.95–5.05 *N*), since the flow time of the solvent varies markedly with concentration. Duplicate determinations on a large number of samples indicated a precision of ±0.02 in the intrinsic viscosity (average deviation from the mean).

This method overcomes any aggregation or retrogradation of the starch substance. For example, non-retrograded wheat A-fraction had an intrinsic viscosity of 1.54 ± 0.03. When this material was dissolved in boiling water at 0.2% concentration and retrograded by prolonged refrigeration, the intrinsic viscosity of the product was 1.50. In another test, corn B-fraction was precipitated from aqueous solution by three different methods: (a) by gross addition of methanol, (b) by slow addition to excess methanol, and (c) by addition of 10% methanol followed by freezing, thawing, filtering and spontaneous air-drying.[3] These three products had radically different solubility behavior, both in water and in 1 *N* potassium hydroxide, yet their intrinsic viscosities were 1.32, 1.28 and 1.30, respectively. However, the method has not been reliable for evaluating the viscosity of unmodified granular starches, apparently due to persistent granule structure which is not completely disaggregated either by pregelatinization in boiling water or by treatment with 1 or 5 *N* alkali.

The slope of the viscosity curve (η_{sp}/concn., against concentration) was determined for each sample, but this value appeared to have no significance. In general, the higher the viscosity, the greater was the slope.

The use of intrinsic viscosity does not entirely eliminate the energy characteristics of the viscometer. For example, the intrinsic viscosity of a commercial 75-fluidity corn starch was 0.53 with a No. 50 Cannon–Fenske pipet, 0.48 with a No. 100 pipet, and 0.33 with a No. 200 pipet. The No. 100 pipets employed in these studies gave flow times of approximately forty-five seconds for distilled water. Identical intrinsic viscosities were obtained with a regular Ostwald pipet of similar flow time.

Retrogradation Time.—It was of interest to compare the relative retrogradation tendencies of various linear starch substances, particularly to explain the low retrogradation of tapioca A-fraction. Retrogradation has been entirely a qualitative characteristic which is difficult to translate into quantitative terms. As an approximation, the retrogradation tendency is here expressed as the time required for development of initial turbidity in a 1% solution of the linear substance. Admittedly, the criterion and mode of testing are not good. It is often difficult to estimate the point at which turbidity first appears, particularly with linear substances which require more than fifteen to twenty hours for retrogradation. While flocculation normally occurs soon after the initial appearance of turbidity, a number of samples showed initial turbidity followed by a long period during which there was no further change. As a further criticism of the data, it was not feasible to run these tests at constant temperature, despite the known influence of temperature on retrogradation.

One hundred mg. (on dry basis) of the linear substance was dissolved in 2.0 ml. of 1 *N* potassium hydroxide solution. The mixture was stirred occasionally for one to two hours to effect a perfectly clear solution, 5.5 ml. of water added and the solution neutralized to phenolphthalein with 1 *N* hydrochloric acid. Since *p*H has a marked influence on retrogradation, 0.5 ml. of *p*H 6.3 phosphate buffer solution was added (16.4% with respect to anhydrous KH_2PO_4 and 3.6% to anhydrous K_2HPO_4). The solution was transferred to a stoppered 5-inch test-tube which was placed in a device designed to rotate some fifteen tubes end-over-end at a rate of about 20 r. p. m. Incidence of the characteristic blue-white haze as viewed against a black background was taken as the time of retrogradation. In some cases, shreds of insoluble material were formed during the neutralization; however, this did not significantly influence the time of retrogradation. Two to six tests were run on each sample here reported; precision was of the order of ±15%.

Reducing Value.—A variety of oxidizing agents and different conditions of oxidation have been investigated for aldehydic end-group assay of the A-fraction. Hypoiodite methods (variations of the Harris[5], Kline–Acree,[6] and Willstätter–Schudel techniques) were completely useless, since a large and indeterminable amount of iodine was consumed in oxidation of hydroxyl groups along the starch chain. This over-oxidation increased progressively (a) with increasing *p*H levels from 8.7 to 11.9, (b) with increasing time and temperature of reaction, and (c) with increasing concentration of iodine. No method could be devised to limit the oxidation to terminal aldehyde (*e.g.*, by use of borate buffer) or to correct for over-oxidation (by plotting iodine consumption against reaction time and extrapolating to zero time). The same criticisms applied to oxidation with bromine–potassium bromide mixtures at buffered *p*H levels between 4.5–7.0. While ferricyanide,[7] alkaline copper[8] and alkaline 3,5-dinitrosalicylate reagents appeared somewhat more selective toward terminal aldehyde, the reducing values by these methods were influenced to a major degree by concentration of oxidizing agent, the *p*H of the medium, and the time and temperature of the reaction. As a further complication, these last three oxidizing agents do not yield a stoichiometric relationship between glucose and maltose; hence, any extension to the higher polysaccharides is entirely arbitrary. It is therefore concluded that absolute evaluation of terminal aldehyde is not possible with any of the above reagents.

However, some relative index of reducing value was required for comparison of various linear subfractions. While alkali numbers have been determined on most of the samples here reported, this value is primarily a test for hydrolytic degradation, not a relative index of molecular weight. The colorimetric 3,5-dinitrosalicylate method of K. H. Meyer and his associates[9,10] was finally employed because of its simplicity and because it gave more reproducible results than the copper, ferricyanide or hypoiodite method. Furthermore, the intensity of color produced with either maltose or A-fraction followed Beer's law; the reducing value was therefore independent of the size of sample. Meyer's technique was modified in several respects. When the dinitrosalicylate reducing value was plotted against time of digestion at 65°, it was found that the initial primary oxidation was not always complete in thirty minutes; oxidations were therefore conducted for one hour to bring the reducing value into the more uniform over-oxidation range. An amount of the linear starch substance equivalent to 2–4 mg. of maltose was transferred to a clean dry 6 × 0.75 inch test-tube. Fifteen ml. of alkaline dinitrosalicylate reagent (666 mg. of twice-recrystallized 3,5-dinitrosalicylic acid dissolved in 200 ml. of 1 *N* potassium hydroxide) was added by pipet, and the sample dispersed by thorough mixing with a stirring rod. The mixture was allowed to stand with occasional stirring for an hour, or until the sample completely dissolved. The solution was then heated for one hour in a thermostated bath at 65°, cooled, quantitatively rinsed into a 50-ml. volumetric flask and diluted to mark. Blanks were simultaneously run on 15-ml. portions of the dinitrosalicylate reagent. Light transmission at 5000 Å. (predetermined as the point of maximum color development) was compared against the blanks, using 1-cm. cuvettes in a Beckman quartz spectrophotometer. In order to standardize the method, 1–5-mg. samples of maltose (analyzed by the Kline–Acree technique) were digested in similar fashion and transmission at 5000 Å. determined against comparable blanks. Percentage transmission was plotted against mg. of maltose hydrate to give a calibration curve.

(5) Martin, Smith, Whistler and Harris, *J. Research Nat. Bur. Standards*, **27**, 449 (1941).

(6) Kline and Acree, *Bur. Standards J. Research*, **5**, 1063 (1930).

(7) Gore and Steele, *Ind. Eng. Chem., Anal. Ed.*, **7**, 324 (1935); Farley and Hixon, *ibid.*, **13**, 616 (1941).

(8) Richardson, Higginbotham and Farrow, *J. Textile Inst.*, **27**, 131 (1936).

(9) Meyer, Noelting and Bernfeld, *Helv. Chim. Acta*, **31**, 10 (1948).

(10) Noelting and Bernfeld, *ibid.*, **31**, 286 (1948).

TABLE I

PROPERTIES OF THE PENTASOL-SEPARATED FRACTIONS ISOLATED FROM AUTOCLAVED STARCH SOLUTIONS; A-FRACTIONS RECRYSTALLIZED TO CONSTANT IODINE AFFINITY WITH *n*-BUTYL ALCOHOL

Parent starch		A-Fraction					B-Fraction			
Source	% Iodine affinity	Batch[a]	% Iodine affinity	[η]	Alkali number	D. P.[b]	Batch[a]	% Iodine affinity	[η]	Alkali number
Corn	5.30[c]	C-71/73-A	19.05	..	..		C-1/9-B	..	1.35	...
		C-85/89-A	18.90	1.19	20.2		C-10/12-B	..	1.30	4.6
		C-107/111-A	19.07	1.23	20.4	800	C-81/89-B	0.6	1.17	5.0
		C-112/134-A	...	..	20.7		C-90-B	..	1.22	...
		C-141-A[d]	...	1.45	18.7		C-107-B	.7	1.21	...
		C-146-A	19.35	1.13	23.5		C-109-B	.9	1.24	4.3
							C-137-B	..	..	4.1
							C-141-B[d]	..	1.35	4.6
Wheat	5.21	Wh-1/2-A	19.90	1.54	20.6	860	Wh-1-B	.56	1.14	4.6
							Wh-2-B	.44	1.22	4.3
Sago	5.10	S-1/2-A	18.52	1.13	17.4	740	S-1-B	.2	0.82	5.1
							S-2-B	.2	0.80	5.5
Easter lily	6.5[e]	L-3-A	20.03	1.06	19.4	620	L-3-B	.35	1.26	4.0
Potato	4.13	P-3/4-A	19.84	1.95	10.3	930	P-3/4-B	.4	1.45	6.4
(Maine)		P-5/6-A	19.96	1.75	12.1					
Potato	..	.....	...	..	..		P-1-B	.4	1.53	4.9
(German)							P-2-B	.4	1.50	5.2
Tapioca	3.27	T-3/4-A	18.55	2.25	12.8	1300	T-3-B	.0	1.27	3.8
(Dominican)							T-4-B	.0	1.23	3.7
Tapioca (Java)	3.30	T-1/2-A	18.6							

[a] Batch designations are given to facilitate cross reference and to identify samples investigated by other laboratories. Thus C-71/73-A indicates a composite sample of the corn A-fractions from Runs 71 to 73, inclusive. [b] Degree of polymerization, as determined from osmotic pressure by Potter and Hassid.[1] [c] This represents an average value for commercial dent corn starch. [d] Corn starch was solubilized by pregelatinization in liquid ammonia according to the method of Hodge, Montgomery and Hilbert.[13] Product was then dissolved in hot water, fractionated with Pentasol and the A-fraction thrice recrystallized with *n*-butyl alcohol. [e] High iodine affinity is not necessarily a characteristic of Easter lily bulb starch. Defatted starches from Croft, Ace, Estate and Creole varieties of Easter lily bulbs (from Vaughn Seed Co.) analyzed 5.16, 5.88, 5.43 and 5.36% iodine affinity, respectively.

By use of the latter, color development in the starch sample was calculated in terms of mg. of maltose hydrate per gram of starch substance. Two or more determinations were run on each sample; average deviation from the mean was ±0.04 mg. of maltose hydrate. It should be stressed that these values cannot be translated into molecular weight. Much higher reducing values are obtained by digesting for five minutes at 100°. The use of Rochelle salt[10] in the digestion mixture merely depresses the reducing value without decreasing the rate of over-oxidation.

Discussion

There has been a tendency to consider that hypothetically "pure" linear material has an iodine-binding capacity of 20.0%. This value is frequently employed for calculation of the percentage of linear material in various starch preparations. The present work shows that no such criterion is possible, since the iodine affinity depends on the source of the A-fraction and on the methods of fractionation and recrystallization. The A-fractions listed in Table I were all recrystallized to constant maximum iodine affinity by identical methods of precipitation with *n*-butyl alcohol. They may surely be considered as "pure" substances in the sense that the B-fraction has been completely removed, yet their iodine affinities range from 18.5 to 20.0%. In several unrecorded instances, corn A-fraction was recrystallized by cooling only to 35–40° and centrifuged without refrigeration. The resulting products had iodine affinities in the range of 20.5–20.8%, apparently due to subfractionation and loss of linear material of somewhat lower iodine affinity. When Pentasol was employed as recrystallizing agent (Table II), the iodine affinities were consistently and substantially lower. While one or two recrystallizations with *n*-butyl alcohol sufficed to give a constant maximum iodine affinity, successive recrystallizations with Pentasol gave a very slow but progressive increase in iodine affinity, with no evidence of a constant maximum even after seven recrystallizations of corn A-fraction. Similarly, the A-fractions from thin-boiling corn starches have iodine affinities lower than that of unmodified corn A-fraction (Table III). As will be shown more definitely by subfractionation studies, the total A-fraction represents a graded spectrum of molecular types, certainly differing with respect to chain length and perhaps even containing irregularities of linkage. Since these factors must necessarily influence the iodine affinity, no standard linear material can possibly be established which will apply equally to all A-fractions, regardless of source, hydrolytic level or manner of purification. Hence, it is strongly recommended that the linear characteristic of starches be expressed merely in terms of iodine affinity, with no reference to percentage of linear substance.

TABLE II

PROPERTIES OF THE FRACTIONS ISOLATED FROM BOILED STARCH SOLUTIONS BY PENTASOL SEPARATION; A-FRACTIONS RECRYSTALLIZED WITH PENTASOL

	A-Fraction					B-Fraction			
Starch	Batch	No. of recrystns.	% Iodine affinity	[η]	Alkali number	Batch	% Iodine affinity	[η]	Alkali number
Corn	C-148/150-A	3	16.06	1.35	..	C-148-B	0.31	1.35	...
		5	17.86	1.27	..	C-149-B	.44	1.37	6.2
		7	18.10	1.26	21.6				
Brazilian tapioca	T-7/9-A	2	17.15	2.75	..	T-7-B	.14	1.21	3.5
		4	17.75	2.22	12.8	T-8-B	.15	1.25	3.9
						T-9-B	.11	1.35	3.4
Idaho potato	P-7/9-A	2	17.03	2.33	..	P-7-B	.17	1.58	3.7
		4	19.14	2.31	13.3	P-8-B	.14	1.49	3.7
						P-9-B	.15	1.49	4.0

TABLE III

PROPERTIES OF THE PENTASOL-SEPARATED FRACTIONS FROM ACID-MODIFIED CORN STARCHES; A-FRACTIONS TWICE RECRYSTALLIZED WITH PENTASOL

Parent starch				A-Fraction						B-Fraction		
Hours conversion	% Iodine affinity	[η]	Alkali number	Yield, %[a]	% Iodine affinity	[η]	Alkali number	Reducing value[b]	Retrogradn. time, hr.	% Iodine affinity	[η]	Alkali number
				0.075 *N* HCl at 50°								
5	4.81	1.06	13.0	28	15.38	1.01	23.6	5.95	5	0.37	0.85	6.3
16	4.77	0.66	18.0	22	14.25	0.71	27.7	7.41	4	.31	.56	10.9
26	4.75	.47	21.6	25	14.85	.59	32.7	10.45	2	.26	.42	15.1
40	4.69	.37	27.2	30	15.10	.57	37.6	10.70	1	.23	.34	19.4
				0.3 *N* HCl at 50°								
2	4.68	.89	13.9	29	15.29	.91				.39	.75	
7	4.74	.44	22.6	30	14.85	.54				.25	.40	
16	4.40	.24	34.8	27	15.55	.37				.19	.23	

[a] Yields of A-fraction are based on once-recrystallized product. [b] Reducing value toward dinitrosalicylate, expressed as mg. of maltose hydrate per gram of starch substance (dry basis).

The iodine affinities of the B-fractions likewise show a variation, from 0.0% for Dominican tapioca to 0.6–0.7% for corn starch. It has not been positively established whether this represents a residual trace of unremoved linear material, or whether certain B-fractions possess a small but definite iodine-binding capacity. The latter explanation seems more plausible. Otherwise, it would be difficult to explain why Pentasol consistently gives B-fractions of very low or negligible iodine affinity from potato and tapioca starches, while the B-fractions from the cereal starches are substantially higher in iodine-binding capacity. It has been claimed that the iodine affinity of the B-fraction can be reduced to zero by treatment with cotton. However, this is apparently due to the introduction of fatty substances from the cotton, thereby concealing the presence of residual iodine-binding material. If alcohol-defatted cotton is employed, there is no reduction of residual iodine affinity. In accord with theories suggested by Kerr[11] and more recently elaborated by K. H. Meyer,[12] a portion of the total B-fraction may have a few outer branches of sufficient unobstructed length to bind a small amount of iodine, though too short or too infrequent to precipitate with Pentasol.

Intrinsic viscosities also reveal substantial differences between the various A-fractions and likewise between the various B-fractions. In general, the fractions isolated from boiled starch pastes have somewhat higher intrinsic viscosities than those from autoclaved pastes. Despite careful buffering, autoclaving probably causes a slight degradation of the starch substance. For this reason, prolonged boiling in the presence of excess Pentasol is now preferred as a means of solubilizing starch prior to fractionation. To avoid autoclaving, use of the Waring Blendor has been suggested to disintegrate swollen starch pastes for fractionation. However, the B-fraction undergoes degradation under the violent shearing action of the Blendor, seemingly by a "mechanical hydrolysis" of the molecule. For example, a hot 3% corn starch paste (buffered at *p*H 6.3) was disintegrated in the Blendor for fifteen minutes, then fractionated with Pentasol and the A-fraction thrice recrystallized with *n*-butyl alcohol. Intrinsic viscosities of the A and B fractions were 1.39 and 1.07, respectively. The A-fraction was not degraded, perhaps because of its smaller molecular size together with the possibility that it can align itself along the flow lines and thus escape mechanical rupture.

(11) Kerr, "Chemistry and Industry of Starch," Academic Press, New York, N. Y., 1944, p. 154.

(12) Meyer, Bernfeld, Rathgeb and Gurtler, *Helv. Chim. Acta*, **31**, 1536 (1948).

In another instance, a buffered 3% solution of corn B-fraction was agitated for one hour in the Blendor, then precipitated with methanol and dried. The intrinsic viscosity was lowered from 1.17 to 0.95 by this treatment. Pregelatinization in liquid ammonia (as recommended by Hodge, Montgomery and Hilbert[13]) provides an excellent but somewhat inconvenient method for dissolving granule structure without degradation (*cf.* Batch C-141 in Table I).

During acid-modification of granular corn starch (Table III), both fractions appear to be hydrolyzed at approximately the same rate, as indicated by increase in alkali number. In comparison with these laboratory-modified starches, the intrinsic viscosities of commercial thin-boiling corn starches (sulfuric acid modification) were as follows: 15-fluidity, 1.09; 40-fluidity, 0.90; 50-fluidity, 0.73; 60-fluidity, 0.62; 75-fluidity, 0.46; 90-fluidity, 0.38.[14] These values have had practical application in determining the hydrolytic level of various starch derivatives and of pregelatinized starches. Thus, when a 75-fluidity corn starch was gelatinized and dried on heated rolls, the product had an intrinsic viscosity of 0.45. Similarly, a granular starch ether of low degree of substitution prepared from 40-fluidity starch had an intrinsic viscosity of 0.92.

The intrinsic viscosity may have theoretical application in indicating the mechanism of enzyme action on the starch fractions. For example, the β-amylase limit dextrin from waxy maize starch had an intrinsic viscosity of 1.25 and an alkali number of 5.5 (values for the parent starch substance were 1.21 and 3.6, respectively). Since intrinsic viscosity is essentially a measure of molecular shape (*i. e.*, the "axial ratio" of length of molecule to diameter), the similar values for

TABLE IV

CHARACTERISTICS OF THE LINEAR SUBFRACTIONS FROM CORN, POTATO AND TAPIOCA STARCHES

Source	Subfraction	Yield, %	Iodine affinity, %	[η]	Alkali number	Reducing value[a]	Retrogradn. time, hr.
Corn	1-a	32	18.72	1.36	..	..	5
C-146-A[b]	1-b	63	18.53	0.94	24.3	6.11	4
	1-c	5	...	0.51	..	..	..
Same[b]	3-a	18	19.15	1.26	22.9	..	3
	3-b	25	19.08	1.28	20.7	4.57	6
	3-c	19	18.71	1.03	23.5	..	..
	3-d	38	17.86	0.82	28.0	5.99	2
Same	11-a	26	19.48	1.29	21.0	4.60	3
	11-b	41	19.69	1.19	22.3	5.06	5
	11-c	33	19.07	0.80	28.1	9.69	1
Corn	13-a	34	17.83	1.65	14.4	4.17	6
C-148/150-A	13-b	39	18.57	1.12	19.1	5.66	4
3 × recryst.	13-c	19	18.54	0.87	27.6	6.63	3
	13-d	8	11.53	0.82	23.4	..	..
Same	14-a	30	17.20	1.60	18.0	4.12	5
	14-b	25	17.88	1.26	21.2	3.75	4
	14-c	34	19.37	1.06	26.3	7.34	3
	14-d	11	13.30	1.02	20.7	7.37	2
Potato	2-a	46	20.70	1.78	14.5	3.38	8
P-5/6-A[b]	2-b	35	20.23	1.55	19.7	..	4
	2-c	19	17.60	1.12	18.4	..	4
Same[b]	4-a	19	20.22	2.18	14.1	2.77	18
	4-b	59	20.00	1.86	9.7	2.59	15
	4-c	21	18.31	1.25	14.9	4.28	7
Same[b]	5-a	21	20.12	2.19	10.7	..	13
	5-b	31	19.98	1.90	10.3	2.53	13
	5-c	33	...	..	..	..	..
	5-d	15	16.38	0.97	13.9	..	4
Same	6-a	67	20.54	1.88	9.9	2.52	15
	6-b	27	19.63	1.35	13.6	3.80	4
	6-c	6	18.45	..	..	...	2
Same	7-a	33	20.60	1.91	13.8	3.01	14
	7-b	42	20.64	1.78	13.8	2.86	6
	7-c	25	18.75	1.01	19.0	..	2
Same	8-a	60	20.48	2.01	9.3	2.54	18
	8-b	40	20.13	1.37	13.4	3.60	6
Same	9-a	49	20.49	2.05	9.2	2.64	22
	9-b	34	20.39	1.44	11.8	4.22	7
	9-c	17	18.29	1.23	18.6	..	4
Same	10-a	34	20.32	2.09	10.3	2.97	24
	10-b	14	20.39	1.60	13.7	..	..
	10-c	28	20.63	1.43	12.3	4.33	4
	10-d	23	19.07	1.30	18.1	..	..
Same	12-a	17	20.35	2.16	14.5	..	13
	12-b	39	20.66	1.83	10.0	2.79	11
	12-c	24	20.62	1.37	16.8	3.28	3
	12-d	21	20.11	1.34	17.0	3.71	6
Potato	17-a	18	19.73	2.63	11.4	2.32	50
P-7/9-A	17-b	17	19.77	2.03	13.4	2.77	15
2 × recryst.	17-c	14	19.98	1.64	15.5	3.51	8
	17-d	14	20.12	1.49	18.9	3.89	5
	17-e	14	19.86	1.45	18.2	4.02	6
	17-f	23	19.05	1.32	19.5	4.45	6
Tapioca	15-a	11	19.34	3.34	11.5	..	..
T-7/9-A	15-b	23	19.34	2.98	13.3	1.76	..
2 × recryst.	15-c	32	19.69	2.31	14.5	2.29	20
	15-d	20	19.90	1.96	13.9	2.66	10
	15-e	14	18.36	1.73	15.5	..	..
Same[c]	16-a	13	19.51	2.95	13.0	..	20
	16-b	33	19.26	2.21	15.0	2.35	15
	16-c	23	19.39	1.57	16.3	3.39	10
	16-d	22	19.33	1.32	18.9	4.02	7
	16-e	9	19.88	1.32	17.4	..	10

[a] Reducing value toward dinitrosalicylate, expressed as mg. of maltose hydrate per gram of starch substance (dry basis). [b] Runs 1–5 inclusive employed cyclohexanol as fractional precipitant. Due to its higher solubility in water, considerably larger quantities of this agent were employed than with octyl alcohol. Runs 6–17 inclusive were conducted with octyl alcohol. [c] Run 16 may have been slightly degraded during subfractionation.

(13) Hodge, Montgomery and Hilbert, *Cereal Chem.*, **25**, 19 (1948).

(14) Industrial fluidity values represent the ml. of 5% starch paste in 1% sodium hydroxide solution passed by a standard fluidity funnel in seventy seconds (Buel, 8th Intern. Congr. Pure Applied Chem., *Orig. Com.*, **13**, 63 (1912)). It will be noted that these values show good correlation with intrinsic viscosity.

waxy maize and its limit dextrin are in accord with the concept of a highly branched globular molecule; the limit dextrin would be smaller in size but similar in shape. In another case, corn A-fraction was treated with β-amylase[15] and samples withdrawn at several stages during the conversion. From intrinsic viscosities and alkali numbers of the residues, it appears that the enzyme attacks and destroys the shorter molecules first, leaving a residue of longer average chain length than the parent A-fraction:

Conversion, hr.	Degradation, %	Alkali no. of residue	$[\eta]$ of residue
0	0	20.4	1.23
1.75	41	17.4	1.39
6.0	61	16.3	1.38

The subfractions obtained by partial precipitation with cyclohexanol or octyl alcohol show a progressive gradation in intrinsic viscosity, alkali number, dinitrosalicylate reducing value and retrogradation time (Table IV). The subfraction first precipitated has the highest intrinsic viscosity and the lowest terminal aldehyde content, apparently consisting of those molecules of longest chain length. When the cumulative percentage yield of the successive subfractions is plotted against intrinsic viscosity as shown in Fig. 2, a frequency distribution curve is obtained indicative of a continuous series of homologous linear chains. There is no evidence of two or more separate and sharply defined component substances. Intrinsic viscosities of the various

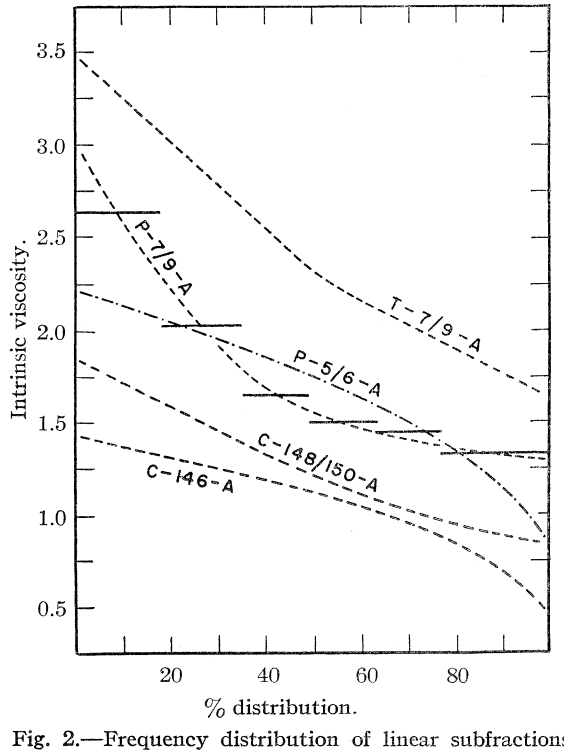

Fig. 2.—Frequency distribution of linear subfractions from various A-fractions plotted against their respective intrinsic viscosities. Method of plotting is shown for subfractionation No. 17 (twice-recrystallized potato A-fraction P-7/9-A); curves for other A-fractions are similarly derived.

(15) The enzyme used in these studies was furnished through the kindness of Miss Edna M. Montgomery, Northern Regional Research Laboratory, Peoria, Illinois.

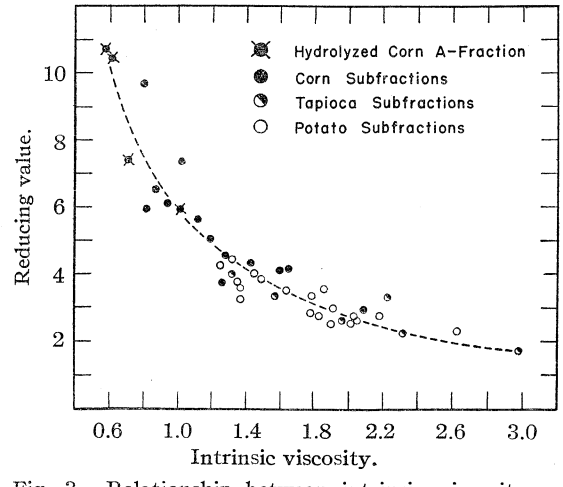

Fig. 3.—Relationship between intrinsic viscosity and dinitrosalicylate reducing value of various linear starch substances.

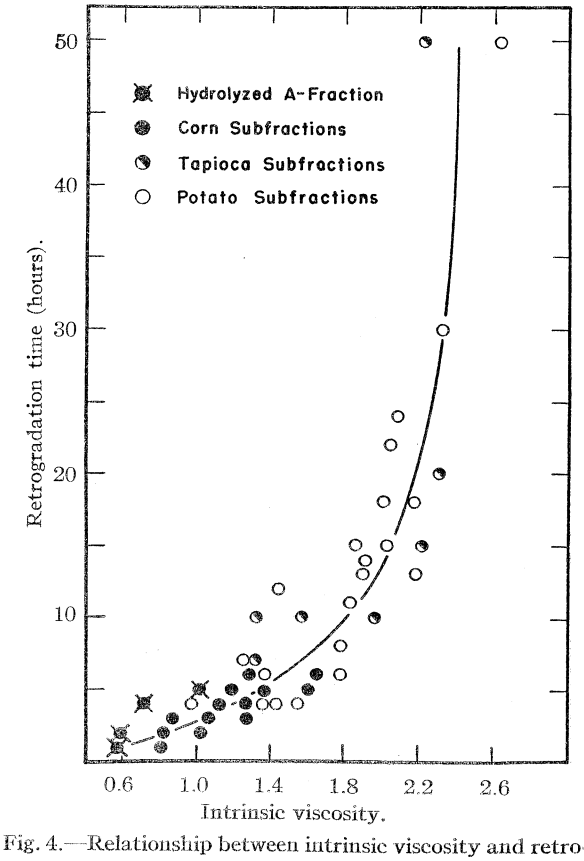

Fig. 4.—Relationship between intrinsic viscosity and retrogradation time of various linear starch substances.

subfractions show excellent correlation with dinitrosalicylate reducing value (Fig. 3) and with retrogradation time (Fig. 4), independent of the source of the subfraction. In addition, the intrinsic viscosities of the various A-fractions are arranged in the same order as their osmotic molecular weights, as determined by Potter and Hassid (Table I). Hence, the primary difference between tapioca, potato and corn A-fractions appears to be merely a matter of relative chain length. It does not seem probable that the A-fraction of one starch is strictly linear while that of another starch is slightly branched; such a situation would radically alter the relationship between intrinsic viscosity and reducing value. Since the shorter subfractions of potato A-fraction and the longer subfractions of corn A-fraction have the same intrinsic viscosity, dinitrosalicylate reducing value and retrogradation time, it must be assumed that they are molecularly identical. It has been claimed that tapioca A-fraction does not retrograde because its chain molecule is too long to permit ready orientation to an aggregated state.[16] Present evidence supports this theory, since the retrogradation tendency of the subfractions is inversely related to intrinsic viscosity. The theory is no longer tenable that the low-retrogradation tendency of tapioca starch is due to a slight branching peculiar to its A-fraction molecule.[16] Maximum retrogradation is observed with the hydrolyzed corn A-fractions down to an intrinsic viscosity of 0.57 (Table III). Somewhere below this level, a reversal must occur as the linear fragments become too short to retrograde.

Iodine affinities of the various fractions and subfractions are somewhat at variance with the foregoing concept of homologous series of linear chains. The following irregularities may be noted:

1. The B-fractions originally isolated from corn and potato starches by primary separation with *n*-butyl alcohol had iodine affinities of 1.5–1.7%,[2] as compared with present values of 0.0–0.6% by Pentasol precipitation. Since *n*-butyl alcohol gave only 22–23% yield of A-fraction from corn starch, while Pentasol gave 28–29%, it was previously assumed that Pentasol was a "more effective" fractionating agent.

2. In the present studies, maximum iodine affinity is rapidly attained by one or two recrystallizations with *n*-butyl alcohol, while repeated recrystallizations with Pentasol give a very slow increase in iodine affinity, without reaching the maximum value of the product recrystallized with *n*-butyl alcohol. Yet the lower iodine affinity of the Pentasol-recrystallized product cannot possibly be attributed to contamination by B-fraction.

3. There is no correlation between iodine affinity and intrinsic viscosity or reducing value of the various linear subfractions. Likewise, there are substantial differences between the iodine affinities of the acid-modified corn A-fractions and of the linear subfractions of comparable intrinsic viscosity.

4. In the subfractionation of Pentasol-recrystallized A-fractions, the composite iodine affinity of the subfractions is substantially higher than that of the parent A-fraction. There is less discrepancy with the A-fractions recrystallized by *n*-butyl alcohol. In all cases, the final subfractions have the lowest iodine affinity.

To explain these anomalies, it is suggested that corn, potato and tapioca starches contain a minor proportion of material intermediate between strictly linear and highly branched molecules.[17] These transition types may conceivably range from branched molecules with long exterior branches to predominantly linear molecules containing a relatively small number of branches. This intermediate material is apparently precipitated by Pentasol but not by *n*-butyl alcohol; on this basis, its presence in corn starch is estimated at 5–7% of the total starch substance. In collaborative studies, W. Z. Hassid is endeavoring to isolate and identify this material. From present concepts of the dual enzymatic synthesis of starch, it seems entirely reasonable that such an intermediate range of molecular types might be formed. Except for the somewhat questionable criterion of β-amylase conversion, it is not possible at this time to distinguish between strictly linear and slightly branched starch substances. To prepare fractions with minimum inclusion of such intermediate types, it would seem advisable to conduct the primary separation with Pentasol and to recrystallize the A-fraction with *n*-butyl alcohol.

Summary

As a preferred mode of fractionation, starch is gelatinized in a buffered Pentasol–water mixture, gently boiled under reflux for several hours, then cooled and refrigerated to precipitate the linear A-fraction. This technique avoids the slight hydrolytic degradation occasioned by autoclaving and likewise permits direct fractionation of nondefatted cereal starches.

Improved methods have been developed for characterizing the starch fractions in terms of (a) intrinsic viscosity in 1 *N* potassium hydroxide solution, (b) iodine affinity by potentiometric titration, (c) reducing value toward alkaline 3,5-dinitrosalicylate reagent, and (d) retrogradation tendency of the linear component. These methods have been employed to describe and differentiate the linear A-fractions and branched B-fractions from corn, wheat, sago, Easter lily, potato and tapioca starches. In addition, these criteria have had useful application in detecting minor hydrolytic changes in the starch substance,

(16) Kerr, *Paper Trade J.*, **115**, no. 22, 30 (1942).

(17) The existence of an intermediate fraction has been suggested by Kerr and Trubell, *Paper Trade J.*, **117**, no. 15, 25 (1943).

in evaluating various modified starches, and in elucidating the action of β-amylase on the starch fractions. A study of the reducing values of the A-fraction toward hypoiodite, bromine, alkaline copper, ferricyanide and alkaline dinitrosalicylate indicates that none of these reagents is specific for terminal aldehyde groups.

A technique has been devised for subfractionating the A-fraction by successive partial precipitations with *n*-octyl alcohol. The A-fraction appears to consist of a continuous series of homologous linear polymers, rather than a limited number of discrete components. The linear material of longest chain length (as indicated by intrinsic viscosity and reducing value) is precipitated first by octyl alcohol, followed successively by subfractions of progressively shorter chain length. The ease of retrogradation of a linear starch substance is inversely related to its chain length. Linear subfractions of equal intrinsic viscosity and reducing value have the same retrogradation tendency, irrespective of their source. Thus the lower retrogradation of tapioca and potato starches must be attributed to the longer chain length of their A-fractions and not to anomalous branching.

However, indirect evidence from iodine affinities suggests the presence of a material intermediate between the strictly linear and the highly branched fractions, possibly amounting to 5–7% of the total starch substance in the case of corn starch. This material is precipitated by Pentasol but not by *n*-butyl alcohol. To minimize contamination of the fractions by this intermediate material, it is recommended that Pentasol be used for the primary separation and *n*-butyl alcohol for recrystallization.

ARGO, ILLINOIS RECEIVED FEBRUARY 8, 1949

[CONTRIBUTION FROM THE DIVISION OF PLANT NUTRITION AND FOOD TECHNOLOGY, COLLEGE OF AGRICULTURE, UNIVERSITY OF CALIFORNIA]

Starch. III. Structure of Apple Starch

BY A. L. POTTER, W. Z. HASSID AND M. A. JOSLYN

While all starches possess certain fundamental common structural features, it is now recognized that starches from different sources vary in the following respects: (1) proportion of the two constituents, amylose and amylopectin, (2) average length of the amylose chains, (3) average chain length of the amylopectin branches in the molecule, (4) molecular size of amylose and of amylopectin.

Practically all the available information regarding starch structure has been derived from work on cereal and tuber starches, chiefly corn and potato. It was therefore of interest to examine a fruit starch in order to ascertain whether or not its structure differs from that of the cereal and tuber starches previously studied.

The starch was isolated from apples and separated by Schoch's "Pentasol" precipitation method[1] into amylose and amylopectin. The yield of amylose was 24.8% of the total starch. Analysis of the whole starch by Schoch's[2] modification of Bates and collaborators'[3] potentiometric iodine titration method showed an amylose content of 26.5%. The intrinsic viscosity of the amylose was 0.99 and that of the amylopectin was 0.96.

Treatment with crystalline β-amylase hydrolyzed the amylose to the extent of 90% maltose. With amylopectin the hydrolysis ceased when 63.5% was degraded to maltose.

Upon acetylation of the two fractions with acetic anhydride at room temperature and the determination of their osmotic pressures, a number-average molecular weight of 160,000 (560 glucose residues) was obtained for the acetylated amylose and 1,200,000 (4200 glucose residues) for the acetylated amylopectin.

In a previous study[4] the number-average molecular weights of six acetylated amylose components from starches of six different plant sources ranged from 180,000 to 370,000. The acetylated amylopectins from the same sources ranged from 2,000,000 to 10,000,000.

The same osmotic pressure–concentration relationship was used as previously reported for the other acetylated amyloses and amylopectins.[4] Using the values $n = 1.39$ and 2.25 for acetylated apple amylose and acetylated amylopectin, respectively, and plotting π/C against C^n, straight lines were obtained. Employing this method, the intercept of the coördinate could be determined with greater accuracy, thus resulting in more reliable molecular weight determinations.

End-group determination by the periodate oxidation method showed an average of 24 glucose residues per end-group for the amylopectin. For the amylose an average chain-length of 530 glucose residues was obtained. The latter value is in fair agreement with 560 obtained by osmotic pressure measurements, indicating that, like po-

(1) T. J. Schoch, "Advances in Carbohydrate Chemistry," edited by Pigman and Wolfrom, Academic Press, Inc., New York, N. Y., Vol. I, 1945, pp. 258–261.

(2) T. J. Schoch, THIS JOURNAL, **71**, 4066 (1949).

(3) F. L. Bates, D. French and R. E. Rundle, *ibid.*, **65**, 142 (1943).

(4) A. L. Potter and W. Z. Hassid, *ibid.*, **70**, 3774 (1948).

tato and Easter lily amylose,[4] a single chain represents one amylose molecule. The apple amylopectin data are in accord with the data obtained for other amylopectins, showing that the molecule consists of a great number of branched chains averaging approximately 24 glucose residues per end-group.

The study of the apple starch did not reveal any anomalous features concerning its structure. It appears to be similar to that of the cereal and tuber starches previously examined, except that the molecular weights of the apple starch are lower.

Experimental

Preparation of Apple Starch.—The starch was prepared from Newtown Pippin apples grown in Willow Glen district of San Jose, California. Approximately 25 lb. of apples were harvested early in August, stored for a week at 0°, then crushed in an apple grater and pressed in a hydraulic press, using wooden racks and canvas cloths. The press juice was collected and treated with 5 g. of potassium metabisulfite ($K_2S_2O_5$) to inhibit browning. The press cake was mixed with an equal weight of water and pressed again. The juice was stored at room temperature until the starch settled, the supernatant liquid was decanted and the sediment washed with water to remove pulp particles by flotation. The starch was then resuspended in water and the washing was repeated several times until all the pulp particles and soluble material was removed. The starch was filtered on a Buchner funnel, washed with ethanol and dried *in vacuo* at 60°. The fatty acids were removed from the dry material according to Schoch's[5] method by means of five successive twenty-four-hour extractions with hot 85% methanol. The yield was 23 g. When viewed under the microscope the granules appear spherical or sometimes slightly irregular. Their size varies from 2.5 to 10 μ.

Separation of the Starch into Amylose and Amylopectin.—The two fractions were separated according to Schoch's method.[1] A 2% suspension was made, using 20 g. of defatted apple starch, gelatinized on a steam-bath and autoclaved for three hours at 18 lb. pressure. After the addition to the hot solution of 10% (by volume) "Pentasol" and cooling, the amylose precipitated in the form of spherocrystals. The crude material was purified by reprecipitating four times with butanol.

The amylopectin was isolated from the first mother liquor by the addition of methanol. The precipitate was dissolved in water and the amylose impurities removed by the addition of butanol. A yield of 4.96 g. of amylose and 12.4 g. of amylopectin was obtained. The amylose yield constitutes 24.8%.

The proportion of amylose and amylopectin was determined in the apple starch by using the potentiometric iodine titration method of Bates, French and Rundle as modified by Schoch.[2] The iodine bound by the amylose was found to be 19.0% whereas that of the amylopectin was 0.1%. The unfractionated starch absorbed 5.1% iodine, showing a 26.5% amylose content.

Intrinsic Viscosity.—In evaluating the intrinsic viscosities of the fractions, the relative viscosity was determined in an Oswald type viscosimeter, using 1 *N* potassium hydroxide solution as a solvent. Determination of four concentrations between 0.1 and 0.4% were made in a constant temperature bath at 35 ± 0.01°. The log of the relative viscosity was plotted against concentration and the intrinsic viscosity was evaluated by multiplying the value of the slope of the line by 2.3.[6] The intrinsic viscosity [η] of the amylose was found to be 0.98 and that of amylopectin 0.95.

Acetylation.—Two-gram samples of the starch fractions were dispersed in formamide and acetylated at room temperature with acetic anhydride in the presence of pyridine as previously described.[4] The yield of acetylated amylopectin was 88% and that of the acetylated amylose 90%. An acetyl value of 43.6% was obtained for the acetylated amylose and 44% of the acetylated amylopectin. The calculated $COCH_3$ content for the triacetate $(C_6H_7O_5(CH_3CO)_3)_n$ is 44.8%. The specific rotation of both the acetylated amylopectin and amylose in chloroform (*c*, 2) was $[\alpha]_D$ +170°.

TABLE I

OSMOTIC PRESSURE DATA FOR ACETYLATED APPLE STARCH FRACTIONS

Concn., *C*, g. per l.	$C^{1.39}$	Osmotic pressure, π (g. per sq. cm.)	π/C
	Amylose		
2.83	4.2	0.350	0.182
5.74	11.4	0.920	.235
7.17	15.4	1.30	.266
10.05	24.7	2.18	.319
	Amylopectin		
	$C^{2.25}$		
12.3	280	0.325	0.0389
15.1	450	0.540	.0525
17.6	630	0.760	.0634
20.0	840	1.06	.0778

Determination of Molecular Weights.—The molecular weights of the acetylated apple amylopectin and amylose were determined by osmotic pressure measurements, using chloroform as a solvent. The method employed was the same as that previously used for the determination of a number of acetylated starch fractions from various plant sources.[4] The osmotic pressure was measured for each acetylated starch fraction at several different concentrations (Table I).

The intercept of the coördinate was determined by plotting π/C against C^n and the molecular weight was calculated using the van't Hoff equation. From the intercepts of the ordinates values of π/C were obtained equal to 0.157 and 0.0210 for acetylated amylose and amylopectin, respectively. These values corresponded to a number-average molecular weight of 160,000 for acetylated amylose of 1,200,000 for acetylated amylopectin.

End-Group Determination of Amylopectin and Amylose by Periodate Oxidation.—A series of five 0.2-g. samples of amylopectin were oxidized with 0.37 *M* sodium periodate at 2° according to the method previously described.[7] After ten hours the samples were taken at five-hour intervals and analyzed for formic acid by titrating with 0.01 *N* barium hydroxide. The number of ml. of base (5.2) at twenty-five hours was taken as the end-point for the amylopectin. The average number of glucose residues per end-group for amylopectin, calculated on the basis of one mole of formic acid produced per chain, was found to be 24.

Duplicate 0.5-g. amylose samples were similarly oxidized with sodium periodate for twenty-five hours. The acid produced required 1.75 ml. of 0.01 *N* barium hydroxide for neutralization. The average chain-length of amylose, calculated on the basis of 3 moles of formic acid produced per chain, was 530 glucose residues.

Hydrolysis with β-Amylase.—A 0.02-g. sample of polysaccharide was dissolved in 1 ml. of 1 *N* potassium hydroxide, diluted to 35 ml. and mixed with 5 ml. of 2 *M* acetate buffer at *p*H 4.7. One drop of crystalline β-amylase[8] solution, containing approximately 500 Schwimmer units, and a drop of toluene were added to the mixture

(5) T. J. Schoch, THIS JOURNAL, **64**, 2954 (1942).

(6) S. Arrhenius, *Z. physik. Chem.*, **1**, 285 (1887); E. O. Kraemer and W. D. Lansing, *J. Phys. Chem.*, **39**, 153 (1935); *Ind. Eng. Chem.*, **30**, 1200 (1938).

(7) A. L. Potter and W. Z. Hassid, THIS JOURNAL, **70**, 3488 (1948).

(8) A. K. Balls, M. K. Walden and R. R. Thompson, *J. Biol. Chem.*, **173**, 9 (1948).

and the hydrolysis was allowed to proceed for twenty-four hours. Another drop of β-amylase was then added and the mixture was allowed to remain at room temperature for another twenty-four hours. The reducing value was then determined by oxidation with ferricyanide[9,10] and calculated as maltose.

The amount of polysaccharide originally present in the sample was found by determining the glucose obtained when a 2-ml. aliquot portion was treated with 1 *N* sulfuric acid for two and one-half hours at 100°. On this basis, the extent of the amylopectin hydrolyzed with β-amylase to maltose was estimated to be 63.5%. The limit of amylose hydrolysis with this enzyme was 90%.

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Summary

Apple starch was separated into amylose and amylopectin, the amylose content being 24.8% of the total. Osmotic pressure measurements of the acetylated fractions gave a number-average molecular weight of 160,000 (560 glucose residues) for the acetylated amylose and 1,200,000 (4200 glucose residues) for the acetylated amylopectin.

End-group determination by periodate oxidation showed an average of 24 glucose residues per end-group for the amylopectin and a chain-length of 530 glucose residues for the amylose. Since the end-group value for amylose is in fair agreement with the value of 560 obtained from osmotic pressure measurements, it is assumed that a single chain represents one amylose molecule.

The data indicate that apple starch is similar in structure to the cereal and tuber starches, with the difference that the molecular weights of its components are smaller.

(9) W. Z. Hassid, *Ind. Eng. Chem., Anal. Ed.*, **9**, 228 (1937).

(10) W. Z. Hassid, R. M. McCready and R. S. Rosenfels, *ibid.*, **12**, 142 (1940).

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Chain Initiation in Styrene Emulsion Polymerization[1]

BY WENDELL V. SMITH

Introduction

The chain length and rate of polymerization in emulsion are controlled principally by the relationship between two quantities, the rate of chain initiation and the rate of chain propagation. In contrast with bulk polymerization, the rate constant for the termination step does not play a significant role in the mechanism of emulsion polymerization.[1a] The rate of chain propagation in styrene polymerization has already been considered[1a] and this paper discusses the rate of the initiation step in styrene polymerization.

Three methods are used for investigating the rate of initiation. The first is based on the observation that fragments of the chain initiator, persulfate, are chemically combined with the polymer.[2] It consists in determining how rapidly these fragments become combined by measuring the rate of polymerization and the radioactivity of polystyrene prepared using radioactive persulfate as initiator. The second consists in determining the initial rate of polymer particle formation from measurements of the size of the particles and the rates of growth of the particles, making use of a previously developed theory relating these.[1a] The third consists in determining the rate of molecule formation from the molecular weight of polymer and the rate of polymerization.

Experimental Procedures

Radioactive Potassium Persulfate.—The radioactive S^{35} was received as a trace constituent of potassium chloride from Clinton Laboratories (now Oak Ridge National Laboratory) on allocation by the U. S. Atomic Energy Commission.

The active sulfur in the irradiated unit was isolated as barium sulfate by boiling with bromine in water solution then precipitating with barium ion. The barium sulfate (1.3 mg.) was converted to sulfate free potassium persulfate by dissolving in concentrated sulfuric acid, adding potassium sulfate and electrolyzing cold. The precipitated potassium persulfate after washing and drying (0.35 g.) contained 12% of the total sulfur; it was made up to a 1.81% solution. After the preliminary measurements the persulfate was regenerated by a new electrolysis at which time it was further diluted with inactive sulfur.

Determination of Sulfur Content of Polystyrene from its Radioactivity.—All radioactivities were determined using a Radiation Counter Laboratories thin mica window Geiger–Müller counter tube and scaling circuit.

The resolving time[3] of 2.5×10^{-4} sec. requires a correction of only 0.25% for a counting rate of 10 per sec.

The range of the β-radiation from S^{35} is quite

(1) Presented at the North Jersey Section Meeting-in-Miniature, January 10, 1949, Newark, N. J.

(1a) W. V. Smith and R. H. Ewart, *J. Chem. Phys.*, **16**, 592 (1948); W. V. Smith, THIS JOURNAL, **70**, 3695 (1948).

(2) W. V. Smith and H. N. Campbell, *J. Chem. Phys.*, **15**, 338 (1947); W. E. Mochel and J. H. Peterson, THIS JOURNAL, **71**, 1426 (1949).

(3) A. F. Reid, A. S. Weil and J. R. Dunning, *Anal. Chem.*, **10**, 824 (1947).

short; Libby[4] gives the aluminum range as 13.5 mg./sq. cm. Thus for active samples which are appreciably thicker than this, the radiation escaping from unit surface is independent of the thickness of the sample and, for a given concentration, depends only on the absorption characteristics of the material comprising the sample.

For this investigation the absorption characteristics of the materials comprising the samples are characterized sufficiently when a relationship is determined between the radiation from an infinitely thick sample (*i. e.*, thickness greater than the range) and that from a sample thin enough that absorption of radiation within the sample can be neglected. Thus, if I_0 is the radiation from a mass, m, of sample thin enough that self-absorption can be neglected, and if I_∞ is the radiation from an area, A, of the sample which has a thickness greater than the range of the radiation in the sample, then there exists a relation

$$I_0/m = \alpha I_\infty/A$$

where α is a characteristic of the absorption of the material.

The value of α for water as defined by the above equation was determined as follows: A water solution of the active persulfate (0.02 mg./ml.) was placed in an aluminum dish 1 inch in diameter giving a sample thickness of 300 mg./sq. cm. The radiation intensity from the surface of the sample escaping through a circular window 1 cm. in radius was

$$I_\infty/A = (3.176 - 0.394)/\pi = 0.886 \text{ cm.}^{-2} \text{ sec.}^{-1}$$

where 3.176 sec.$^{-1}$ was the rate of reception of impulses by the counter when the sample was in place and 0.394 sec.$^{-1}$ was the background rate. Next a sample of the solution was evaporated to dryness in an aluminum dish, giving a film of thickness 0.02 mg./sq. cm., which was thin enough to neglect self-absorption. The intensity of radiation obtained from this gave

$$I_0/m = (15.5 - 0.4)/100 = 0.151 \text{ mg.}^{-1} \text{ sec.}^{-1}$$

Thus for water

$$\alpha_\omega = 0.151/0.886 = 0.170 \text{ cm.}^2/\text{mg.}$$

To compare the absorption of polystyrene with that of water a sample of polystyrene was prepared in emulsion using radioactive potassium persulfate. This active sample, polymer A was mixed with 32 parts of a low molecular weight inactive polystyrene. A portion of the mixed benzene solution was evaporated to dryness in an aluminum dish to give a polystyrene film of thickness 56 mg./sq. cm. The intensity of radiation from this film measured through a 1-cm. radius window gave for the undiluted polymer A

$$I_\infty/A = 33(1.337 - 0.338)/\pi = 10.5 \text{ cm.}^{-2} \text{ sec.}^{-1}$$

For measuring the radiation from a thin film of the polymer a film containing 0.853 mg. of the undiluted polymer A was used. Since the thickness of this film was 0.17 mg./sq. cm. it was necessary to apply a small correction for self-absorption. This was done assuming exponential absorption so that the intensity I from area A of a film of thickness l is given by

$$I/A = (I_0/m) \int_0^l e^{-\alpha l}\, dl$$

For sufficiently small values of αl this gives

$$I_0/m = (I/m)(1 + \alpha l/2)$$

For

$$\alpha = 0.17 \text{ cm.}^2/\text{mg.}$$

and

$$l = 0.17 \text{ mg./cm.}^2$$

the correction factor is 1.015 so

$$I_0/m = 1.015\,(1.826 - 0.338)/0.853 = 1.77 \text{ mg.}^{-1} \text{ sec.}^{-1}$$

Thus

$$\alpha_p = 1.77/10.5 = 0.169 \text{ cm.}^2/\text{mg.}$$

which is practically the same as that found for water.

The value of the "absorption coefficient," α, found for water and polystyrene in this investigation is considerably smaller than the value of 0.32 sq. cm./mg. reported by Henriques[5] and coworkers for absorption in benzidine sulfate. It is believed that this difference reflects largely the different techniques used in determining the "absorption coefficient" rather than different absorption characteristics of the polystyrene or water and benzidine sulfate.

The comparison between water and polystyrene in this investigation was made using a continuous film of the polymer in the radiation measurements. However, for the subsequent measurements of the activities of different polymer samples it was more convenient to determine the activity of the polymer when it was in the form of a fine powder, as that is the condition in which it was isolated from the latex. Consequently a series of comparisons was made of the intensity of radiation from the same polystyrene in a continuous film and in powder form. These comparisons consistently showed that the radiation from the film was less than that from the powder, giving the relation: activity of film = 0.965 × activity of powder. This correction factor was used in all calculations.

The sulfur contents of the active polymers were determined by making a direct comparison between the activity of the purified polymer and that of the over-all latex. Since the total sulfur content of the latex was known from the ingredients comprising the charge, the sulfur content of the polymer was calculated from the ratio of the activities. Errors due to fluctuations in the sensitivity of the counting mechanism were minimized by counting the polymer and latex with a minimum time interval between measure-

(4) W. F. Libby, *Anal. Chem.*, **19**, 2 (1947).

(5) F. C. Henriques, Jr., G. B. Kistiakowsky, C. Margnetti and W. G. Schneider, *Ind. Eng. Chem., Anal. Ed.*, **18**, 349 (1946).

ments. With the very low activity polymer produced at 30.5° the counting rate with the sample in the counter was only slightly greater than the background, so a long series of alternate counting with and without the sample in place was made.

Polymerization.—The polymers used for the radioactivity determinations were made separately from those used for polymer yield and molecular weight determinations to avoid unnecessary manipulations with active polymer. A typical charge was made up by adding to a test-tube: 3.00 ml. of a 0.55% (by weight) S. F. Flakes soap solution, 0.300 ml. of a 1.81% radioactive potassium persulfate solution and 2.00 ml. of distilled styrene. The test-tube and charge were cooled with ice and the vapor space swept out with nitrogen, after which the test-tube was sealed. The charge was then placed on a rotating carriage in a water-bath thermostated at the desired temperatures until substantially complete polymerization had taken place. The test-tube was opened and a 1-ml. portion of latex was diluted with 100 ml. of water, then flocculated by addition of hydrochloric acid. After warming, filtering and washing with water and methanol, the polymer was dried on the filter by radiation with an infrared lamp while air was simultaneously sucked through it. It was then ready for comparing its radioactivity with that of a sample of the original latex as described above.

The method of purification proved to be quite important for obtaining significant results. Thus the first procedure investigated consisted in coagulating by adding the latex to a large amount of methanol, then dissolving the precipitated polymer in benzene and reprecipitating with methanol. However, when this method was tested on latex prepared from inactive potassium persulfate, but to which active persulfate was added after polymerization, the polymer was found to be active and no amount of subsequent purification would render it appreciably less active. In contrast, when this same experiment was done using the method of purification finally adopted as described above the dried polymer was inactive.

The charges used for rate of polymerization and molecular weight determination were made up practically the same as those described above. However, they were coagulated by transferring the entire charge to 100 ml. of methanol containing 2 ml. of a 5% aqueous solution of hydroquinone as a short-stop. The precipitated polystyrene was filtered, washed twice with boiling methanol, then dried overnight on a vacuum line. Representative data on polymerization time and polymer yield for the series used in comparing with the radioactivity measurements are given in Table I. The last time in each sequence corresponds with the time used for polymerizing the samples with radioactive persulfate.

TABLE I

RATES OF STYRENE EMULSION POLYMERIZATIONS

30.5°; 0.5% soap; 0.172% persulfate

Time, min.	60	120	180	240	300	330
G. polymer per ml. water	0.0177	0.0357	0.0807	0.120	0.164	0.182
Intrinsic viscosity	8.39	11.9	15.6	16.1	17.4	17.3

50°

Time, min.	30	60	90	120	150	180	240
G. polymer per ml. water	0.0314	0.0854	0.194	0.269	0.366	0.440	0.482
Intrinsic viscosity	5.82	7.60	8.83	9.23	9.72	9.63	9.01

70°

Time, min.	10	20	30	40	50	60	90
G. polymer per ml. water	0.074	0.175	0.273	0.357	0.452	0.48	0.51
Intrinsic viscosity	4.28	4.80	5.38	5.05	5.29	5.07	3.86

90°

Time, min.	5	10	15	20	25	30
G. polymer per ml. water	0.095	0.244	0.364	0.458	0.497	0.505
Intrinsic viscosity	1.25	1.36	1.43	1.42	1.39	1.42

From the last charge of each sequence a small quantity of latex was saved for particle size determination, which was done by means of electron microscope photographs of the particles. For each latex examined the diameters of 100 particles were measured. From these diameters the average volume of the particles was calculated and used with the polymer yield to calculate the number of particles per ml. of water solution.

Molecular Weight.—The molecular weights were estimated from intrinsic viscosities which were determined in benzene, using a Fenske viscometer. A single concentration of polystyrene was used and the intrinsic viscosity was calculated from the relation

$$\eta_{sp}/c_v = [\eta] + 0.375[\eta]^2 c_v$$

where c_v is the concentration of the polymer in grams per 100 ml. of solution.

The relationship between intrinsic viscosity and molecular weight for polystyrene prepared in oil phase[6] has been established over a molecular weight range from 10^4 to 6×10^5. Since most of the polymers in the present investigation had molecular weights above this range, extrapolation of the relationship was carried out using Debye's theory of solution viscosities.[7] In Debye's theory the relationship between intrinsic viscosity and molecular weight can be represented by the conventional equation

$$[\eta] = KM^a$$

where the exponent, a, is substantially constant over a limited molecular weight range but decreases slowly to a value of $1/2$ as the molecular weight increases. Debye has established the nature of the relation between a and molecular weight. Thus, the procedure used was to fit the above equation to the experimental data,[6] then to extrapolate using Debye's calculated relationship between a and molecular weight. While leaving much to be desired, this method of estimating the molecular weight appeared to be the best available. The low molecular weight polystyrene prepared in emulsion at 90° had the same relationship between intrinsic viscosity and osmotic molecular weight as the polymers referred to above[6]; thus, the emulsion process of polymerization does not produce any particularly unusual molecular weight distribution.

Results

The first step in the investigation consisted in determining how many atoms of sulfur are com-

(6) Mayo, Gregg and Matheson, to be published; also see R. H. Ewart and H. C. Tingey, paper presented at 111th meeting of A. C. S., April, 1947.

(7) P. Debye, *J. Chem. Phys.*, **14**, 636 (1946); P. Debye and A. M. Bueche, *ibid.*, **16**, 573 (1948).

bined with one molecule of polymer. The results are given in Table II.

TABLE II

SULFUR CONTENTS OF POLYSTYRENE POLYMERIZED WITH RADIOACTIVE PERSULFATE

Temp., °C.	Activity of pol., % of that of latex	G. polymer per mole sulfur	Mol. weight	Atoms of sulfur per polymer molecule
		0.5% soap; 0.165% persulfate		
30.5	0.281	43.5×10^6	20×10^6	0.46
50	2.70	4.52×10^6	6.2×10^6	1.4
70	19.9	0.62×10^6	1.4×10^6	2.3
90	85.1	0.144×10^6	0.274×10^6	1.9
		0.5% soap; 0.511% persulfate		
70	12.4	0.33×10^6	0.53×10^6	1.6
		2.0% soap; 0.165% persulfate		
70	11.7	1.05×10^6	2.1×10^6	2.0

The sulfur content in column 3 is obtained from the radioactivity of the polymer as discussed above. The molecular weight is obtained from the intrinsic viscosity of the last sample in each sequence of Table I. This intrinsic viscosity was converted to number average molecular weight as described above. The last column giving the atoms of sulfur per polymer molecule is, of course, the quotient of the two preceding columns. This quotient approximates two for the higher temperature polymers but is much less than that for the polymer prepared at 30°.

The number of particles produced in the emulsion polymerization of styrene depends primarily on the rate of particle formation, the rate of particle growth and the amount of soap available. A previous approximate discussion of this problem[1a] indicates that the number N, of polymer particles produced per ml. of water solution up to the time that all the soap becomes adsorbed on polymer particles should be given by a law of the type

$$N = k(\rho/\mu)^{2/5}(a_s S)^{3/5}$$

where k is a numerical constant with a value between 0.37 and 0.53, ρ is the initial rate of formation of polymer particles per ml. of water solution, μ is the rate of increase in volume of a polymerizing polymer particle, and $(a_s S)$ is the interfacial area of the initial soap micelles per ml. of water solution. Thus measurements of the number of particles and rate of polymerization should yield information on the initial rate of formation of polymer particles. The second column of Table III gives the average volumes of the polymer particles produced in the last sample of each sequence of runs listed in Table I.

From this volume and the polymer content of Table I the number of particles per ml. is calculated and given in column 3. From the polymer content as a function of time given in Table I, the rate of polymerization is calculated by

TABLE III

TOTAL NUMBER AND INITIAL RATE OF FORMATION OF PARTICLES

Temp., °C.	Average volume of particles, cc.	Number of particles,[a] N	Rate of pol. per particle, g./sec.	Initial rate of particle formation,[a] ρ, sec.$^{-1}$
		0.5% soap; 0.172% persulfate		
30.5	1.90×10^{-15}	2.54×10^{14}	4.2×10^{-20}	2.6×10^{11}
50	8.05×10^{-16}	6.0×10^{14}	7.8×10^{-20}	4.2×10^{12}
70	4.45×10^{-16}	1.08×10^{15}	1.44×10^{-19}	3.3×10^{13}
90	3.15×10^{-16}	1.53×10^{15}	2.63×10^{-19}	1.5×10^{14}
		0.5% soap; 0.516% persulfate		
70	3.86×10^{-16}	1.25×10^{15}	1.27×10^{-19}	4.3×10^{13}
		2.0% soap; 0.172% persulfate		
70	1.95×10^{-16}	2.47×10^{15}	1.13×10^{-19}	2.6×10^{13}

[a] Per ml. of water solution (excluding polymer).

fitting the data (except for the high conversions) with a least-squares straight line. This rate divided by the number of particles gives the rate of polymerization per particle given in column 4. The value of the initial rate of particle formation given in the last column is calculated from the equation given above. In making the calculation the lower value of k, namely, 0.37, was used. The interfacial area for soap micelles was taken to be 6×10^6 cm.^{2}/g. The rate of polymerization per particle given in column four was multiplied by 2.6 to obtain the rate of volume increase, μ. The factor of 2.6 comes from the measured ratio between volume of swollen particle and weight of polymer found for polystyrene latex particles swollen to equilibrium with liquid styrene at 50°.[1a] These values for the initial rate of particle formation cannot be considered to be at all accurate since small errors in the particle size measurements become greatly magnified in calculating ρ due to raising to the power 15/2.

Under conditions of constant molecular weight and rate of polymerization the rate of polymer molecule formation is given by dividing the rate of polymerization by the molecular weight. The effect of concentration of polymer particles on rate of molecule formation is shown in Table IV.

TABLE IV

RATE OF POLYMER MOLECULE FORMATION—EFFECT OF NUMBER OF POLYMER PARTICLES

Soap conc., %	Number of particles[a]	Rate of polymn.,[a] g./sec.	Intrinsic viscosity	Molecular weight	Rate of molecule formation,[a] sec.$^{-1}$
		50°; 0.172% persulfate			
2.0	.....	8.80×10^{-5}	10.6	8.2×10^6	6.5×10^{12}
0.5	6.0×10^{14}	4.70×10^{-5}	9.5	6.8×10^6	4.2×10^{12}
.67	.....	4.23×10^{-5}	9.3	6.6×10^6	3.9×10^{12}
.22	.....	2.08×10^{-5}	6.6	3.5×10^6	3.6×10^{12}
(Seed)[b]	5.8×10^{13}	8.46×10^{-6}	4.1	1.5×10^6	3.4×10^{12}
(Seed)[b]	2.9×10^{13}	4.68×10^{-6}	2.8	0.85×10^6	3.3×10^{12}

[a] Per ml. of water solution (excluding polymer). [b] These charges were prepared using a small amount of previously polymerized polystyrene latex as seed but with no added soap.

The number of polymer particles and hence rates of polymerization were varied by varying

the soap concentration and in two cases by using seed polystyrene particles with no added soap. The rates of polymerization given are from least-squares treatment of the yield data in the range in which the yield appears linear with time. The intrinsic viscosity given in column four is the average for the three or four last runs in each sequence which appear to have substantially constant intrinsic viscosities. The molecular weight was estimated from the intrinsic viscosity as discussed above. The rate of molecule formation is the rate of polymerization multiplied by Avogadro's number and divided by the molecular weight. This table indicates that the rate of molecule formation approaches a constant for the lower particle concentrations but becomes greater for the higher concentrations; in fact, the data suggest that the molecular weight may be approaching a maximum limiting value at the highest particle concentrations. The simplest interpretation is that the molecular weight is limited in the high region by chain transfer with styrene monomer and that the rate of initiation is constant. When the number of particles is small enough, free radicals enter the particles sufficiently rapidly that almost all the polymer molecules are formed by mutual termination of radicals and only a negligible fraction by self-transfer. The 50° data are consistent with the assumptions of a constant rate of initiation and a self-transfer constant of 10^{-5}. This order of magnitude is the same as that to be reported by Mayo, Gregg and Matheson[6] for transfer with the monomer in oil phase.

The effect of persulfate concentration on the rate of molecule formation is shown in Table V.

The various quantities in this table are obtained in the same manner as the corresponding quantities in Table IV. These data show the expected increase in rate of molecule formation with increase in concentration of persulfate. At the higher temperature, 70°, the rate of molecule formation is very nearly proportional to the persulfate concentration. At 50° this does not appear to be the case but the lack of proportionality may be due to the fact that an appreciable fraction of the molecules are formed by transfer with styrene when the persulfate concentration is low.

To obtain the temperature coefficient, studies were made at the four temperatures given in Table VI. Again the various quantities are obtained in the same manner as those in Table IV. Analysis of these data by the Arrhenius rate equation using the method of least squares gives 28 kcal. for the activation energy of molecule formation.

The rate of sulfur combination, initial rate of particle formation and rate of polymer molecule formation must all be related to the rate of chain initiation process and hence they must themselves be interrelated. They are compared in Table VII.

The rate of sulfur combination is obtained by dividing the rate of polymerization (Tables IV, V and VI) by the grams of polymer per mole of sulfur (Table II), then multiplying by Avogadro's number. The initial rate of polymer particle formation is the same value as that given in Table III. For comparison the rates of molecule formation from Tables IV, V and VI are multiplied by 2 and inserted in Table VII. The factor of 2 is used because the formation of each molecule requires two free radicals. These three quantities agree within an order of magnitude indicating that, indeed, all three are determined principally by the rate of initiation reaction. The comparison of the rate of sulfur combination with the

TABLE V

RATE OF POLYMER MOLECULE FORMATION—EFFECT OF PERSULFATE CONCENTRATION

Persulfate concn., %	Number of particles[a]	Rate of polymn.,[a] g./sec.	Intrinsic viscosity	Molecular weight	Rate of molecule formation,[a] sec.$^{-1}$
		50°; 0.5% soap			
0.172	6.0×10^{14}	4.70×10^{-5}	9.5	6.8×10^{6}	4.2×10^{12}
.190	.....	4.62×10^{-5}	8.2	5.1×10^{6}	5.5×10^{12}
.516	.....	5.26×10^{-5}	7.13	4.0×10^{6}	8.0×10^{12}
		70°; 0.5% soap			
.172	1.08×10^{15}	1.56×10^{-4}	5.2	2.3×10^{6}	4.1×10^{13}
.516	1.25×10^{15}	1.59×10^{-4}	2.56	0.73×10^{6}	1.3×10^{14}

[a] Per ml. of water solution (excluding polymer).

TABLE VI

RATE OF POLYMER MOLECULE FORMATION—EFFECT OF TEMPERATURE

(0.5% soap, 0.172% persulfate)

Temp., °C.	Number of particles[a]	Rate of polymn.,[a] g./sec.	Intrinsic viscosity	Molecular weight	Rate of molecule formation,[a] sec.$^{-1}$
30.5	2.54×10^{14}	1.06×10^{-5}	16.9	20×10^{6}	3.2×10^{11}
50	6.0×10^{14}	4.70×10^{-5}	9.5	6.8×10^{6}	4.2×10^{12}
70	1.08×10^{15}	1.56×10^{-4}	5.2	2.3×10^{6}	4.1×10^{13}
90	1.53×10^{15}	4.03×10^{-4}	1.4	0.30×10^{6}	8.1×10^{14}

[a] Per ml. of water solution (excluding polymer).

TABLE VII

COMPARISON OF QUANTITIES DETERMINED CHIEFLY BY RATE OF FREE RADICAL FORMATION

Temp., °C.	30.5	50	70	90	70	70
Soap concn., %	0.5	0.5	0.5	0.5	0.5	2.0
Persulfate concn., %	.172	.172	.172	.172	.516	.172
Rate of sulfur combination[a]	1.5×10^{11}	6.3×10^{12}	1.5×10^{14}	1.7×10^{15}	2.9×10^{14}	1.6×10^{14}
Rate of particle formation[a]	2.6×10^{11}	4.2×10^{12}	3.3×10^{13}	1.5×10^{14}	4.3×10^{13}	2.6×10^{13}
2 × rate of molecule formation[a]	6.4×10^{11}	8.4×10^{12}	8×10^{13}	1.6×10^{15}	2.6×10^{14}	1.1×10^{14}

[a] Rates are given in number, atoms or molecules per second per ml. of water solution.

rate of molecule formation is really the same comparison which was made in Table II. While the initial rates of polymer particle formation are consistently lower than the rates of molecule formation, not much significance can be attached to this because of the larger error and uncertainty involved in calculating the initial rate of particle formation. Of the three methods for determining the rate of free radical formation by the initiation reaction, the rate of molecule formation is the most reliable.

Summary

The rate of persulfate combination from radioactivity measurements, the initial rate of polymer particle formation from polymer particle size measurements, and the rate of molecule formation from molecular weight measurements have been obtained for styrene emulsion polymerization, and all three quantities agree within an order of magnitude. This indicates that all three are determined principally by the rate of formation of free radicals.

The rate of free radical formation does not appear to depend on the interfacial area between organic and aqueous phases.

PASSAIC, N. J. RECEIVED APRIL 27, 1949

[CONTRIBUTION NO. 262 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

The Structure of Neoprene. IV. Infrared Spectra and Spectral Changes with Crystallization[1]

BY W. E. MOCHEL AND M. B. HALL

Infrared spectroscopy has been valuable in elucidation of some structural features of high polymers and was therefore applied to the current examination of neoprene (polychloroprene). The infrared spectrum of neoprene has been reported previously[2] and the statement has been made that there are differences between polychloroprenes made under different conditions of polymerization.[3] However, no description of the differences has appeared. In the present study, examination of Neoprenes Type GN and Type CG and analysis of the dichroic effects in their spectra together with comparison with the infrared absorption of polybromoprene have yielded a more complete and reliable interpretation of the spectrum of neoprene than was previously available. These particular neoprenes were selected for study because they are illustrative of the effect of polymerization temperature on the rate of crystallization,[4] *i. e.*, Neoprene Type CG, made at 10°, crystallizes in a few hours at room temperature while Neoprene Type GN, made at 40° in essentially the same emulsion system, requires many days for crystallization to a comparable extent. The crystallization of neoprenes in general has been well established[5] by X-ray diffraction, dilatometry and other methods but the structural differences responsible for observed differences in crystallization rates have not been clearly demonstrated.

Experimental

Materials.—For many of the experiments commercial samples of Neoprene Type CG and Neoprene Type GN were used. To remove undesirable polymerization adjuvants from such samples, they were extracted with acetone in A.S.T.M. extractors or were dissolved in benzene and completely precipitated with methanol. Laboratory samples were also prepared using the emulsion system previously described.[4] The polymers were isolated from the alkaline latices by coagulation with large volumes of alcohol, since it was found that this procedure gave products practically free from sodium rosinate, rosin and other polymerization residues. The polymers were dried *in vacuo* at room temperature and kept under nitrogen.

To prepare films the dry polymers were dissolved in benzene to form solutions of known concentration which were used to cast films inside glass rings on a mercury surface. After the film was dry the ring could be lifted and the attached film examined directly or transferred to another specimen holder. Films were also prepared directly from the latices by filtration on porous battery cups.[6] Films 20–35 microns in thickness were generally used for infrared studies.

Instruments.—Two different instruments were used to obtain the data presented here. For most of the work in the wave length range 2–14 microns there was used a prism instrument after

(1) Part III, Mochel and Nichols, THIS JOURNAL, **71**, 3435 (1949).

(2) Sears, *J. Appl. Phys.*, **12**, 35 (1941); Barnes, Williams, Davis and Giesecke, *Ind. Eng. Chem., Anal. Ed.*, **16**, 9 (1944); Dinsmore and Smith, *Anal. Chem.*, **20**, 11 (1948).

(3) Thompson and Torkington, *Trans. Faraday Soc.*, **41**, 255 (1945).

(4) Walker and Mochel, Proc. Inter. Rubber Tech. Conf., London, 1948, Preprint No. 11.

(5) (a) Carothers, Williams, Collins and Kirby, THIS JOURNAL, **53**, 4203 (1931); (b) Sebrell and Dinsmore, *India Rubber World*, **103**, No. 6, 37 (1941); (c) Bunn, *Proc. Roy. Soc. (London)*, **A180**, 82 (1942); (d) Clews, *ibid.*, **A180**, 100 (1942); (e) Wood, "Advances in Colloid Science," Vol. 2, edited by Mark and Whitby, Interscience Publishers, Inc., New York, N. Y., 1946, p. 79.

(6) Dales, Abernathy and Walsh, "Neoprene Latex Type 571," No. 43-2, du Pont Rubber Chemicals Division, February, 1943; Flint, "Chemistry and Technology of Rubber Latex," D. Van Nostrand Company, Inc., New York, N. Y., 1938, p. 688.

the design of Wright,[7] employing a 60° rock salt prism with a six-inch base. The 2–4-micron range was examined in the same instrument at a resolution sufficient to show clearly the chlorine isotope split in hydrogen chloride, by replacing the prism with a 7200-lines-per-inch grating. The recording system employed a split beam and the ratio recorder described by Wild.[8]

In most of the work a Nernst filament was used as source for the 15–23-micron region to avoid the sharp minimum at 16.2 microns in the globar emission. The radiation was polarized when desired by reflecting it at the Brewsterian angle from a selenium mirror according to the method of Pfund.[9] Since the beam striking the selenium mirror is converging, all the rays cannot be incident at exactly the Brewsterian angle, and hence complete polarization cannot be achieved.[10] However, this was not an important limitation since complete orientation could not be produced in the polymer samples under study. In general, the absorption bands reported are accurate to 5 wave numbers except in the cases of overlapping bands, where somewhat greater error may be involved.

For some of the work in the range 2-15 microns and for all of the work at longer wave lengths, a Perkin–Elmer spectrometer was used with a rock salt prism for some purposes and a potassium bromide prism for others. The light entering the Perkin–Elmer instrument was polarized when desired by use of the selenium mirror. The reflection from the selenium mirror was arranged to cause reinforcement of the polarization produced by the prism in the spectrometer.

Results and Discussion

Crystallization Effects.—The most striking feature in the spectra of the neoprenes is the existence in crystallized polymer of strong bands which do not appear in the completely amorphous material. Thus Neoprene Type CG, normally crystalline at room temperature, exhibits absorption bands at 578, 781 and 955 wave numbers (cm.$^{-1}$) which do not appear in the spectrum of the non-crystalline Neoprene Type GN (Fig. 1). These bands do not appear in the spectrum of Neoprene Type CG until the polymer crystallizes and they are present in the spectrum of Neoprene Type GN when the polymer is crystallized by stretching to 800–1000% elongation. (A very weak band at 781 cm.$^{-1}$ appeared in the spectra of some aged, unstretched Neoprene Type GN samples.) They can also be intensified in crystalline Neoprene Type CG by stretching the sample and examining it in that condition. Although these bands appear in the spectrum for

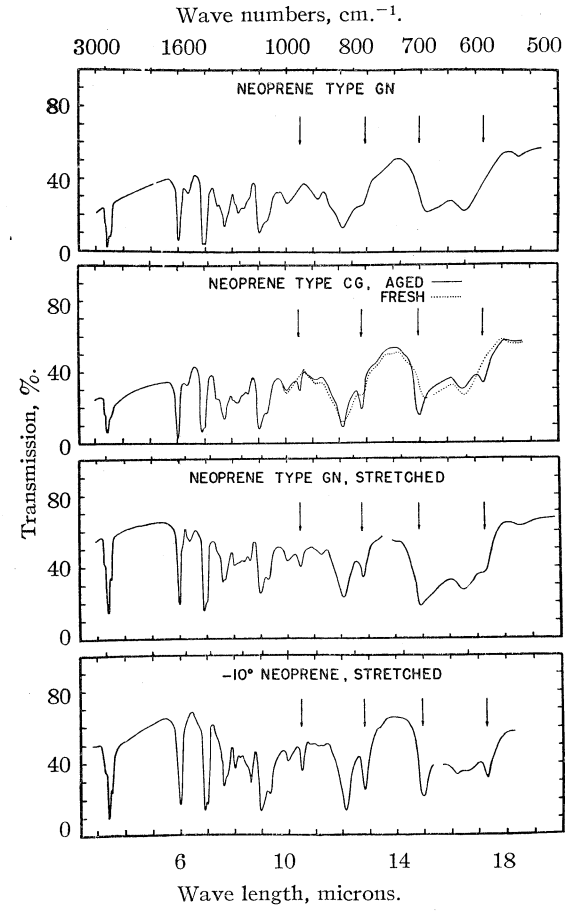


Fig. 1.—Comparison of the infrared spectra of unstretched Neoprene Type GN one day old, unstretched Neoprene Type CG fresh and one day old, stretched Neoprene Type GN and stretched neoprene made at −10°. The arrows indicate absorption bands which are associated with crystallization.

Neoprene Type GN examined while it is stretched, a stretched and then relaxed sample fails to show the bands. Furthermore, these absorption bands disappear from the spectrum of a sample of Neoprene Type CG heated to 50° to melt the crystallites. These absorption bands therefore definitely appear to be associated with crystallization in neoprene.[11]

It was also found that a band maximum at 658 cm.$^{-1}$ exhibited by both polymers is greatly enhanced by crystallization and shifted some 10 cm.$^{-1}$ to 667 cm.$^{-1}$. Crystallization causes less pronounced spectral changes in a group of maxima between 1150 and 1250 cm.$^{-1}$ amounting essentially to an increase in intensity of the bands at

(7) Wright, *Ind. Eng. Chem., Anal. Ed.*, **13**, 1 (1941).

(8) Wild, *Rev. Sci. Instruments*, **18**, 436 (1947).

(9) Pfund, *Astrophys. J.*, **24**, 19 (1906).

(10) Since the work described here was done, Pfund has designed an improved polarizer which overcomes this difficulty; see Pfund, *J. Optical Soc. Am.*, **37**, 558 (1947).

(11) Differences in the spectra of low molecular weight materials as a result of state of aggregation have been reported: *e. g.*, see Thompson, *Nature*, **158**, 234 (1946), and Richards and Thompson, *Proc. Roy. Soc.*, (*London*), **A195**, 1 (1948). Williams and Taschek, *J. Appl. Phys.*, **8**, 497 (1937), observed in the spectrum of natural rubber stretched radially, the appearance of a relatively intense band at 2084 cm.$^{-1}$ where there is no intense absorption in the unstretched material.

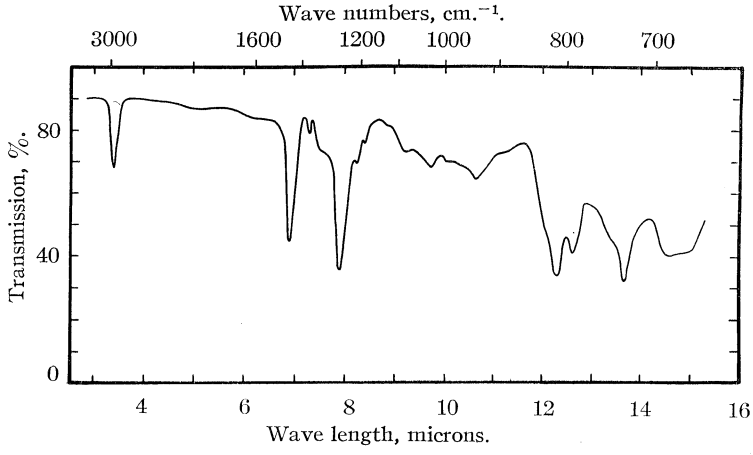


Fig. 2.—Infrared absorption spectra of chlorinated neoprene.

1162 and 1250 cm.$^{-1}$. A weak, perpendicular band which is enhanced by crystallization occurs at about 475 cm.$^{-1}$ in the spectra of crystalline samples. Its presence in other records is doubtful because of the overlapping water vapor rotation lines.

An experimental polychloroprene[12] made at −10° crystallizes in a few seconds, compared to hours for Neoprene Type CG and days for Type GN, but with the exception of somewhat greater intensity in the crystalline-phase bands, it shows no marked spectral differences from Neoprene Type CG.

Except for these crystalline-phase bands there appear to be no significant differences qualitatively among the infrared absorption patterns of the various neoprenes under discussion.[13] Careful examination at high resolution in the 3-micron region, using a grating, revealed no differences in C–H vibrations. There was no evidence for the presence of side vinyl groups from 1,2- or 3,4-addition polymer.[14] Furthermore, chlorinated neoprenes[15] made from both Type GN and Type CG appeared identical in infrared absorption, indicating no difference in structure (Fig. 2). Of course, any geometrical differences in arrangement about the double bonds of the respective neoprenes would be lost on chlorination.

Dichroism.—Examination of stretched Neoprenes Type CG and Type GN with polarized infrared radiation revealed a strong dichroism.[16] The crystalline-phase bands are very prominent for stretched films examined with direction of stretch perpendicular to the vibration plane[17] but are absent or relatively insignificant when the direction of stretch is parallel to the vibration plane (Fig. 3). In addition, several other absorption bands of stretched neoprene are dichroic. For example, it has been shown that the band at 1667 cm.$^{-1}$ in neoprene is similar in dichroism to that of balata, the natural *trans*-polyisoprene. In both polymers this band has maximum intensity when the direction of stretch is perpendicular to the vibration plane. On the other hand, the 1667 cm.$^{-1}$ band of Hevea

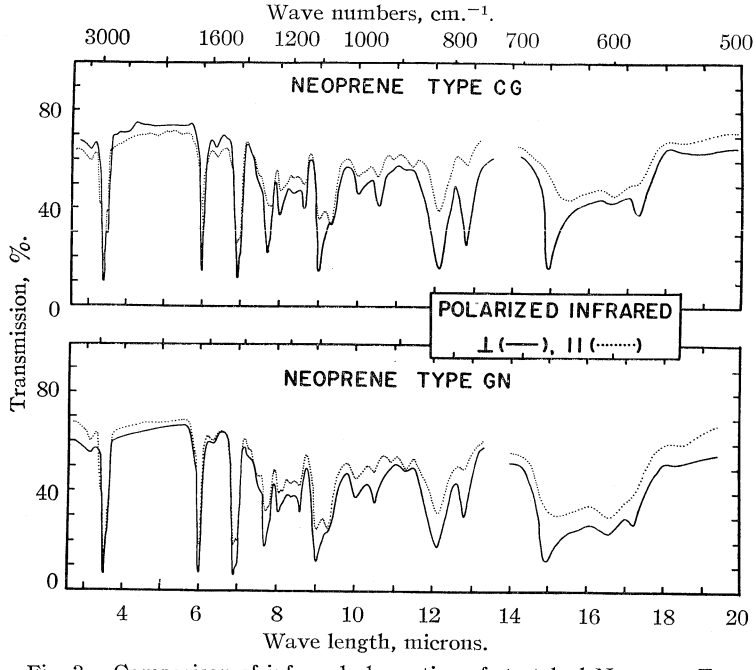


Fig. 3.—Comparison of infrared absorption of stretched Neoprene Type CG and Neoprene Type GN when examined with polarized infrared radiation. Perpendicular (⊥) refers to results obtained when the direction of stretch was perpendicular to the vibration plane.

(12) The authors are indebted to Dr. R. S. Barrows of the Organic Chemicals Department, Jackson Laboratory, E. I. du Pont de Nemours and Company, for supplying this polymer.

(13) The spectra exhibit slight quantitative differences which have not been completely established as yet.

(14) Unpublished ozonolysis studies confirm the absence of appreciable amounts of side vinyl groups. *Cf.* also Rabjohn, *et al.*, THIS JOURNAL, **69**, 314 (1947).

(15) Carothers, U. S. Patent 2,067,172, Jan. 12, 1937.

(16) There have appeared in the literature several reports of other studies of polymers by means of polarized infrared. See Thompson and Torkington, *Trans. Faraday Soc.*, **41**, 260 (1945); Mann and Thompson, *Nature*, **160**, 17 (1947); Thompson, *J. Chem. Soc.*, 289 (1947); Sutherland and Jones, *Nature*, **160**, 567 (1947); Elliott and Ambrose, *ibid.*, **159**, 641 (1947); Glatt and Ellis, *J. Chem. Phys.*, **15**, 880, 884 (1947); *ibid.*, **16**, 551 (1948); Elliott, Ambrose and Temple, *ibid.*, **16**, 877 (1948).

(17) A band that is stronger when the direction of stretch and the vibration plane are perpendicular than when they are parallel will be referred to as a "perpendicular" band as distinct from a "parallel" band, the intensity of which is a maximum when the vibration plane and direction of stretch are parallel.

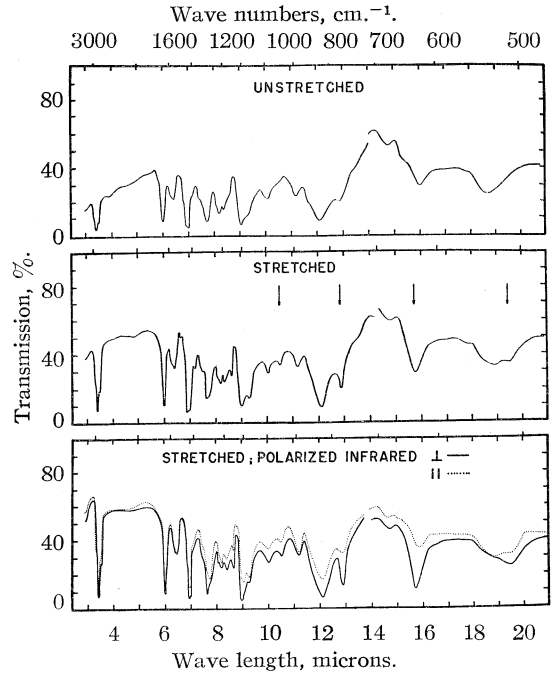


Fig. 4.—Infrared absorption spectra of polybromoprene unstretched, stretched approximately 500% and examined with polarized infrared radiation.

rubber, the *cis*-isomer,[18] has its maximum intensity when the direction of stretch is parallel to the vibration plane of the polarized radiation.[19]

Polybromoprene.—To ascertain which of the bands in the neoprene spectrum result from vibrations involving the C–Cl bonds, samples of polybromoprene[20] were prepared at 40° and their infrared spectra studied using both polarized and non-polarized radiation (Fig. 4). The spectra obtained were very similar, even with respect to dichroism and effects of crystallization, and they demonstrated that the vibrations appreciably involving the C–Cl bonds all lie at longer wave lengths than 15 microns (667 cm.$^{-1}$). The band at 826 cm.$^{-1}$ (12.1 microns) in all polychloroprene spectra and the band that appears at 781 cm.$^{-1}$ when the sample is stretched or when crystallization occurs on aging, occur at 824 and 776 cm.$^{-1}$, respectively, in the polybromoprene spectrum.

Poly-2,3-dichloro-1,3-butadiene.—Another reference compound examined was poly-2,3-dichloro-1,3-butadiene,[21] which was informative in indicating that the band at 1078 cm.$^{-1}$ in the neoprene spectrum involves a bending of the olefinic C–H bond in the plane parallel to the chains. Such a vibration is expected to give rise to a band in the neighborhood of 1100 cm.$^{-1}$. The band at 1078 cm.$^{-1}$ in the neoprene spectrum, rather than the one at 1112 cm.$^{-1}$, is probably the expected one since the only band near this position in the spectrum of polydichlorobutadiene, which has no olefinic C–H, is a perpendicular band at 1095 cm.$^{-1}$ resembling the 1112 cm.$^{-1}$ band of neoprene (Fig. 5). The 1078 cm.$^{-1}$ band, on the other hand, shows little or no dichroism. The various other C–H bending and stretching and double bond stretching bands occur at the expected positions.

A hysteresis in the relation between polarized infrared absorption and stretching was indicated in the case of Neoprene Type GN, suggesting a slow change in ordering or orientation following stretching. The dichroism of the bands at 578, 667, 781 and 955 cm.$^{-1}$ increased slowly over a period of several days following stretching.

Molecular weight was eliminated as an important factor in the changes of infrared absorption observed since no significant differences were found in the spectra of fractions of Neoprene Type CG ranging from 23,000 to 210,000 and fractions of Neoprene Type GN ranging from 44,000 to 250,000 in molecular weight. Furthermore, there were no apparent differences between sol and gel samples of the same polymer.

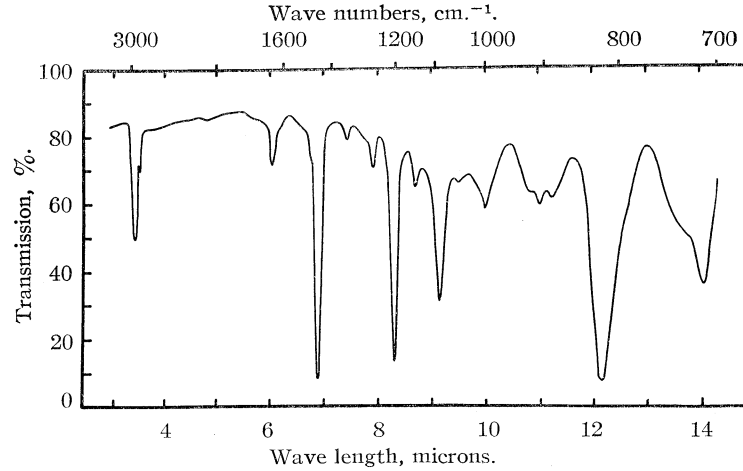


Fig. 5.—Infrared absorption of poly-2,3-dichlorobutadiene examined unstretched.

Interpretation of Results

Table I gives a description of representative neoprene spectra and lists assignments, some of them tentative, of the stronger bands to vibrating groups.

Neglecting small frequency (less than about 5 cm.$^{-1}$) and intensity differences, the only prominent bands present in neoprene, but absent in

(18) Meyer and Mark, *Ber.*, **61**, 1939 (1928); Fuller, *Ind. Eng. Chem.*, **28**, 907 (1936); Bunn, *Proc. Roy. Soc. (London)*, **A180**, 40, 67, 82 (1942).

(19) Sutherland and Jones, *Nature*, **160**, 567 (1947).

(20) Carothers, Kirby and Collins, THIS JOURNAL, **55**, 789 (1933).

(21) Berchet and Carothers, *ibid.*, **55**, 2004 (1933).

TABLE I

INFRARED SPECTRA AND INTERPRETATION

Observed bands,[a] in cm.$^{-1}$											
Neoprene Type GN		Neoprene Type CG					−10° Neoprene	Polybromoprene			
Non-polarized infrared		Non-polarized infrared			Polarized stretched		Non-polarized stretched	Non-polarized infrared		Polarized stretched	
Unstretched	Stretched	Unstretched Fresh	Aged	Stretched	⊥[c]	∥[c]		Unstretched	Stretched	⊥	∥
	580		578	580	578	584[b]	580		505	505	505[b]
602	602	602	602	602	602	602	602	530	530	530	530
658	667	656	667	667	670	658	670	625	635	638	633
780[b]	780	781[b]	781	781	781	781[b]	781	776[b]	776	776	776[b]
826	826	826	826	826	826	826	826	824	824	824	824
890[b]	890	890	890[b]	890[b]	890[b]	890	890[b]	893	893	893	893
927[b]	927	927	927[b]	927[b]	927	927	927				
	955		955	955	955	955	955		953	953	953
1002	1002	1002	1002	1003	1002	1002	1002	1000	1000	1000	1000
1078	1078	1078	1078	1078	1078	1078	1078	1075	1075	1075	1075
1113	1116	1112	1116	1117	1121	1112	1120	1105	1110	1118	1105
1162	1162	↑	1162	1162	1162	1162	1162	1156	1156	1156	1156
1195	1195		1195	1195	1195	1195	1195	1195	1195	1195	1195
1225	1225		1225	1225	1225	1225	1225	1220	1220	1220	1220
1250	1250		1250	1250	1250	1250	1250	1250	1250	1250	1250
1305	1305		1305	1305	1305	1305	1305	1300	1300	1300	1300
1315	1315		1315	1315	1315	1315	1315	1312	1312	1312	1312
1432	1432	No	1432	1432	1432	1432	1432	1432	1432	1432	1432
1449	1449	data	1449	1449	1449	1449	1449	1439	1439	1439	1439
				1563	1563	1563		1563	1563	1563	1563
1667	1667		1667	1667	1667	1667	1667	1667	1667	1667	1667
2860	2860		2860	2860	2860	2860	2860	2860	2860	2860	2860
2940	2940		2940	2940	2940	2940	2940	2940	2940	2940	2940
3010	3010	↓	3010	3010		3010	3010	3000	3000	3000	3000

[a] Potassium bromide prism used for region 450 to 700 cm.$^{-1}$; rock salt prism used for region 700 to 4000 cm.$^{-1}$. [b] Very weak bands which are sometimes imperceptible. A very weak absorption in some neoprene spectra near 475 cm.$^{-1}$ has been neglected. [c] A perpendicular band (⊥) has maximum absorption when the direction of stretch is perpendicular to the vibration plane. A parallel band (∥) has maximum absorption in parallel position.

polybromoprene, are those at 578 and 667 cm.$^{-1}$ and the broad absorption around 602 cm.$^{-1}$. These bands in neoprene have certain characteristics that serve to identify the corresponding bands in the polybromoprene spectrum. The band that appears at 578 cm.$^{-1}$ at the edge of the broad 602 cm.$^{-1}$ absorption in the spectrum of crystalline neoprene, but not in amorphous neoprene, is a perpendicular-type band. A much weaker band at 505 cm.$^{-1}$, a shoulder only, at the edge of the 530 cm.$^{-1}$ absorption is probably the corresponding band in the polybromoprene spectrum, since it also is a perpendicular band with intensity in the unstretched polymer diminished relative to that in the stretched polymer.

The 658 cm.$^{-1}$ band of non-crystalline neoprene appears with greatly enhanced intensity and with its peak shifted some 10 cm.$^{-1}$ to 667 cm.$^{-1}$ in the crystalline neoprene. It is likewise a perpendicular-type band. The band in the stretched polybromoprene spectrum at 635 cm.$^{-1}$ behaves similarly in each respect and otherwise resembles the 667 cm.$^{-1}$ band of neoprene. It is therefore believed to arise from a vibration of the same form.

The absorption in neoprene with its center at 602 cm.$^{-1}$ and that in polybromoprene with its center at 530 cm.$^{-1}$ probably arise from the same vibrations, since they are both broad absorptions insensitive to crystallization and only very slightly dichroic in stretched samples.

Evidently, then, the vibrations giving rise to bands at 578, 602 and 667 cm.$^{-1}$ in the neoprene spectrum strongly involve the C–Cl bond. Of these, the 578 and 602 cm.$^{-1}$ bands apparently result from vibrations in which the chlorine component is about the same as it would be in a hypothetical diatomic radical C–Cl, since replacement of chlorine by bromine shifts the bands about the amount estimated for a similar sub-

TABLE I (*Continued*)

Remarks	Assignments
Shifted about 70 cm.$^{-1}$ by Cl $->$ Br substitution. Appears with crystallization. Strongly perpendicular[c]	Vibrations involving CCl bond strongly. Cl motion about same as in simple CCl structure
Broad (about 50 cm.$^{-1}$). Shifted about 70 cm.$^{-1}$ by Cl $->$ Br substitution. Very little dichroism	
Peak frequency decreased about 30 cm.$^{-1}$ by Cl $->$ Br substitution. Strongly enhanced by crystallization. Strongly perpendicular	Vibration involving CCl bond. Cl motion less than in simple CCl
Appears with crystallization. Very strongly perpendicular. Frequency lowered about 5 cm.$^{-1}$ by Cl $->$ Br substitution	
Shoulder at about 855 cm.$^{-1}$ fades and band narrows with crystallization. Strongly perpendicular	Probably CH_2 deformation vibration
Very weak, parallel band. Stronger, but less parallel in polybromoprene	
Very weak, parallel band	
Appears with crystallization. Strongly perpendicular	Suggest sum frequency: 955 = 781 + 174
	Suggest sum frequency: 1002 = 826 + 176
Apparently little or no dichroism	Olefinic CH parallel bending vibration
Strongly dichroic	
Envelope of four overlapping bands; 1162 and 1250 cm.$^{-1}$ bands strongly perpendicular and enhanced by crystallization, especially stretching	
Other overlapping shoulders at about 1290, 1350 and 1390 cm.$^{-1}$; 1315 cm.$^{-1}$ band strongly perpendicular	
Apparently perpendicular	CH_2 bending vibrations
Perpendicular	
Broad absorption sometimes present	
Perpendicular	Double bond stretching vibration
At least five bands on grating records: at about 2835, 2850, 2920, 2950, and 3020 cm.$^{-1}$ for neoprenes; at about 2825, 2840, 2915, 2945 and 3000 cm.$^{-1}$ for polybromoprene	Saturated CH stretching
	Olefinic CH stretching

stitution in the C–Cl radical. In the case of the 667 cm.$^{-1}$ band the shift is less than that predicted for the C–Cl radical. The band at 826 cm.$^{-1}$, which appears in the spectra of all neoprenes, cannot involve the C–Cl bond appreciably because it occurs within two wave numbers of the same place in the polybromoprene spectrum. The high intensity of this 826 cm.$^{-1}$ band in neoprene and the fact that it is strongly perpendicular suggest that it arises from a vibration consisting essentially of a hydrogen deformation, since it does not arise from a vibration involving the chlorine atom.[22]

The similarities between the bands at 781 cm.$^{-1}$ and 955 cm.$^{-1}$ and between those at 826 cm.$^{-1}$ and 1002 cm.$^{-1}$ suggest that the 955 and 1002 cm.$^{-1}$ bands are sum frequencies involving a vibration of about 175 cm.$^{-1}$ plus the 781 and 826 cm.$^{-1}$ bands, respectively.

(22) A perpendicular band at 735 cm.$^{-1}$ in polythene has been assigned to a hydrogen deformation vibration on the basis of deuterium substitution data; Sheppard and Sutherland, *Nature*, **159**, 739 (1947).

The appearance of strong absorption bands as a result of crystallization of the polymer is a phenomenon that apparently has not been recognized previously in high polymers. Evidently it is a factor that must not be neglected in the interpretation of the spectra of polymers. In the spectrum of neoprene the crystalline-phase bands appear to be associated with several different vibrations. The band at 578 cm.$^{-1}$ involves strong motion of the chlorine atom while those at 781 and 955 cm.$^{-1}$ involve very little. All of these bands are of maximum intensity in the oriented polymer when the vibration plane and direction of stretch are perpendicular and are absent or nearly so when the vibration plane and direction of stretch are parallel.

That such bands should appear as a result of crystallization is curious. One might have expected a large decrease—rather than an increase—in the intensity of a strongly dichroic band as a result of simply orienting the sample, as in stretching. For, neglecting background, a perfectly oriented sample would be transparent to one

component of radiation of the wave length of a completely perpendicular or parallel band. Hence, when non-polarized radiation is used, Beer's law should not apply for dichroic bands of oriented samples. This effect would, therefore, tend to counteract and thus partially obscure the observed increase in absorption.

While we have been unable to confirm any of several explanations for these bands apparently caused by crystallization, at present we are inclined to consider them the result of very large intensity increases in imperceptible absorptions of the amorphous polymer. Considered from the point of view of the simple classical theory, the rate of absorption of energy from the infrared field by the absorbing structures will increase with the amplitude of vibrations in those structures. Accordingly, we might expect bands to be greatly enhanced if increasing order in the sample suppresses the processes responsible for removal of absorbed energy from the vibrating groups.

That more extensive modes of vibration should develop upon crystallization or that a recoupling of vibrating components should render infrared-active in the crystalline polymer a vibration which was inactive in the amorphous material, would imply an extension of the regions of rigidity requiring stronger forces than appear to be involved in crystallization or would imply the existence of very unlikely, unstable equilibria. A simple explanation of the appearance of the bands in terms of combination frequencies, resonance splitting, or in terms of the changes in the mutual electrostatic interaction of proximate, similar (and also similarly oriented) vibrating groups is unsatisfactory because of such factors as the sharpness of the bands and the absence of other expected components.

The differences in chemical structure between Neoprene Type CG and Type GN must be relatively small since they are not revealed by infrared. Furthermore, it is probable that the differences are only in degree, which would be revealed only by precise quantitative measurements. The spectra have not been completely elucidated but there is no evidence to indicate the presence of any 1,2- or 3,4-polychloroprene.[23] This has also been the result of an independent observation.[24] *cis*- and *trans*-2-chloro-2-butenes were examined by infrared as possible reference compounds to distinguish *cis* and *trans* structures in neoprene, but apparently were too low in chain length to serve as reference compounds, since the absorption bands were considerably shifted in many cases from their positions in the neoprene spectrum.

(23) Patat in an I. G. Report dated February 17, 1943, reported by the U. S. Technical Oil Mission, (Reel No. 53, Bag 3413, Frames 00385–00392) stated that in polycholoroprene made in emulsion at 0°, 1,2-polymers predominate but at 60°, 1,4-polymerization is most prevalent. The present authors, on the basis of results obtained in this Laboratory, cannot agree with such a hypothesis.

(24) Sheppard and Sutherland, *Faraday Soc. Discussion*, **2**, 374 (1947).

Acknowledgments.—The authors are indebted to their colleagues, Drs. J. R. Downing, S. L. Scott and C. J. Mighton for the initial discovery that the infrared spectra of Neoprenes Type GN and Type CG are different and to Miss Doris Huck for her assistance with the infrared measurements. Acknowledgments likewise are made to Drs. A. W. Kenney, D. M. McQueen, G. D. Patterson and B. C. Pratt for aid and encouragement and to many staff members of the Organic Chemicals Department of this Company for valuable criticisms and advice. The authors are particularly thankful to Professors R. C. Lord, F. T. Wall, J. A. Wheeler and the late A. H. Pfund for many helpful discussions.

Summary

Infrared absorption spectra of amorphous and crystalline Neoprenes Type CG and Type GN have been studied in the wave length range 2–23 microns. Spectra of polybromoprene and poly-2,3-dichloro-1,3-butadiene, the dichroism of stretched samples and spectral changes accompanying crystallization have been used to assign most of the strong bands to vibrations of more or less limited regions of the molecule. The spectra appear to be unchanged by variations in molecular weight or sol–gel relationships.

Spectral changes, some very pronounced, accompany crystallization of neoprene, either in the unstretched state or following stretching. Perceptible spectral changes were found to occur for several days following stretching of Neoprene Type GN, which crystallizes slowly. These spectral changes, particularly the surprising appearance of strong absorption bands when the polymer crystallizes, are of interest because of their relation to order in the polymer. The appearance of bands because of crystallization has been tentatively ascribed to very large intensity increases in normally imperceptible absorptions of the amorphous polymer caused by suppression in the ordered molecules of some processes responsible for dissipation of absorbed energy from the vibrations.

WILMINGTON, DEL. RECEIVED MAY 5, 1949

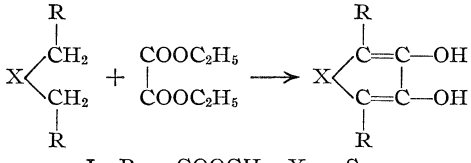
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Ultraviolet Absorption Spectra and Acidic Strengths of Certain Dihydroxythiophene-1-oxides and 1-Dioxides[1,2]

BY RICHARD H. EASTMAN AND ROBERT M. WAGNER[3]

Introduction

As part of a program devised to evaluate the electrical effect of the sulfur atom in various states of oxidation on contiguous groups in organic molecules we have prepared 2,5-dicarbomethoxy-3,4-dihydroxythiophene (I),[4] 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-oxide (II), 2,5-dicarbethoxy - 3,4 - dihydroxyethiophene - 1 - dioxide (III), 3,4-dihydroxy-2,5-diphenylthiophene-1-dioxide (IV), 2,5-dicarbethoxy-3,4-dihydroxyfuran (V),[5] 2,5-dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI)[6], and N-ethyl-2,5-dicarbethoxy-3,4-dihydroxypyrrole (VII)[7] by the oxalic ester condensations as indicated schematically:



I R = $COOCH_3$; X = S
II R = $COOC_2H_5$; X = SO
III R = $COOC_2H_5$; X = SO_2
IV R = C_6H_5; X = SO_2
V R = $COOC_2H_5$; X = O
VI R = $COOC_2H_5$; X = CH_2
VII R = $COOC_2H_5$; X = C_2H_5N

The electrical effect of the sulfur atom in various states of oxidation (Compounds I, II, III, IV) and that of other hetero-atoms (Compounds V, VII) on the properties of the ester condensation products has been assessed by measurement of acidic strengths and ultraviolet absorption spectra.

Experimental[8]

A. Preparation of Compounds. 2,5-Dicarbomethoxy-3,4-dihydroxythiophene (I).—The compound was prepared according to the directions given by Hinsberg.[4] Our material had m. p. 177° (reported 177°) and gave a green color with ferric chloride in alcohol.

2,5-Dicarbethoxy-3,4-dihydroxythiophene-1-oxide (II).—To fifteen grams of ethyl thiodiacetate dissolved in 20 ml. of acetone was added 7.5 ml. of 30% hydrogen peroxide solution. After four days acetone was removed at reduced pressure, benzene was added and the mixture was distilled until the distillate was clear. The residue on distillation yielded 9.0 g. of **ethyl sulfinyldiacetate**, an oil of b. p. 140–146° (4 mm.).

Eight grams of ethyl sulfinyldiacetate and 5.3 g. of ethyl oxalate were added to a solution of 1.7 g. of sodium dissolved in 30 ml. of absolute methanol. The reaction mixture was heated under reflux for one hour, allowed to stand twelve hours, and then decomposed by addition to three times its volume of water which contained 2.2 ml. of concentrated hydrochloric acid. The precipitate which appeared was separated by filtration, washed with methanol and crystallized from methanol four times to yield 1.2 g. of white needles, of m. p. 121–122°. The compound gave a green color with ferric chloride in alcohol and analyzed for 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-oxide (II). The equivalent weight was determined as described below under C.

Anal. Calcd. for $C_{10}H_{12}O_7S$: C, 43.5; H, 4.38; neut. equiv. (two acidic groups), 138. Found: C, 43.8; H, 4.55; neut. equiv., 137.

2,5-Dicarbethoxy-3,4-dihydroxythiophene-1-dioxide (III).—**Sulfonyldiacetic acid**[9] was prepared in 85% yield by hydrogen peroxide oxidation of thiodiacetic acid in glacial acetic acid. Our material had m. p. 184–185° (reported[7] 182°) after crystallization from concentrated hydrochloric acid.

A mixture of 98.0 g. of sulfonyldiacetic acid, 135 ml. of 95% ethanol, 2.0 g. of toluenesulfonic acid, and 500 ml. of benzene was refluxed with an attached water separator until no water appeared in the condensate. The reaction mixture was washed thoroughly with water, the benzene was removed by distillation, and the residue was distilled at reduced pressure to yield 118 g. of **ethyl sulfonyldiacetate,**[10] a colorless oil of b. p. 178–181° (5 mm.), d^{27} 1.258, $n^{25}D$ 1.4652.

To a warm solution of 20 g. of sodium in 200 cc. of absolute ethanol was added, in portions with stirring, a mixture of 44 g. of ethyl oxalate and 69 g. of ethyl sulfonyldiacetate. When the mildly exothermic reaction had subsided, the reaction mixture was heated for one hour on the steam-bath. The mixture was centrifuged and the gummy solid obtained was spread on glass plates where it dried in twelve hours to a bright-yellow powder. Forty-three grams of the yellow powder was dissolved in 150 ml. of water and acidified to *p*H 1 with concentrated nitric acid, and to the solution was added, with stirring, a solution of 150 g. of mercurous nitrate in 150 ml. of dilute nitric acid. The precipitated mercurous salt was separated by filtration, washed with water, and suspended in 100 ml. of water. To the suspension was added an excess of concentrated hydrochloric acid. The calomel which precipitated was separated by filtration and the filtrate was concentrated to one-third its original volume by distillation at reduced pressure. The crystalline material which separated was collected, washed with concentrated hydrochloric acid, crystallized twice from small volumes of 20% hydrochloric acid, and twice from benzene after drying to yield 17 g. of 2,5-dicarboxy-3,4-dihydroxythiophene-1-dioxide (III) in the form of white cubes of m. p. 116–117.5°.

Anal. Calcd. for $C_{10}H_{12}O_8S$: C, 41.1; H, 4.14; neut. equiv., 146 (two acidic groups); C-methyl, 2 (two ethyl ester groups); active H, 2 per mol. wt., 292. Found: C, 41.4; H, 3.98; neut. equiv., 146; C-methyl, 1.88; active H, 1.97, 2.00.

The compound is very soluble in water to give a yellow

(1) A portion of this work was reported at the meeting of The American Association for the Advancement of Science in Berkeley, California, in June, 1948.

(2) The work reported here is taken from the Doctoral Dissertation of Robert M. Wagner in the Department of Chemistry at Stanford University.

(3) Present address: General Electric Company, Richland, Washington.

(4) Hinsberg, *Ber.*, **43**, 901 (1910); **45**, 2413 (1912).

(5) Johnson and Johns, *Am. Chem. J.*, **31**, 290 (1906).

(6) Dieckmann, *Ber.*, **27**, 966 (1894).

(7) For a similar synthesis see Johnson and Bengis, THIS JOURNAL, **33**, 741 (1911).

(8) All melting points are uncorrected.

(9) Prepared originally by permanganate oxidation: Loven, *Ber.* **17**, 2818 (1884).

(10) Loven, *ibid.*, **17**, 2821 (1884).

solution, crystallizable from strongly acidic, aqueous solutions and benzene, is strongly acidic in reaction (*cf.* Discussion) and gives a wine-red coloration with ferric chloride in water or alcohol.

The solubility in water and the high acidity of 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxide caused difficulty in the isolation of the compound. Thus, although the compound is soluble in ether, a strongly acidified solution of the above-described reaction mixture could be extracted continuously with ether without any of the free acid appearing in the ether phase. Isolation was achieved by formation of the barium salt which was insoluble in 1:1 ethyl alcohol–water, followed by reaction of it with the calculated amount of sulfuric acid, and by the use of a cation exchange resin in the hydrogen cycle; but both of these methods proved inferior to the above-described separation through the mercurous salt.

3,4-Dihydroxy-2,5-diphenylthiophene-1-dioxide (IV).—Five grams of dibenzyl sulfone, 3.0 g. of ethyl oxalate, and 3.0 g. of dry sodium methoxide were heated together for one hour during which time 2.9 ml. of low-boiling liquid distilled from the reaction mixture. The dark residue was dissolved in 100 ml. of water and the solution was acidified to *p*H 2 with concentrated hydrochloric acid. The solid which separated was collected and crystallized from 1:3 ethanol–benzene to give 3.5 g. of 3,4-dihydroxy-2,5-diphenylthiophene-1-dioxide, white crystals of m. p. 232–233°.

Anal. Calcd. for $C_{16}H_{12}O_4S$: C, 64.1; H, 4.06; S, 10.7; neut. equiv., 150 (two acidic groups). Found: C, 64.2; H, 4.12; S, 10.7; neut. equiv., 148.

The substance gave an orange color with ferric chloride in alcohol and dissolved in dilute sodium bicarbonate to give a deep yellow solution. Its neutral equivalent was determined by titration in an anhydrous medium as described below under C.

2,5-Dicarbethoxy-3,4-dihydroxyfuran (V).—The compound was prepared according to the directions given by Johnson and Johns.[5] Our material had m. p. 190° (reported[5] 189–190°) and gave a purple color with ferric chloride solution in alcohol.

2,5-Dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI).—The compound was prepared according to the method of Dieckmann.[6] Our sample had m. p. 118° (reported[6] 118°) and gave a wine-red color with ferric chloride in alcohol.

N-Ethyl-2,5-dicarbethoxy-3,4-dihydroxypyrrole (VII).—**Ethylimino-bis-acetonitrile** was prepared by the method of Knoevenagel and Mercklin,[11] characterized as its hydrochloride of m. p. 112–113° (reported[11] 112–113°) and converted to **diethyl N-ethyliminodiacetate** by alcoholysis according to Curtius.[12] Our sample of the latter compound had b. p. 210–225° (11 mm.).

Five grams of diethyl N-ethyliminodiacetate and 3.5 g. of ethyl oxalate were added to a solution of 1.5 g. of sodium in 60 ml. of absolute ethanol. The reaction mixture was heated gently for one hour, distilled nearly to dryness in a stream of nitrogen, and the residue was dissolved in 50 ml. of water. Acidification of the solution with 5.3 ml. of concentrated hydrochloric acid threw down a white precipitate which was collected, washed with water, and crystallized from 50% alcohol to yield 0.7 g. of N-ethyl-2,5-dicarbethoxy-3,4-dihydroxypyrrole, white crystals of m. p. 83–83.5°.

Anal. Calcd. for $C_{12}H_{17}O_6N$: C, 53.1; H, 6.33; N, 5.17. Found: C, 53.4; H, 6.38; N, 5.13.

The compound was insoluble in water, gave a green ferric reaction in alcohol, and was decomposed by alkali as evidenced by the appearance of a transient yellow coloration when the substance was dissolved in dilute sodium hydroxide.

B. Determination of Ultraviolet Absorption Spectra.—The absorption characteristics of the compounds were studied in a variety of media using a Beckman Quartz Spectrophotometer, Model DU. The instrument was balanced by varying the slit width with the sensitivity knob kept three and one-half turns from the extreme clockwise position giving a maximum nominal band width of 2 mμ, and measurements were made at 5 mμ intervals.

The absorption characteristics of the compounds in the various media did not change during the time required for the observations, and, with the single exception of the study of N-ethyl-2,5-dicarbethoxy-3,4-dihydroxypyrrole which decomposed in alkaline media, there was no evidence, spectrophotometric or other, for decomposition of the compounds under the conditions employed. Thus, compounds I, VI and VII were recovered unchanged by dilution after one hour of solution in concentrated sulfuric acid. The spectra are reported in Figs. 1–4.

C. Determination of Acidic Strengths.—Titration curves for the compounds were obtained in water and in an anhydrous medium composed of isopropyl alcohol and propylene glycol according to the method of Palit[13] using a Beckman *p*H meter. When the *p*H meter was used in the anhydrous medium, it was found necessary to equilibrate the glass electrode for several hours with the medium before use.

The pK values are taken as equal to the *p*H value at the half-neutralization points for the corresponding acidic hydrogens where the shape of the titration curve shows typical weak acid behavior.

The pK' values are similarly derived from titrations carried out in the anhydrous medium and are considered to be of value in establishing relative acidic strengths only. The similar calculation of the pK_2' values for the second enolic hydrogens of compounds I, II, III and IV is of little significance since in the titrations of these compounds the precipitation of a sodium or potassium salt commenced shortly after the equivalence point for the first hydrogen was reached. On the basis of the equilibria involved, this precipitation of the anion as a salt causes the acid to appear stronger than it actually is. Such values for pK_2' are bracketed in Table I.

The titration curves are plotted in Figs. 5 and 6, and the corresponding pK and pK' values are summarized in Table I. Some reference compounds are included to establish the validity of the method.

TABLE I

ACID STRENGTHS

Compound	In water pK_1	In water pK_2	In anhydrous medium[a] pK_1'	In anhydrous medium[a] pK_2'
Picric acid	Strong		Strong	
III	Strong	Strong[b]	Strong	(4.1)
Malonic acid	2.9	6.1	4.5	7.8
IV	*ca.* 4.3	...	5.0	(10.0)
Benzoic acid	4.2		6.2	
II	...	...	6.8	(9.5)
Acetic acid	4.8		7.2	
I	...	...	7.7	(9.9)
VI	...	...	7.9	10.4

[a] The pK' values are considered to be of value in determining relative acidic strengths only (*cf.* discussion under part C in Experimental Section). [b] While this article was in process of publication, Professor F. O. Koenig and Lorraine Mildred Winslow of the Department of Chemistry at Stanford University made an accurate determination of pK_2 for 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxide (III) by the methods of Hamer [THIS JOURNAL, **56**, 860 (1934)] and Harned and Ehlers [*ibid.*, **54**, 1350 (1932)]. The value for pK_2 so obtained was 2.59 which may be compared with the value 1.92 obtained by Hamer for the bisulfate ion.

Although the titration data are plotted in terms of per cent. neutralized in Figs. 5 and 6, the determinations were

(11) Knoevenagel and Mercklin, *Ber.*, **37**, 4093 (1904).

(12) Curtius, *J. prakt. Chem.*, **96**, 285 (1917).

(13) Palit, *Ind. Eng. Chem., Anal. Ed.*, **18**, 246 (1946).

carried out on weighed samples and, thus, served to determine the equivalent weights of the substances studied.

The insolubility of 3,4-dihydroxy-2,5-diphenylthiophene-1-dioxide in water precluded determinations of its acidity by titration in water. However, a saturated solution of the substance in water had a concentration by weight analysis of 4.7×10^{-4} mole per liter and showed *p*H 3.9. These data indicate an approximate pK_1, neglecting the second hydrogen, of 4.3.

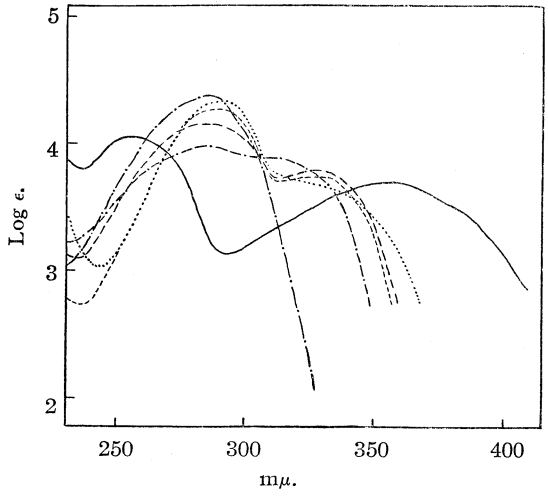


Fig. 1.—Ultraviolet absorption spectra in 1 *M* alcoholic hydrogen chloride: —, 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxide (III); – – – –, 2,5-dicarbomethoxy-3,4-dihydroxythiophene (I); — —, 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-oxide (II); —·—, 2,5-dicarbethoxy-3,4-dihydroxyfuran (V); — —·, 2,5-dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI); . . . . . , N-ethyl-2,5-dicarbethoxy-3,4-dihydroxypyrrole (VII).

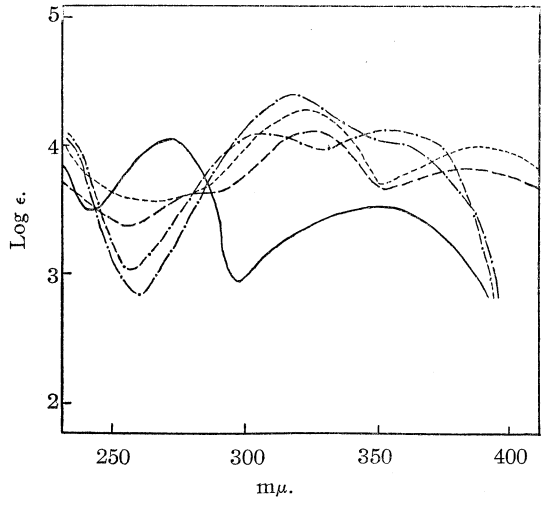


Fig. 2.—Ultraviolet absorption spectra in 5% potassium hydroxide: —, 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxide (III); – – – –, 2,5-dicarbomethoxy-3,4-dihydroxythiophene (I); — — —, 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-oxide (II); —·—, 2,5-dicarbethoxy-3,4-dihydroxyfuran (V); — —·, 2,5-dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI).

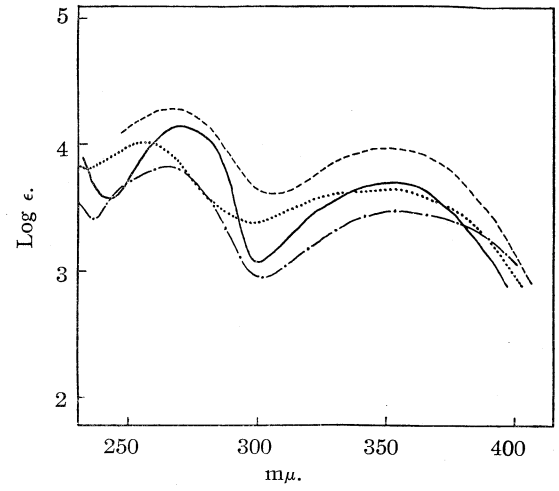


Fig. 3.—Ultraviolet absorption spectra of 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxide (III) in various media: —, water; —·, 95% ethanol; – – – –, glacial acetic acid; . . . . . , 9 *M* sulfuric acid.

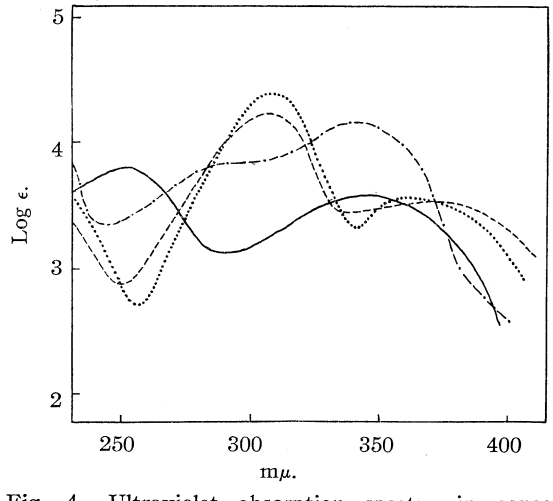


Fig. 4.—Ultraviolet absorption spectra in concentrated sulfuric acid: —, 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxide (III); – – – – –, 2,5-dicarbomethoxy-3,4-dihydroxythiophene (I); . . . . . , N-ethyl-2,5-dicarbethoxy-3,4-dihydroxypyrrole (VII); — —·, 2,5-dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI).

Discussion

Comparison of the pK_1' values for the first enolic hydrogens of 2,5-dicarbomethoxy-3,4-dihydroxythiophene (I) ($pK_1' = 7.7$) and 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-oxide (II) ($pK_1' = 6.8$) indicates that the sulfoxide group exerts only a slightly stronger proton-releasing effect on the enolic hydrogen than does a sulfide function in the same position. This observation is in accord with the reported[14] failure of bis-(phenylsulfinyl)-methane to show acidic properties. The near identity of the ultraviolet absorption spectra of the two compounds (I and

(14) Shriner, Struck and Jorison, THIS JOURNAL, **52**, 2060 (1930).

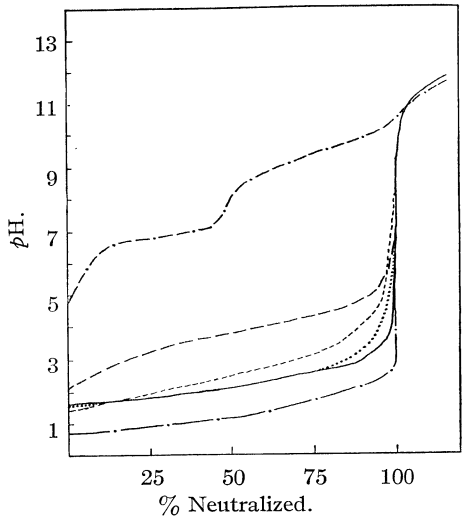


Fig. 5.—Titration curves in water: —, sulfuric acid; ..... and —·, 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxide (III), 0.02 and 0.25 *M*, respectively; — —·, 2,5-dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI); — — —, thiodiacetic acid; – – – –, sulfonyldiacetic acid.

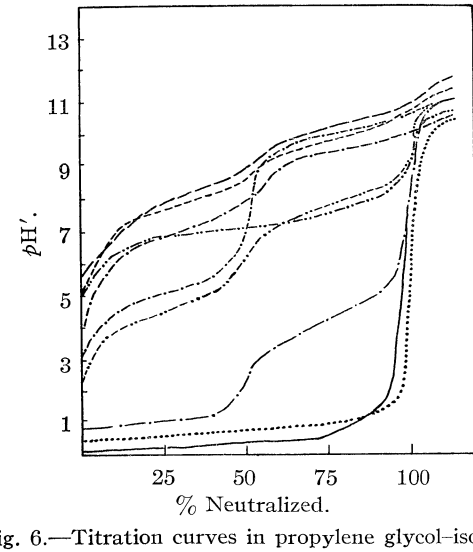


Fig. 6.—Titration curves in propylene glycol–isopropyl alcohol: —, sulfuric acid; —·, 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxide (III); ....., picric acid: – – – –, 2,5-dicarbomethoxy-3,4-dihydroxythiophene (I); — — —, 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-oxide (II); — —·, 2,5-dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI); —·—, 3,4-dihydroxy-2,5-diphenylthiophene-1-dioxide (IV); · · —, acetic acid; · · — —, malonic acid.

II) in alcoholic hydrogen chloride (Fig. 1), in which medium the substances may be assumed to be present as undissociated molecules, further emphasizes the similarity of the electrical effect of the groups –S– and –SO– on attached groups. Both the sulfide and sulfoxide functions appear, however, to exert an electron-attracting influence relative to a methylene group in the same position as evidenced by comparison of the pK_1' values for the thiophene derivatives (I and II) with that for 2,5-dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI) (pK_1' = 7.9). The similarity in the absorption spectra of the three thiophene derivatives (I, II, III), the cyclopentadiene derivative (VI), and 2,5-dicarbethoxy-3,4-dihydroxypyrrole (VII) (Fig. 1) finds explanation in the observation that the systems –CO–C(CH_3)=CH– and –CO–C(Br)=CH– have the same ultraviolet absorption spectra and that in general the concept of cross conjugation is without physical basis.[15]

The appearance of a single absorption maximum for 2,5-dicarbethoxy-3,4-dihydroxyfuran (V) (Fig. 1) in acidic solution taken with the appearance of the two characteristic bands in alkaline medium (Fig. 2) suggests that the furan derivative is present in the acidic solution in a different molecular form than that of the thiophene, pyrrole and cyclopentadiene derivatives (I, II, III, VI, VII) under the same conditions.

The ultraviolet absorption spectra of the 2,5 - dicarbethoxy - 3,4 - dihydroxythiophene - 1-dioxide (III) (Figs. 1, 2, 3, 4) in various media are similar to those of the other compounds studied insofar as the two characteristic bands are present. In the case of the sulfone (III), however, the intensity of absorption is lower for both bands, the short wave length band is considerably shifted to shorter wave lengths, and the position of maximum absorption for the long wave length band is little altered by changes in the medium (*cf.* Figs. 1, 2, 3). The latter situation is not the case with the thiophene (I) and thiophene-1-oxide (II) derivatives in which the low intensity bands, as well as the high intensity bands, undergo marked bathochromic shifts in going from moderately acidic to alkaline media, *i. e.*, from neutral molecule to conjugate base. This observation that the presence of the enolic hydrogens in III has little to do with the ultraviolet absorption characteristics of the compound suggests that the electron distribution is not much dependent upon the presence of the enolic hydrogens, a situation tantamount to ascribing to the sulfone (III) a very high level of acidity.

Such is indeed the case. From the titration curve for the compound in the anhydrous medium (Fig. 6), in which acetic acid shows approximately a four hundred-fold decrease (pK' = 7.2) relative to its strength in water (pK = 4.8), it is evident that the first enolic group of the sulfone (III) still shows strong acid behavior. The basicity of the anhydrous medium, is, however, enough lower than that of water to bring out the weak acid nature of the second enolic hydrogen of III, which was not observed in the titration of the compound in water (*cf.* Fig. 5). Although the titration procedure was not extended to even less basic solvents in order to evaluate a relative acid-

(15) Woodward, THIS JOURNAL, **63**, 1123 (1941).

ity for the first hydrogen of the sulfone (III), it is apparent from the curve (Fig. 6) that the compound is at least as strong an acid as picric acid ($pK = 1$). It is probably stronger with regard to the first enolic hydrogen since even in 0.25 molar solution the second hydrogen of III showed strong acid behavior (Fig. 5) and the first and second dissociation constants of dibasic acids having proximate acidic groups usually differ by a factor of at least three powers of ten.

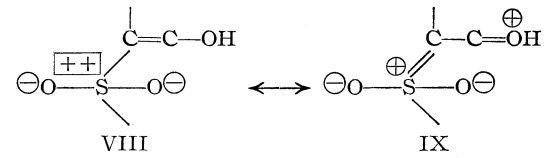
The ultraviolet absorption spectra for the compound (III) in 1 M alcoholic hydrogen chloride, 9 M sulfuric acid, and concentrated sulfuric acid (Figs. 1, 3, and 4) show little difference which suggests that, in contrast to the behavior of the much less strongly acidic I, VI, and VII under similar conditions (*cf.* Fig. 4 and the discussion below) the thiophene dioxide (III) is present, not as its conjugate acid, but rather in molecular form in concentrated sulfuric acid. Such behavior would be expected of only the most weakly basic substances, and hence of only the strongest acids when the molecule in question has ampholytic character.

In the anhydrous medium the first enolic hydrogen of 3,4-dihydroxy-2,5-diphenylthiophene-1-dioxide (IV) shows an acidic strength (pK_1' 5.0) only 3-fold less than that of the first hydrogen of malonic acid (pK_1' 4.5, pK_1 2.9) in the same medium. Because of its low solubility in water the diphenylthiophene derivative (IV) could not be titrated in aqueous solution. However, it is apparent that the compound is as strong an acid as a typical carboxylic acid in water (pK 5). An approximate determination of the acidic strength in water, as described under C in the Experimental Section, gave pK_1 4.3.

It is apparent from these considerations that the strong electron-attracting influence of the sulfonyl group is transmitted through the carbon–carbon double bond to the enolic hydroxyl groups in the compounds studied. Indeed, the effect is greater than that exerted by a carbethoxyl group in the same position as indicated by a comparison of the acidic strengths of 2,5-dicarbomethoxy-3,4-dihydroxythiophene (I) (pK_1' 7.7) and 2,5-dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI) (pK_1' 7.9) with those of the thiophene derivatives III and IV. This conclusion is in accord with the observation that bis-(phenylsulfonyl)-methane dissolves in aqueous sodium hydroxide and may be alkylated by treatment of the alkaline solution with alkyl halides[14] while malonic ester is unreactive in the same sense under the same conditions.

Since, in the compounds studied, the powerful electron-attracting influence of the sulfonyl group is transmitted through a double bond it is concluded that the effect is not one of simple induction but is better symbolized by the resonance hybridization VIII ⟷ IX.

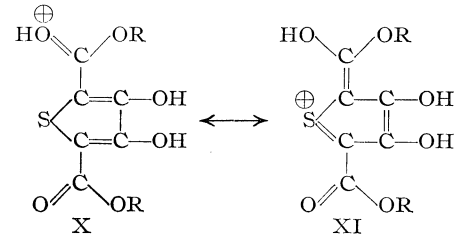
Structures VIII and IX involve a sulfur atom with a decet of electrons. Such an expansion of the octet, involving the unused d orbitals of the



VIII IX

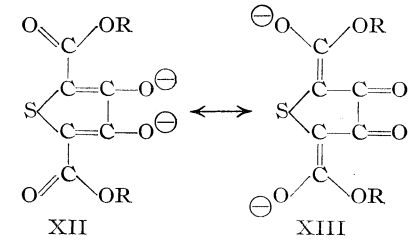
sulfur atom has been suggested by various investigators to explain the physical and chemical properties of organic and inorganic compounds of sulfur.[16] The work reported here thus provides additional experimental evidence in support of this hypothesis.

We turn now to a consideration of the marked bathochromic shifts observed in the spectra of 2,5-dicarbomethoxy-3,4-dihydroxythiophene (I) and N-ethyl-2,5-dicarbethoxy-3,4-dihydroxypyrrole (VII) in going from a 1 M alcoholic hydrogen chloride medium to a concentrated sulfuric acid medium (*cf.* Figs. 1 and 4). Both I and VII are weakly acidic, and unlike 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxide (III), might be expected to be converted to their conjugate acids in concentrated sulfuric acid. In view of the failure of thiophene and pyrrole to show basic properties attributable to their hetero atoms, and the reported[17] conversion of carboxylic esters to their conjugate acids by concentrated sulfuric acid we propose structures of the type X ⟷ XI for the conjugate acids of the thiophene derivative I and the pyrrole VII, present in solutions of the compounds in concentrated sulfuric acid.



X XI

In these structures, no charge separation is required by the resonance hybridization. The same situation obtains in the conjugate bases of the type XII ⟷ XIII, and it is not surprising that both the conjugate acids and the conjugate bases have spectra shifted bathochromically relative to the neutral molecules.[18,19]



XII XIII

(16) For discussions of earlier work on the expanded sulfur valence shell problem, *cf.* Fehnel and Carmack, THIS JOURNAL, **71**, 84, 231 (1949); Heymann, *ibid.*, 260 (1949); Fehnel, *ibid.*, 1063 (1949).

(17) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, p. 45–47.

(18) Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939).

(19) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, p. 61.

The bathochromic shift observed in the case of 2,5-dicarbethoxy-3,4-dihydroxycyclopentadiene-2,4 (VI) in going from alcoholic hydrogen chloride as solvent to concentrated sulfuric acid contrasts with the hypsochromic shift in the case of the sulfone (III) under the same conditions (Figs. 1, 3, 4), and is interpreted as involving conjugate acid formation at a carbethoxyl group in VI with consequent elimination of charge separation in the resonating chromophoric system.

Summary

A study of the acidic strengths and ultraviolet absorption spectra of certain dihydroxythiophene-1-oxides and 1-dioxides has provided further evidence for an expanded valence shell for the sulfur atom in the sulfone configuration.

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[CONTRIBUTION FROM THE RICHARDSON CHEMISTRY LABORATORY OF TULANE UNIVERSITY]

Inorganic Complex Compounds Containing Polydentate Groups. II. The Complexes Formed between Triethylenetetramine and the Nickel(II) Ion

BY HANS B. JONASSEN AND B. E. DOUGLAS[1,2,3]

The stereochemical configuration of the quadricovalent complexes of the nickel(II) ion has been extensively investigated. This ion has been shown to be able to direct its valence bonds toward the corners of a tetrahedron[4,5,6,7] and of a plane.[6,7,8,9]

Various criteria have been used to obtain information about the configuration of these complex compounds. Lifschitz and co-workers[10] attempted to relate color and magnetic properties to bond direction. Yellow compounds were classed as planar because of diamagnetism; blue paramagnetic compounds indicated tetrahedral bond direction. This distinguishing characteristic, however, breaks down in many cases.

Mellor and co-workers[7] found that the electronegativity of the coördinating group influences the stereochemical configuration. The very electronegative donor atom, oxygen, imposes tetrahedral sp^3 bonds upon the nickel(II) ion. As the electronegativity decreases through nitrogen to sulfur, the bonds are directed toward the corners of a coplanar square. In the compounds containing four nitrogen donor atoms the statistical distribution is about half planar, half tetrahedral. Many complexes of this type can show both configurations.[10] Other factors such as steric hindrance due to coördinating groups and functional groups attached to donor atom also affect the configuration of these complexes.

In most of these complexes the coördinating group is a mono- or bidentate group. Very few quadridentate complexes containing the same donor atom have been investigated. In all of these cases[8,9,11] the configuration of the coördinating group imposes a planar configuration upon the complex.

This study was undertaken to determine the type of configuration of the complex or complexes formed between the nickel(II) ion and triethylenetetramine ($NH_2C_2H_4NHC_2H_4NHC_2H_4NH_2$) (abbreviated trien). This quadridentate base can orient itself with little difference in strain around a metal ion exhibiting tetrahedral or planar valence bond direction.

Since the configuration of the trien molecule does not impose a definite bond direction upon the central ion, this investigation may throw more light upon the factors which influence the direction of valence forces in the complexes containing the nickel(II) ion.

Since the nickel(II) ion also has a tendency to form octahedral complexes, the data obtained in this study may also indicate the ease of conversion of nickel(II) complex ions from tetra- to hexacoördination. This may lead to some information about the configuration of the tetracoordinated complexes since Dwyer and Mellor[12] found that planar diamagnetic nickel(II) complex ions show little tendency to assume sixfold coordination. Paramagnetic tetrahedral complex compounds, however, can easily be converted to an octahedral configuration by the uptake of two more donor groups.

Experimental

A. Spectrophotometric Studies. 1. Absorption Data.—Standard solutions of 0.05 *M* nickel chloride and 0.05 *M* trien were used in the absorption studies. Fixed amounts of nickel chloride were mixed with varying amounts of trien to give solutions with the following ratios

(1) Based upon the M.S. thesis of B. E. Douglas, Tulane University, 1947.

(2) Presented in part before Division of Physical and Inorganic Chemistry at the 112th American Chemical Society Meeting, New York, September, 1947.

(3) Present address: Department of Chemistry, Pennsylvania State College, State College, Pa.

(4) L. O. Brockway and P. L. Cross, *J. Phys. Chem.*, **13**, 828 (1935).

(5) W. Klemm and K. H. Raddatz, *Z. anorg. allgem. Chem.*, **250**, 204 (1942).

(6) I. Lifschitz and K. M. Dijkema, *Rec. trav. chim.*, **60**, 581 (1941).

(7) D. P. Mellor and and J. Craig, *J. Proc. Royal Soc. New South Wales*, **74**, 475 (1941).

(8) G. T. Morgan and F. N. Burstall, *J. Chem. Soc.*, 1672 (1938).

(9) I. Woodward, *J. Chem. Soc.*, 601 (1940).

(10) I. Lifschitz, J. G. Bos and K. M. Dijkema, *Z. anorg. allgem. Chem.*, **242**, 97 (1939).

(11) P. Ray and H. Ray, *J. Indian Chem. Soc.*, **21**, 163 (1944).

(12) E. P. Dwyer and D. P. Mellor, THIS JOURNAL, **63**, 81 (1941).

of nickel chloride to trien: 1:2, 2:1, 3:2, 1:1, 2:3, 1:2, 1:4. A drop of hydrochloric acid was added to each of the first three solutions to prevent hydrolysis of the non-complexed nickel(II) ion. The optical density values of the solutions were determined between the wave lengths of 500 and 1000 mμ using a Beckman spectrophotometer and matched Corex cells with a depth of 1 cm. The optical density curves are shown in Fig. 1. No change in absorption characteristics was obtained after the ratio of nickel(II) to trien becomes smaller than 2:3. The optical density values for the 1:2 and 1:4 nickel(II) ion to trien solutions are therefore not shown.

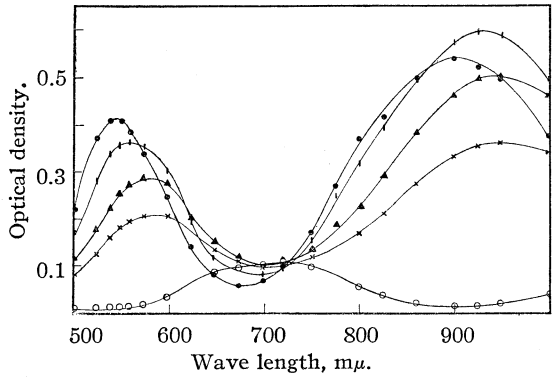


Fig. 1.—Absorption curves for solutions containing 0.05 *M* of nickel chloride and 0.0 to 0.075 *M* of trien: —O—, 0.05 *M* nickel chloride; —×—, ratio of 2:1 (Ni^{+2}:trien); —▲—, ratio of 3:2 (Ni^{+2}:trien); —|—, ratio of 1:1 (Ni^{+2}:trien); —●—, ratio of 2:3 (Ni^{+2}:trien).

Discussion.—As Fig. 1 shows the absorption characteristics of solutions containing a mole ratio of nickel(II) ion to trien of 2:1, 3:2 and 1:1 are very similar indicating the existence of a 1:1 complex [Ni trien]$^{+2}$ ion in the solution. However, after the 1:1 ratio has been exceeded a shift of the absorption maximum towards shorter wave lengths occurs indicating the existence of another colored complex in solution. Since no further change occurs after the ratio becomes smaller than 2:3, the composition of the other complex should correspond to $[Ni_2\ trien_3]^{+4}$ and no other colored complex with a mole ratio smaller than 2:3 should be present in the solution.

2. Continuous Variation Studies.—Solutions 0.1 *M* in nickel chloride and 0.1 *M* in trien were prepared for the continuous variation studies.[13] The optical density of solutions whose total solute concentration was 0.1 *M* with varying amounts of nickel(II) ions and trien was measured at the wave lengths 550, 565, 580, 600 and 860 mμ. In Fig. 2 *x* (the fraction of trien) is plotted against *y* (the difference between the observed optical density of the complex and the optical density calculated for no reaction) for the wave lengths 580 and 860 mμ. Figure 3 shows a similar plot for the nickel chloride–trien system at 550 mμ. In this graph, however, *y'* (*y'* is the difference between the observed optical density and that calculated for the 1:1 complex) is plotted against *x* (fraction of trien).

(13) W. C. Vosburgh and G. R. Cooper, THIS JOURNAL, **63**, 437 (1941).

Discussion.—The continuous variation studies indicate that, in solutions containing nickel(II) ions and trien, the [Ni trien]$^{+2}$ ion is present as is shown by the maxima at $x = 0.5$ in Fig. 2.

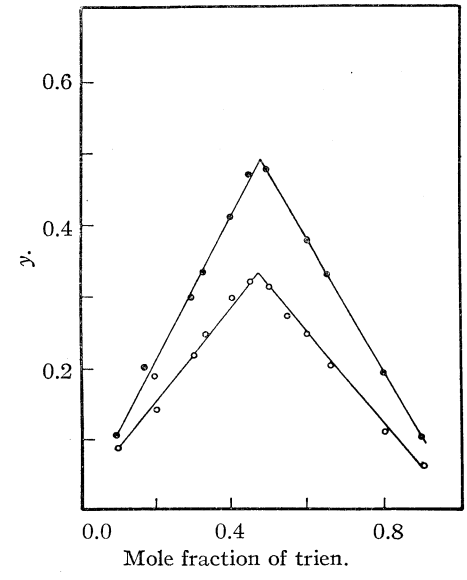


Fig. 2.—Continuous variation studies Ni^{+2}–trien system: ●, 860 mμ; O, 580 mμ.

Figure 3 shows a maximum at $x = 0.6$ indicating the existence of the $[Ni_2\ trien_3]^{+4}$ ion. No other maxima are obtained in these studies substantiating the conclusions drawn from the absorption

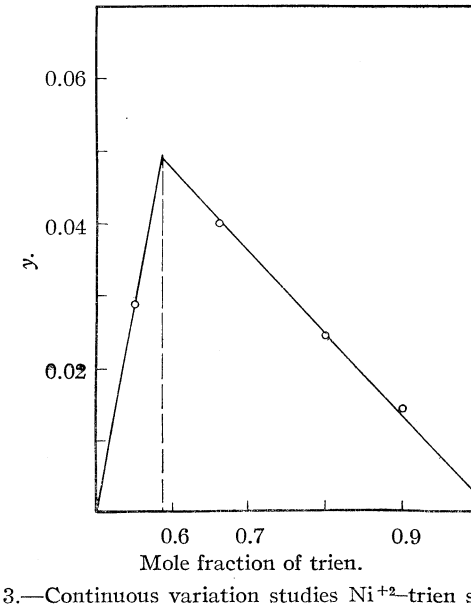


Fig. 3.—Continuous variation studies Ni^{+2}–trien system: O, 550 mμ.

data about the absence of colored complex ions of lower mole ratio in these solutions.

B. Preparation of Complex Compounds

1. Special Reagents.—The trien was a Technical Grade of 79% purity purchased from Eastman Kodak Company, Rochester, New York. The trien used in the absorption studies was distilled over sodium at reduced pressure (the fraction collected boiled at 139–141° at 10 mm. pressure) and was standardized potentiometrically.[14] All other chemicals used were standard reagents of C. P. quality.

2. Preparation of the Nickel(II) Chloride Complex $[Ni_2\ trien_3]Cl_4 \cdot 2H_2O$.—Twenty ml. of a 2 molar solution of trien was added to 10 ml. of 2 molar nickelous chloride with stirring. The color of the solution changed from green to a deep purple. This solution was evaporated almost to dryness, whereupon a mixture of 20 ml. of methyl alcohol and 10 ml. of ether was added. A light pink precipitate settled out immediately. It was washed with 20 ml. of methyl alcohol and 20 ml. of ether and dried in the oven at 65°.

Anal. Calcd. for $[Ni_2\ trien_3]Cl_4 \cdot 2H_2O$: Cl, 19.14; Ni, 15.5; C, 29.2; H, 7.9; N, 22.9. Found: Cl, 19.2; Ni, 15.7; C, 29.3; H, 7.7; N, 23.0.

3. Preparation of the Nickel(II) Nitrate Complex.—The complex nitrate was prepared in the same manner as the chloride. The precipitate obtained is slightly more violet in color.

Anal. Calcd. for $[Ni_2\ trien_3](NO_3)_4 \cdot H_2O$: Ni, 13.8; C, 26.3; H, 6.6; N, 20.4. Found: Ni, 13.9; C, 26.2; H, 6.7; N, 20.3.

4. Preparation of the Nickel(II) Tetrachloroplatinite Complex $[Ni_2\ trien_3][PtCl_4]_2$.—One hundred ml. of 0.01 *M* nickel chloride and 200 ml. of 0.005 *M* trien in aqueous solution were mixed in a beaker. A color change from green to blue to purple occurred. To this purple solution was added slowly and with stirring 100 ml. of 0.01 *M* potassium chloroplatinite. A light pink precipitate settled out of the solution immediately. The precipitate was washed successively with 200-ml. portions of cold water, 95% alcohol and ether. Drying to constant weight led to the formation of a light green precipitate which decomposed at 250–260°.

Anal. Calcd. for $[Ni_2\ trien_3](PtCl_4)_2$: Pt, 30.8; Ni, 9.30; C, 17.1; H, 4.3. Found: Pt, 30.8; Ni, 9.40; C, 16.8; H, 4.2. The loss of weight was found to be 2.66% which corresponds to two molecules of water of hydration in the pink complex compound.

Discussion.—The compounds obtained from the solutions containing nickel(II) ion, chloride or nitrate ions, and trien show a coördination number of 6 with octahedral valence bond distribution.

Since the spectrophotometric investigation of solutions containing nickel(II) ions and trien also indicates the existence of the $[Ni\ trien]^{+2}$ ion, potassium chloroplatinite was added. It was hoped that the large chloroplatinite ion would form a precipitate with the 1:1 complex ion similar to the insoluble [Pt trien] [Pt Cl_4].[15] However, the $[Ni_2\ trien_3]\,[Pt\ Cl_4]_2$ precipitated under these conditions indicating that even though the tetracoördinated $[Ni\ trien]^{+2}$ ion is present in solution its chloroplatinite is more soluble than that of the $[Ni_2\ trien_3]^{+4}$ ion.

(14) H. B. Jonassen, R. B. LeBlanc and R. Rogan, THIS JOURNAL, in press.

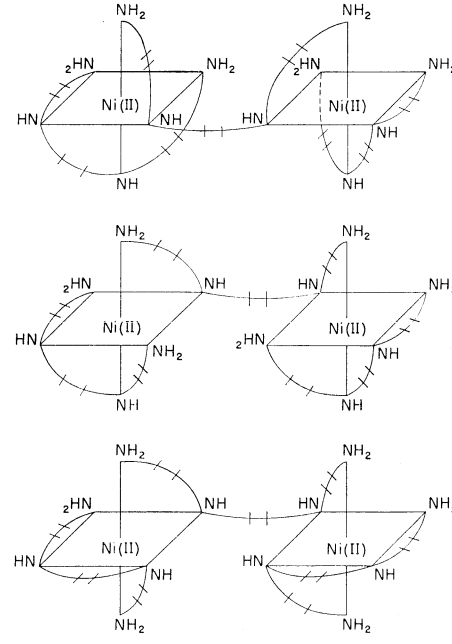
(15) N. L. Cull and H. B. Jonassen, *ibid.*, **71**, 4097 (1949).

C. Attempted Resolution of $[Ni_2\ trien_3]Cl_4$.—To 4 g. of $[Ni_2\ trien_3]Cl_4$ dissolved in 45 g. of water was added 15 g. of ammonium *d*-α-bromocamphor-π-sulfonate. Upon cooling in ice-water and allowing air to blow over the solution, some of the excess resolving agent crystallized out. Further evaporation of the solution of the complex *d*-α-bromocamphor-π-sulfonate produced several fractions. These fractions showed the same rotation and no measurable difference in physical properties. Similar results were obtained with ammonium *d*-tartrate.

Discussion.—Since it was not possible to resolve the complex ion, three possible explanations can be presented.

The diastereoisomers do not differ greatly in solubility. This possibility seems unlikely, however, since two resolving agents were used without effecting resolution.

It may be possible that only the meso forms were present in solution, the structures of which are given below.



$-N{+}{+}N- = -NC_2H_4N-$

Thirdly, it may be that the bonds are predominately ionic and that racemization occurs rapidly. This would produce a mixture with statistical distribution of optically active complexes and the meso forms.

Formation constant determinations in progress at the present time indicate that the formation of the $(Ni_2\ trien_3)^{+4}$ complex is a two-step reaction. The 1:1 complex forms first which is then changed to the $[Ni_2\ trien_3]^{+4}$ complex ion. The most stable binding of two 1:1 complexes to give the $(Ni_2\ trien_3)^{+4}$ ion is through the *cis*-positions of the two complexes. This would indicate $sp.^3$ ionic linkage for the 1:1 complex. This is in line with the observations reported by Dwyer and Mellor.[12]

D. Magnetic Investigations. The mass susceptibilities of $[Ni_2\ trien_3]Cl_4$, $[Ni_2\ trien_3](NO_3)_4$,

and $[Ni_2trien_3](PtCl_4)_2$ were determined on a modified Curie–Cheneveau balance.[16]

The measurements were made at 25° using ferrous ammonium sulfate (μeff = 5.25)[17] as a calibrating agent. From the mass susceptibilities measured at 25° the molecular susceptibility (χ_M) was determined. The effective Bohr magneton numbers were calculated from the formula

$$\mu\text{eff} = 2.83\sqrt{\chi_M T}$$[18]

The average effective moments per Ni(II) ion were:

$[Ni_2\ trien_3]Cl_4$ = 2.93	eff. Bohr magneton numbers
$[Ni_2\ trien_3](NO_3)_4$ = 2.91	eff. Bohr magneton numbers
$[Ni_2\ trien_3][PtCl_4]_2$ = 2.87	eff. Bohr magneton numbers

This is in good agreement with the values expected for two unpaired electrons in the nickel(II) ion with octahedral valence bond direction.

(16) F. W. Grey and Farquarson, *J. Sci. Insti.*, **9**, 1 (1932).
(17) P. W. Selwood, "Magnetochemistry," Interscience Publishers, Inc., New York, N. Y., 1943, p. 155.
(18) Ref. 17, p. 79.

Acknowledgments.—Mr. N. L. Cull prepared the $[Ni_2\ trien_3][PtCl_4]_2$ complex compound. The C, H and N analysis were performed by the Clark Micro Analytical Laboratories, Urbana, Illinois.

Summary

1. Spectrophotometric investigation of the nickel(II) ion–triethylenetetramine system indicates the existence of the colored $[Ni\ trien]^{+2}$ and $[Ni_2\ trien_3]^{+4}$ ions in solution.

2. The following compounds of the $[Ni_2\ trien_3]^{+4}$ ion were prepared: $[Ni_2\ trien_3]Cl_4 \cdot 2H_2O$, $[Ni_2\ trien_3](NO_3)_4 \cdot H_2O$ and $[Ni_2\ trien_3][PtCl_4]_2$.

3. It was not possible to isolate any compounds containing the $[Ni\ trien]^{+2}$ ion.

4. No optically active isomers could be isolated, possibly because of the ionic-metal-to-donor-atom link.

5. Magnetic studies of the compounds of the $[Ni_2\ trien_3]^{+4}$ ion indicate the existence of two unpaired electrons in the octahedral complex compounds.

NEW ORLEANS, LOUISIANA RECEIVED APRIL 18, 1949

[CONTRIBUTION FROM THE RICHARDSON CHEMICAL LABORATORY OF TULANE UNIVERSITY]

Inorganic Complex Compounds Containing Polydentate Groups. III. Platinum(II) and Palladium(II) Complexes with Triethylenetetramine[1,2]

BY HANS B. JONASSEN AND N. L. CULL

Elements showing a coördination number of four may form complex compounds with linkages of either the tetrahedral sp^3 or the planar dsp^2 type. The most abundant and satisfactory evidence for the planar structure may be found among the compounds of bivalent platinum and palladium.[3] The alleged resolution of optically active complex compounds of these ions by Reihlen[4] is the only evidence for a possible tetrahedral structure. However, the optical isomer was never obtained free from the resolving agent. Other workers[5,6] were unable to effect any resolution of platinum(II) and palladium(II) complex compounds. Mills and Quibell[7] and Lidstone and Mills[8] successfully resolved bis-chelate complexes of platinum(II) and palladium(II) which would be optically active if the central ion directed its valence forces toward the corners of a planar square or square pyramid. Dipole moment studies, however, completely eliminate the latter possibility.[9]

(1) Based on a portion of the M.S. thesis of N. L. Cull.
(2) Presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society at the 115th National Meeting at San Francisco, March, 1949.
(3) D. P. Mellor, *Chem. Rev.*, **33**, 137 (1943).
(4) H. Reihlen and K. Nestle, *Ann.*, **447**, 211 (1926).
(5) K. A. Jensen, *Z. anorg. allgem. Chem.*, **241**, 115 (1939).
(6) H. D. K. Drew, F. S. H. Read and H. J. Tress, *J. Chem. Soc.*, 1549 (1937).
(7) W. H. Mills and T. H. Quibell, *ibid.*, 839 (1935).
(8) A. G. Lidstone and W. H. Mills, *ibid.*, 1754 (1939).
(9) K. A. Jensen, *Z. anorg. allgem. Chem.*, **229**, 225 (1936).

Magnetic susceptibility measurements of the complexes of bivalent platinum and palladium have shown them to be diamagnetic,[10,11] which constitutes further evidence for planar dsp^2 linkage.[12]

In this investigation triethylenetetramine ($H_2NC_2H_4NHC_2H_4NHC_2H_4NH_2$) (abbrev. trien) was used as a coördinating agent for platinum(II) and palladium(II) complex compounds. Since trien acts as a quadridentate group,[13,14] its use offers interesting possibilities because the amine with little difference in strain may assume either a planar or a tetrahedral configuration around the central ion.

In the tetrahedral complex the presence of two unpaired electrons in the sp^3 linkage should produce paramagnetism.[12] Furthermore, if the linkage in the tetrahedral complex were mainly covalent[12] the complex should be capable of resolution since its structure is unsymmetrical.

A planar complex on the other hand would show diamagnetism due to dsp^2 type linkage,[12] and would be non-resolvable.

(10) W. Z. Biltz, *Z. anorg. allgem. Chem.*, **170**, 161 (1928).
(11) R. B. Janes, THIS JOURNAL, **57**, 471 (1935).
(12) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1944, p. 118.
(13) H. B. Jonassen and B. E. Douglas, THIS JOURNAL, **71**, 4094 (1949).
(14) F. Basolo, THIS JOURNAL, **70**, 2634 (1948).

Absorption Studies

1. Special Reagents.—Some special reagents were used in the preparation and study of the complexes formed between bivalent platinum and palladium and trien: the trien was Technical Grade 70% pure (70% trien, 30% water) purchased from Eastman Kodak Company, Rochester, New York. The trien for the absorption studies was distilled over sodium at reduced pressures, the fraction collected boiled at 139–141° at 10 mm. pressure. The trien was standardized potentiometrically. The C. P. chloroplatinic acid was obtained from the American Platinum Company of Newark, New Jersey, and the C. P. palladous chloride from Eimer and Amend, New York, N. Y. All other chemicals and reagents used were of standard C. P. quality.

Preparation of Potassium Chloroplatinite.—Five grams of chloroplatinic acid was treated with 1.6 g. of potassium chloride and the resulting potassium chloroplatinate was reduced with sulfur dioxide solution in the manner described by Keller.[15]

2. Experimental.—Standard solutions of 0.001 *M* potassium chloroplatinite, 0.001 *M* potassium chloropalladite and 0.001 *M* trien were used in the absorption studies. Fixed amounts of the potassium chloroplatinite and potassium chloropalladite were mixed with varying amounts of trien in the molar ratios of 1:0, 1:0.5, 1:1, 1:2, 1:5 and 1:10, respectively. The optical densities of these solutions were determined between the wave lengths of 280 and 800 mμ, using a Beckman spectrophotometer and matched Corex cells one centimeter in depth. The optical density values obtained for the potassium chloroplatinite–trien system are shown graphically in Fig. 1, and for the potassium chloropalladite–trien system in Fig. 2. The 1:10 and the 1:5 solutions in both instances showed practically the same absorption spectrum as the 1:2 solution and are not shown on the graphs. Absorption studies using 0.01 *M* potassium chloroplatinite and 0.01 *M* trien were made but the results were not reproducible because of the formation of a precipitate upon standing.

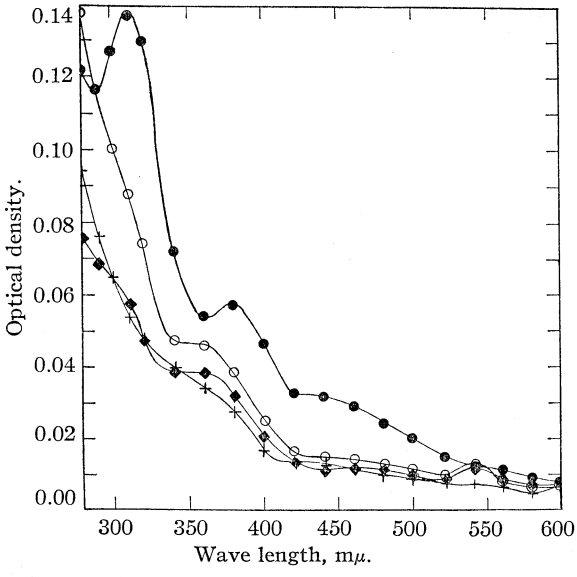


Fig. 1.—Plot of optical density *vs.* wave length for solutions 0.001 *M* in platinum(II) ion with varying concentrations of triethylenetetramine: ●, K_2PtCl_4; O, 1:0.5; ◆, 1:1; +, 1:2.

(15) G. Keller, "Inorganic Syntheses," Vol. II, McGraw-Hill Book Company, Inc., New York, N. Y., 1946, p. 247.

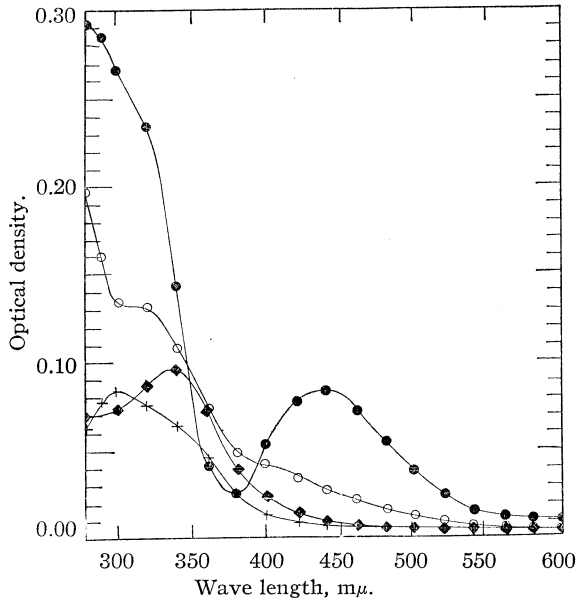


Fig. 2.—Plot of optical density *vs.* wave length for solutions 0.001 *M* in palladium(II) ion with varying concentrations of triethylenetetramine: ●, K_2PdCl_4; O, 1:0.5; ◆, 1:1; +, 1:2.

3. Discussion.—The study of the absorption spectra for the potassium chloroplatinite–trien and the potassium chloropalladite–trien systems clearly indicates the formation of one or more colored complexes in each instance. In the potassium chloroplatinite–trien system a disappearance of the absorption characteristics of the chloroplatinite ion is noted as the mole ratio of trien is increased. A shift of the maxima toward shorter wave lengths is noted for the 1:0.5 and the 1:1 solutions. In the 1:2 solution a disappearance of the characteristic maxima of the chloroplatinite ion occurs. This shifting of the maxima of the absorption curves toward shorter wave lengths is even more marked in the potassium chloropalladite–trien system. It indicates a disappearance of the tetrachloro complexes of bivalent platinum and palladium in solutions of high trien concentration and the formation of one or more trien complexes.

Continuous Variation Studies

Continuous variation studies were also at-

tempted but very little information could be obtained from these. This is not unexpected from theoretical considerations since the difference in the absorption characteristics between the $[PtCl_4]^=$, $[PdCl_4]^=$ ion and the complexes of the system Pt(II) (Pd(II))–trien is very small. Furthermore, replacement of the chloro groups in the tetrachloro compounds by amines is very complex,[16] which makes it very difficult to interpret the results of the continuous variation studies.

Preparations

A. [Pt trien][PtCl$_4$], a Magnus-type Salt.[17]—Potassium chloroplatinite was allowed to react with an aqueous solution of trien in the ratio of 2 moles of trien to 1 mole of potassium chloroplatinite. The reddish purple precipitate which settled out after thirty minutes was filtered, washed successively with 200-ml. portions of cold water, 95% ethyl alcohol and finally with ether. It was dried in an oven at 110–120° overnight. The resultant product was a purple-red powder, non-hygroscopic, and only very slightly soluble in water; yield was approximately 20% of theoretical. The salt was found to decompose at temperatures exceeding 260°.

Anal. Calcd. for [Pt trien][PtCl$_4$]: Pt, 57.5; Cl, 20.9; N, 8.26. Found: Pt, 57.4; Cl, 21.2; N, 8.17.

B. Triethylenetetramineplatinum(II) Ion.—The $[Pt\ trien]^{++}$ ion was prepared by the addition of a large excess of trien to an aqueous solution of potassium chloroplatinite. The color of the solution changes from a cherry red to a light yellow as excess amine is added.

C. The Aminium Salt of Platinum.—Five grams of chloroplatinic acid was reduced to the chloroplatinous acid using sulfur dioxide solution as described by Keller.[18] The color of the solution changes from an orange to a cherry red during the course of the reduction. Approximately 0.01 mole of chloroplatinous acid was diluted to 100 ml. and 2 ml. of 70% trien was added, and the solution allowed to stand overnight. It was filtered and the precipitate was washed successively with 600 ml. of cold water, 300 ml. of 95% ethyl alcohol, and finally with 300 ml. of diethyl ether, and dried at 110° overnight. The resultant powder was light orange, non-hygroscopic, and decomposed at 260–265°; yield was about 10%. The complex was slightly soluble in water, insoluble in all common organic solvents. The effect of *p*H on the formation of the aminium salt was investigated. In general it was found that the aminium salt was formed in solutions of low *p*H (2–3), while the Magnus-type salt of platinum and trien was formed in neutral or basic media.

Anal. Calcd. for $(PtCl_4)_2H_4(trien)\cdot 2H_2O$: Pt, 45.6; Cl, 32.8; N, 6.52. Found: Pt, 45.8; Cl, 33.1; N, 6.74.

D. Triethylenetetraminepalladium(II) Chloropalladite.—A saturated solution of potassium chloropalladite was prepared by treating palladous chloride with a slight excess of potassium chloride. To 100 ml. of the potassium chloropalladite was added dropwise 0.5 ml. of 70% trien. A light brownish-orange precipitate settled out of solution and was filtered off immediately. It was washed with 200 ml. of cold water, 200 ml. of 95% ethyl alcohol and 100 ml. of diethyl ether and dried in an oven at 110–120° overnight. The resultant product was a light tan, non-hygroscopic powder which decomposed at 230–235°. It was found that on standing the filtrate yielded another crop of crystals which were light yellow in color. The metal analyses for the light tan and yellow precipitates were almost identical. The variation in color may be attributed to differences in precipitation conditions and particle size. The precipitates formed were practically insoluble in all common solvents. Total yield was about 40%.

Anal. Calcd. for [Pd trien][PdCl$_4$]: Pd, 42.6; Cl, 28.3. Found: Pd, 42.7; Cl, 27.9.

E. Triethylenetraminepalladium(II) Ion.—The $[Pd\ trien]^{++}$ ion was prepared by adding a large excess of trien to an aqueous solution of potassium chloropalladite. The color of the solution changes from brown to light yellow as excess amine is added.

F. The Aminium Salt of Palladium.—Several attempts were made to prepare the aminium type complex of palladium by treating palladous chloride with excess hydrochloric acid and then adding trien. In all cases, a yellow precipitate was obtained which metal analyses proved to be [Pd trien][PdCl$_4$]. All attempts to form the aminium salt were unsuccessful.

Structural Investigation of Complexes

1. The Complex Compounds Pt$_2$trien Cl$_4$ and Pd$_2$trienCl$_4$: Conductometric Titrations

Experimental.—One hundred ml. of 5.95×10^{-4} [Pt trien][PtCl$_4$] was titrated with 0.09468 *N* silver nitrate using the conductometric method. The distilled water in all solutions was boiled for one half hour prior to use to remove any dissolved gases. A plot of bridge readings against ml. of silver nitrate added is shown in Fig. 3.

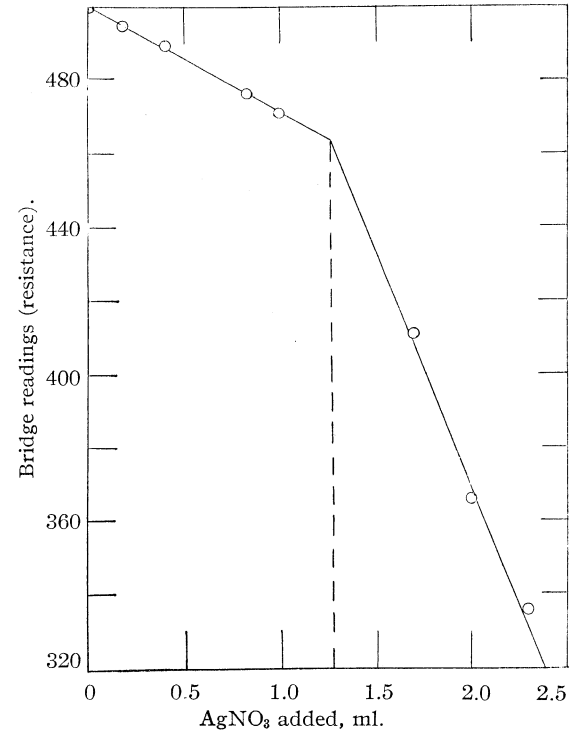


Fig. 3.—Conductometric titration of [Pt(trien)][PtCl$_4$] with $AgNO_3$.

Discussion.—The conductometric titration shows that two equivalents of silver ion is necessary to react with one equivalent of [Pt trien][PtCl$_4$] resulting in a precipitate of silver chloroplatinite. The precipitate formed during this titration has the typical brown color of silver chloroplatinite and analysis showed it to be this compound. These data prove that the 2:1 complex in the basic solution is a Magnus-type salt with a

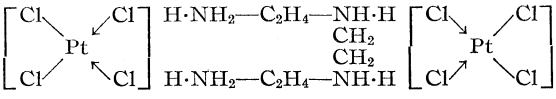
(16) Emeleus and Anderson, "Modern Aspects of Inorganic Chemistry," D. Van Nostrand Company, Inc., New York, N. Y., 1944, p. 105.

(17) G. Magnus, *Poggendorfs Ann.*, **14**, 239 (1828).

(18) G. Keller, "Inorganic Syntheses," Vol. II, McGraw-Hill Book Company, Inc., New York, N. Y., 1946, p. 250.

structural formula of [Pt trien][$PtCl_4$]. Attempts were also made to repeat the above procedure for the 2:1 complex of palladium, but it was so insoluble that no reproducible results could be obtained. By analogy to the platinum complex, however, it would seem that the palladium complex also possesses a Magnus-type structure, *viz.*, [Pd trien][$PdCl_4$].

2. The Complex Compound $Pt_2trienH_4Cl_8$.—The absorption spectrum of a solution of this salt showed the absorption characteristics of the tetrachloroplatinite ion (see Fig. 1) indicating that its structure is



3. The [Pt(trien)]$^{++}$ and [Pd(trien)]$^{++}$ Ions:

A. Attempted Optical Resolution

Experimental.—Several attempts were made to precipitate the [Pt(trien)]$^{++}$ and [Pd(trien)]$^{++}$ ions using a large optically active anion. Saturated solutions of *d*-tartaric acid and *d*-α-bromocamphor-π-sulfonate were added to solutions of the ions. Dry air was blown over the solutions for several hours and the resulting precipitate was tested for platinum. In all instances the tests revealed only the presence of organic material.

Discussion.—Although the 1:1 complex had been isolated for either the Pt(II) or Pd(II) systems, its existence in solution has been shown. By treatment with [$PtCl_4$]$^{=}$ or [$PdCl_4$]$^{=}$ ions the corresponding Magnus-type salts precipitate.

If a covalent tetrahedral [Pt trien]$^{++}$ or [Pd trien]$^{++}$ ion were present in solution a large optically active anion should bring about resolution. Since the fractions obtained contained no platinum the resolving agents must be more insoluble than the platinum salts. No structural information can therefore be obtained from these data.

B. Magnetic Behavior

Experimental.—The magnetic behavior of the solid complexes prepared, *viz.*, [Pt trien][$PtCl_4$], [$PtCl_4$]$_2H_4$(trien)·$2H_2O$, and [Pd trien][$PdCl_4$] was investigated on a Curie–Cheneveau type balance.[19,20] The investigation was made at room temperature (25°). Previously boiled distilled water was used to calibrate the balance. In all instances the salts under investigation were found to be diamagnetic. Average mass susceptibilities found for [Pt trien][$PtCl_4$], H_4(trien)($PtCl_4$)$_2$·$2H_2O$ and [Pd trien][$PdCl_4$] were found to be -0.22×10^{-6}, -0.31×10^{-6} and -0.42×10^{-6} units, respectively.

Discussion.—The diamagnetism exhibited by all of the complexes investigated is in accord with the predictions of theory and constitutes further evidence for the planar structure of bivalent platinum and palladium complexes.[12]

Summary

1. The absorption spectra of the system triethylenetetramine and platinum(II) or palladium(II) ions indicate that one or more complexes are present in these systems.

2. The complex compounds [Pt trien][$PtCl_4$], [Pd trien][$PdCl_4$] and [trienH_4 ($PtCl_4$)$_2$]·$2H_2O$ were prepared and their structures determined.

3. Attempts to resolve the [Pt trien]$^{++}$ and [Pd trien]$^{++}$ ions were unsuccessful.

4. Magnetic investigations of the complex compounds show them to be diamagnetic, indicating planar dsp^2 linkage.

(19) Cheneveau, *Phil. Mag.*, **20**, 357 (1910).

(20) Grey and Farquharson, *J. Sci. Instruments*, **9**, 1 (1932).

NEW ORLEANS, LOUISIANA RECEIVED APRIL 22, 1949

CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CHICAGO]

The Kinetics of the Reaction of Ozone and Chloride Ion in Acid Aqueous Solution

BY LE ROY BROUGH YEATTS, JR.,[1,2] AND HENRY TAUBE

Kinetic investigations of reactions of ozone with reducing agents are in most instances difficult. The reactions are often so rapid that it is difficult to follow the rate, as for example in the reactions with stannous ion, iodide ion or ferrous ion. Often, too, the reaction with the reducing agent induces decomposition of ozone. This is observed in the reactions of ozone with hydrogen peroxide,[3] formic acid,[4] oxalic acid and phosphorous acid.[5] By contrast, in the system under present study, the main net reaction

$$2H^+ + 2Cl^- + O_3 = O_2 + H_2O + Cl_2 \qquad (A)$$

proceeds slowly enough so that the rate may be followed by ordinary methods, and it accounts almost completely for the change in the system. A very slight decomposition of ozone is observed, but since it varies in an erratic way from experiment to experiment it appears to be unrelated to reaction A. Elsewhere[3] it has been shown, and this observation is confirmed by the present work, that the spontaneous decomposition of ozone in acid solution is inhibited by chloride ion.

(1) From a thesis submitted by Le Roy B. Yeatts, Jr., to the Department of Chemistry, Cornell University, in partial fulfillment of the requirements for the Ph.D. degree.

(2) Present address, Lafayette College, Easton, Penna.

(3) Taube and Bray, THIS JOURNAL, **62**, 3357 (1940).

(4) Taube, *ibid.*, **63**, 2453 (1941).

(5) Taube, unpublished observations.

The rate of reaction A has been measured at various concentrations of ozone, chloride ion and hydrogen ion at different temperatures and in the presence of various metal ions that might be expected to act as catalysts.[6] The data on the variation of rate with temperature yield the value of the "*a*" factor which is of particular interest in the present system. The over-all reaction involves a spin change. It seemed of interest to discover whether an abnormally low "*a*" factor, as has been predicted[7] for a reaction of this type if the spin change takes place in the rate determining step, would be observed for reaction A.

Experimental Procedure

For each experiment a large supply of a solution of ozone was prepared by bubbling ozonized oxygen through conductivity water acidified with perchloric acid. This solution was maintained at the particular temperature chosen for the experiment. A series of calibrated reaction cells (designed to minimize gas volume, see Fig. 1) previously cooled to the temperature of the bath, and each containing the required amount of chloride ion, was rapidly filled from the reservoir through a tube issuing from its bottom. The cells were then stoppered and placed in the constant-temperature bath shielded from light, withdrawn at intervals and the ozone and chlorine content determined. The initial concentration of ozone was determined by analysing at once the contents of a cell from which chloride ion had been omitted.

In carrying out an analysis, the cell was attached to the analysis train diagrammed in Fig. 1, air was drawn rapidly through the system and the ozone and chlorine removed from the gas stream by neutral potassium iodide contained in tubes C. It was found that the ozone concentration in the reaction cell fell to 40% of its initial value after an aspiration period of one minute. In making analyses, the aspiration was continued for ten minutes. This is sufficiently long to insure complete removal of ozone and of chlorine.

The method for determining chlorine and ozone depends on the fact that both react with iodide ion, and that the reaction of ozone with iodide ion consumes hydrogen ion quantitatively. An excess of acid in known amount was added to the contents of tubes C, and the total oxidizing agent (T. Ox.) determined by titration with standard thiosulfate. Then iodate in excess was added and the liberated iodine again titrated. The second titration measures the amount of acid left after the ozone has reacted with the iodide ion, and on comparing it with amount of acid added, gives the amount of ozone. The precision of the analytical method may be gaged by comparing the figures for T. Ox at zero time with the concentration of ozone at zero time. The latter figure is based on the acidimetric analysis.

The thiosulfate solution was standardized against potassium iodate and against potassium dichromate. The acid was standardized by means of the iodate method used in the analysis.

All solutions were made up using conductivity water. The perchloric acid was 60% C. P. acid. For most of the experiments, hydrochloric acid of special grade, low in heavy metals, was used as the source of chloride ion. For experiments in which the chloride ion concentration exceeded that of the hydrogen ion, C. P. sodium chloride was added to supply chloride ion. The ionic strength was maintained constant in a series by means of sodium perchlorate. A solution of this salt was prepared by neutralizing perchloric acid with sodium carbonate.

(6) G. R. Hill, THIS JOURNAL, **70**, 1036 (1948).

(7) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, pp. 324–326.

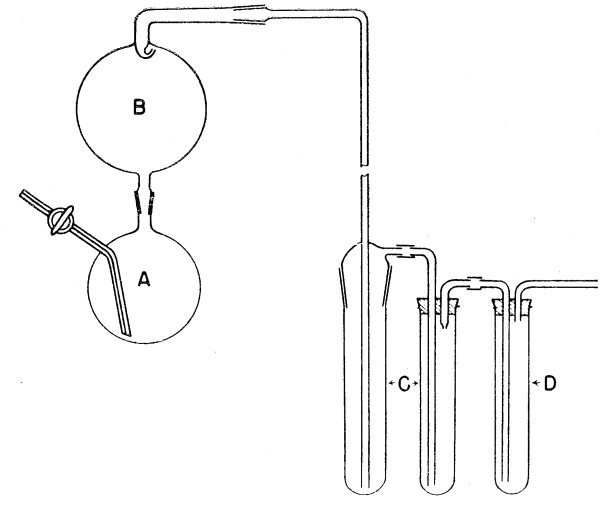


Fig. 1.—Chain used for aspiration of reaction bulbs: A, reaction bulb; B, bulb to prevent entrainment of liquid; C, tubes containing neutral potassium iodide solution; D, trap connected to water aspirator.

An ice–water mixture was used to maintain a temperature of 0°, and a solid dioxane–liquid dioxane mixture for 9.5°.

Throughout the paper, time is expressed in minutes and concentration in moles per liter.

The data are treated with reference to the rate law

$$-\mathrm{d}(O_3)/\mathrm{d}t = k(O_3)(Cl^-) + k^*(O_3) \qquad (I)$$

The second term on the right-hand side allows for the slight decomposition of ozone which accompanies the oxidation of chloride ion. The spontaneous decomposition is first order[8] in the absence of chloride ion, and it was assumed to be first order in the present system also. When this rate law is integrated under the condition that (O_3) is the only concentration variable (other reagents in great excess) it leads to the following form, which is the form applied to the data.

$$k = \frac{2.303}{(Cl^-)_{av}t}\,\frac{\Delta(Cl_2)}{\Delta(O_3)}\,\log\frac{(O_3)_0}{(O_3)_t} \qquad (II)$$

It is evident that as long as the decomposition of ozone is slight (*i.e.*, T. Ox. remains almost constant in an experiment), $\Delta(Cl_2) = \Delta(O_3)$ very nearly and the correction factor $\Delta(Cl_2)/\Delta(O_3)$ is nearly unity. Values of T. Ox. have been reproduced in Tables I, IV, V and VI to indicate how nearly this condition is approached in the experiments.

Results

Variation of Rate with Ozone Concentration.—Table I presents some of the data which show how the rate of reaction varies with the concentration of ozone, the other variables being kept almost constant. The concentration of ozone has been varied by using different initial concentration, and by following the natural decrease with time during an experiment.

(8) Sennewald, *Z. physik. Chem.*, **A164**, 305 (1933).

TABLE I

VARIATION OF RATE WITH CONCENTRATION OF OZONE

μ = *ca.* 0.09; temp. = 0° C.

No.	Time, min.	T. Ox. × 10^4	$(O_3)_t$ × 10^4	(Cl^-) av.	(H^+) av.	k
1	0	5.872	5.872	0.04028	0.04940	....
	853	5.799	3.024	.04000		0.0190
	1089	5.823	2.538	.03995		.0190
2	0	17.17	17.08	.04028	.05107	
	2493	17.04	2.569	.03883		.0196
	2533	17.07	2.437	.03882		.0198
	2645	16.99	2.153	.03879		.0202
3	0	15.16	15.16	.04028	.04770	
	747	14.86	8.438	.03961		.0198
	780	14.87	8.238	.03959		.0198
	1033	14.80	6.810	.03944		.0196
	1062	14.68	6.534	.03942		.0201
4	0	15.21	9.205	.04028	.05175	
	450	15.23	6.275	.03999		.0213
	1490	15.26	2.740	.03901		.0205

The data show that over a range three-fold in initial ozone concentration and about eight-fold for the extreme concentrations, the rate of reaction is first order with respect to ozone concentration. In other experiments also (see below) the ozone concentration changed three or four-fold in an experiment. With the exception of a few early experiments, in none was there evidence for deviation from the first order law beyond what might be attributed to experimental error. In a few of the earlier runs, a decrease of specific rate with time was observed. The precise cause of this drift was not discovered, but it disappeared after some details of the analytical procedure were improved, and did not reoccur in any of the later experiments.

Experiment 4 was conducted by permitting the reaction to proceed for ten hours before the first sample was analyzed. In this period of time the concentration of chlorine built up to about two-thirds that of the ozone for the first sample of the series. The rather good agreement of the specific rates in this run with the others shows that there are no important effects caused by accumulation of products, or by the destruction of a catalyst.

Surface Effect.—To investigate the possibility that the cell surfaces might influence the rate of reaction A, the series of experiments presented in Table II was performed. Comparisons of rate were made varying the surface to volume ratio about four-fold, using in one experiment soft glass beads and in the others pyrex tubing. It may be concluded from the data that the observed rate is independent of surface area in the range studied. The slight increase observed for the packed vessels can be entirely attributed to the higher concentration of acid in these experiments (see below)—in performing the experiments the fact that the packing material occupied some of the volume was overlooked when the hydrochloric acid was measured into the cells.

TABLE II

EFFECT OF VARYING THE SURFACE TO VOLUME RATIO, T = 0°C.

Expt.	Rel. surf.: vol. ratio	Time, min.	$(O_3)_t$ × 10^4	$(Cl^-)_{av.}$	$(H^+)_{av.}$	μ	k
1	1	0	18.92	0.04028	0.05044	0.091	....
	1	963	8.588	.03925	.04941	.089	0.0209
	4.1[a]	0	17.85	.05203	.06165	.114	....
	4.1[a]	992	6.135	.05086	.06048	.111	.0212
2	1	0	19.37	.04028	.04853	.089	....
	1	1016	8.805	.03922	.04747	.087	.0198
	1	1046	8.828	.03923	.04748	.087	.0192
	3.4[b]	0	18.97	.04620	.05418	.100	....
	3.3[b]	1075	7.159	.04459	.05259	.097	.0203
	3.4[b]	1103	7.094	.04543	.05339	.099	.0196
3	1	0	19.79	.04028	.04691	.087	....
	1	990	9.286	.03923	.04586	.085	.0195
	1	1018	9.045	.03921	.04584	.085	.0196
	3.4[b]	0	19.12	.04620	.05256	.099	....
	3.3[b]	1051	7.547	.04461	.05099	.096	.0199
	3.4[b]	1082	7.121	.04543	.05177	.097	.0200

[a] Soft glass beads used. [b] Pyrex tubing used.

Variation of Rate with Concentration of Chloride Ion.—Data bearing on the variation of rate with the concentration of chloride ion are presented in Table III. These data show that the rate of reaction A is accurately first order with respect to chloride ion concentration over the four-fold range investigated.

TABLE III

THE EFFECT OF VARYING CHLORIDE ION CONCENTRATION

μ = *ca.* 0.30: T = 0° C.

Expt.	Time, min.	$(O_3)_t$ × 10^4	$(Cl^-)_{av.}$	$\Delta(Cl_2)$ × 10^4	$(H^+)_{av.}$	k
1	0	11.81	0.1004	....	0.1035	....
	137	8.287	.1000	3.503	.1031	.0255
	273	5.894	.0997	5.906[b]	.1029	.0255
	297	5.531	.0998	6.239	.1029	.0255
2	0	8.590	.1004	....	.1027	....
	149	5.878	.1001	2.750[b]	.1024	.0255
	303	3.982	.0999	4.616	.1022	.0254
3	0	10.57	.02509	....	.1029	....
	292	8.813	.02491	1.757	.1027	.0250
	314	8.709	.02464	1.871	.1027	.0252
	581	7.320	.02477	3.200	.1026	.0251
4	0	8.025	.02509	....	.09957	....
	277	6.688	.02496	1.275	.09944	.0252
	656	5.270	.02479	2.706	.09930	.0254
	682	5.224	.02481	2.757	.09929	.0250

Variation of Rate with the Concentration of Hydrogen Ion.—Table IV presents the results of a series of experiments at constant ionic strength by varying values of hydrogen ion concentrations. The averages of the specific rates for each experiment are plotted against the averages of the hydrogen ion concentrations in Fig. 2. The result shows that the rate law has two terms, one independent of hydrogen ion concentration, and the other, first order in hydrogen ion concentration.

$$d(Cl_2)/dt = k_1(O_3)(Cl^-) + k_2(O_3)(Cl^-)(H^+) \quad (III)$$

At μ = 0.30 and 0°, k_1 = 0.0128 1. mole.$^{-1}$ min.$^{-1}$ and k_2 = 0.124 1.^{2} mole.$^{-2}$ min.$^{-1}$

TABLE IV

VARIATION OF k WITH HYDROGEN ION CONCENTRATION

μ = *ca.* 0.30; T = 0° C.

Expt.	Time, min.	T. Ox. × 10^4	$(O_3)_t$ × 10^4	$(Cl^-)_{av.}$	$(H^+)_{av.}$	k
1	0	17.36	17.36	0.1004	0.01189	....
	305	17.29	11.33	.0998	.01129	0.0139
	330	17.20	10.91	.0987	.01127	.0139
	583	17.23	7.711	.0993	.01094	.0138
	608	17.18	7.432	.0994	.01092	.0138
2	0	19.17	19.03	.1004	.02820	....
	268	19.00	12.19	.0997	.02752	.0166
	297	19.06	11.82	.0986	.02750	.0163
	532	19.01	8.005	.0993	.02710	.0163
3	0	19.49	19.44	.1004	.07317	....
	285	19.40	10.39	.0995	.07227	.0220
	314	19.46	9.853	.0984	.07227	.0220
	555	19.42	5.866	.0989	.07181	.0218
	583	19.45	5.516	.0990	.07178	.0218
4	0	8.007	8.025	.02509	.09957	....
	277	7.963	6.688	.02496	.09944	.0252
	656	7.976	5.270	.02479	.09930	.0254
	682	7.981	5.224	.02481	.09929	.0250
5	0	20.09	20.08	.1004	.2047	....
	143	19.54	11.32	.0985	.2014	.0382
	243	19.80	7.831	.0991	.2035	.0382
	268	19.77	7.126	.0991	.2034	.0381

Variation of the Rate of Reaction with Temperature.—A series of experiments was carried out at 9.5°, keeping μ at 0.3 and varying the concentration of hydrogen ion. The results are presented in Table V, and are shown in graphical form in Fig. 2 (lower curve). The values of k_1 and k_2 at 9.5° are found to be 0.0379 and 0.366, respectively. Two experiments were carried out also at a higher temperature, 25°. Under these conditions the decomposition of ozone becomes marked, and the initial concentration of ozone is low. These factors make the experimental error so great that further work at this temperature was abandoned. The data indicate that the temperature coefficient in the range 9.5 to 25° does not differ seriously from that in the range 0 to 9.5°.

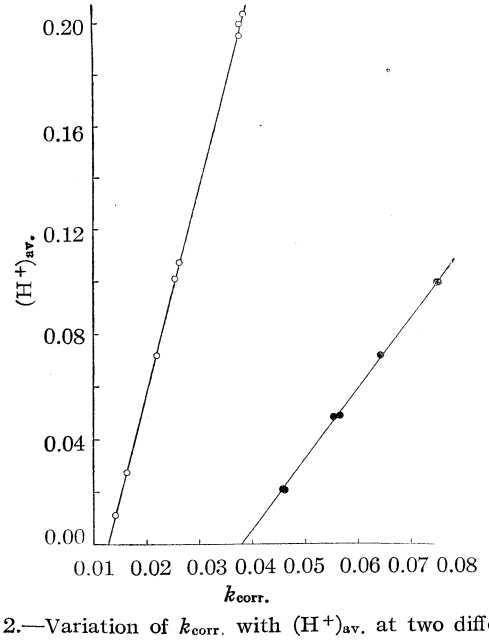


Fig. 2.—Variation of $k_{corr.}$ with $(H^+)_{av.}$ at two different temperatures: O, 0°; ●, 9.5°; μ = *ca.* 0.30.

TABLE V

VARIATION OF k WITH HYDROGEN ION CONCENTRATION AT A HIGHER TEMPERATURE

μ = *ca.* 0.30; T = 9.5° C.

Expt.	Time, min.	T. Ox. × 10^4	$(O_3)_t$ × 10^4	$(Cl^-)_{av.}$	$(H^+)_{av.}$	k
1	0	11.71	11.68	0.05020	0.02111	....
	147	11.57	8.248	.04987	.02078	0.0459
	207	11.47	7.094	.04976	.02067	.0462
	259	11.43	6.328	.04969	.02060	.0454
2	0	12.69	12.70	.05020	.04874	....
	152	12.44	8.171	.04977	.04863	.0550
	196	12.39	7.177	.04968	.04854	.0554
	243	12.36	6.318	.04960	.04846	.0549
3	0	13.08	13.19	.05020	.07271	....
	87	12.91	9.708	.04988	.07239	.0651
	144	12.83	8.095	.04920	.07230	.0642
	204	12.83	6.698	.04959	.07210	.0634
	259	12.72	5.570	.04948	.07199	.0633
4	0	13.76	13.80	.05020	.1008	....
	152	13.38	7.548	.04962	.1002	.0747
	210	13.37	6.065	.04947	.1001	.0749
	261	13.36	5.005	.04936	.1000	.0749

Applying the Arrhenius equation to the data for the temperatures 0 and 9.5°, the values of the activation energy for the hydrogen ion dependent path and the hydrogen ion independent path are calculated to be 17,500 ± 300 and 17,600 ± 300 cal., respectively; the "a" factors are 1.2 × 10^{13} l.^{2} mole.$^{-2}$ min.$^{-1}$ and 1.4 × 10^{12} l. mole.$^{-1}$ min.$^{-1}$, respectively.

Catalysis by Metal Ions.—The influence of metal ions on the rate of reaction was investigated to some extent. The data obtained in this phase of the study are presented in Tables VI and VII.

In Table VII the observed values of k are compared with those expected if metal ion were omitted but the ionic strength kept the same. This comparison necessitates a slight correction for the difference in ionic strength between the solutions used here and those used for the earlier experiments. The correction was made using the Brönsted relation for the variation of specific rate with ionic strength. A correction presumably is required only for the second term of the rate law. In the most extreme case the correction changed the value of k at (H^+) = 0.100 M from 0.0252 at μ = 0.30 to 0.0306 at μ = 0.152.

The comparison of columns 7 and 8 of Table VII shows that Cu^{++} and Fe^{+++} at concentrations near 0.01 M do not exert a marked effect on the rate of reaction A. The correction applied for the ionic strength is undoubtedly too great;

TABLE VI

EFFECT OF VARIOUS POSITIVE IONS ON THE RATE OF REACTION, $T = 0°C.$

Expt.	Subst. added	$(M^{+n}) \times 10^4$	Time, min.	T. Ox. $\times 10^4$	$(O_3)_t \times 10^4$	$(Cl^-)_{av.}$	$(H^+)_{av.}$	μ	k
1	$CuCl_2$	98.11	0	20.57	20.51	0.06975	0.1026	0.182	....
			148	20.37	15.17	.06923	.1021		0.0276
			232	20.36	12.89	.06900	.1019		.0284
			320	20.32	10.86	.06880	.1017		.0283
2	$FeCl_3$	96.86	0	21.77	21.73	.07925	.1026	.211	....
			63	21.54	18.62	.07824	.1023		.0294
			113	21.47	16.72	.07877	.1021		.0279
			191	21.34	14.05	.07852	.1019		.0276
			229	21.27	13.01	.07842	.1018		.0271
3	$CoCl_2$	1.088	0	18.17	18.21	.1004	.1030	.204	....
			102	17.96	8.699	.0986	.1021		.0716
			127	17.89	7.289	.0993	.1019		.0705
			155	17.90	5.934	.0992	.1018		.0711
			183	17.75	4.718	.0991	.1017		.0720
4	$CoCl_2$	2.176	0	21.84	21.78	.05057	.1016	.152	....
			52	21.75	12.81	.05001	.1007		.203
			88	21.78	8.951	.04929	.1003		.205
			114	21.74	6.934	.04909	.1001		.204
			138	21.68	5.458	.04895	.1000		.204
5	$CoCl_2$	4.363	0	20.99	20.92	.05100	.0978	.150	....
			83	20.83	4.367	.04935	.0962		.380
			108	20.79	2.723	.04919	.0960		.381

[a] An average value of ionic strength during the course of an experiment.

TABLE VII

RATE CONSTANT DATA IN PRESENCE OF METALLIC IONS, $T = 0°C.$

Expt.	Subst. added	$(M^{+n}) \times 10^4$	$(Cl^-)_{av.}$	$(H^+)_{av.}$	μ	k if non-catalyzed	k	k_3
1	$CuCl_2$	98.1	0.0690	0.102	0.182	0.0295	0.0284	..
2	$FeCl_3$	96.9	.0785	.102	.211	.0282	.0280	..
3	$CoCl_2$	1.09	.0991	.102	.204	.0287	.0713	38.9
4	$CoCl_2$	2.18	.0493	.100	.152	.0306	.204	39.3
5	$CoCl_2$	4.36	.0494	.0961	.150	.0301	.380	39.6

even assuming that the corrected values are as much as 5% too high, the effect of these metal ions is seen to be very slight. By contrast, cobaltous ion at much lower concentration accelerates the reaction markedly. The data for cobaltous ion have been treated under the assumption that to the two terms of equation III must be added the term $k_3(O_3)(Co^{++})$. Not enough experiments have been done to test the rate law rigorously, but it does describe accurately the present data which cover a two-fold change in (Cl^-), a four-fold change in (Co^{++}) and approximately a five-fold change in (O_3). The value of k_3 at 0° is 39.3 l. mol.$^{-1}$ min.$^{-1}$ It is of interest to note that Co^{++} in the presence of Cl^- does not catalyze the decomposition of ozone, as is the case if chloride ion is absent.[3,6]

Discussion of the Results

Rate law III shows that in acid solution there are two paths for reaction A. A reasonable mechanism for the hydrogen ion independent path is

$$O_3 + Cl^- \xrightarrow{k_1} O_2 + ClO^- \text{ (rate determining)}$$
$$2H^+ + Cl^- + ClO^- = Cl_2 + H_2O \text{ (rapid)}$$

The hydrogen ion dependent path may be supposed to differ only in that each activated complex contains one hydrogen ion in addition to the ozone molecule and chloride ion.

Alternative possibilities for the products formed in the rate determining step have been considered. The most reasonable of these are discussed below, and the arguments which have led to their rejection are presented.

$$\text{(a)} \quad Cl^- + O_3 + H_2O \longrightarrow Cl + HO + HO^- + O_2 \qquad (1')$$

This reaction postulates a one-electron oxidation–reduction process for $O_3 + Cl^-$. Calculation shows this step to be endothermic to the extent of about 45 kcal. This value exceeds the observed activation energy by much more than the error in the calculations, hence reaction 1′ may be ruled out as a possibility. The fact that the catalytic decomposition is very slight also argues against reaction 1′ as the slow step. Atomic chlorine initiates a rather pronounced catalytic decomposition of ozone also in water solution[3]; the decomposition observed in the present system is slight and is unrelated to the main reaction.

$$\text{(b)} \quad Cl^- + O_3 \longrightarrow Cl{-}O{-}O^- + O$$

Using bond energy values and thermal data,[9] ΔH for this reaction is estimated as 62 kcal., which is again much in excess of the observed activation energy.

$$\text{(c)} \quad Cl^- + O_3 \longrightarrow ClO_2^- + O$$

(9) Pauling, "Nature of the Chemical Bond," Cornell University Press, 1939; thermal data from Bichowsky and Rossini, "Thermal Chemistry of Chemical Substances," Reinhold Publishing Corp., New York, N. Y.

This reaction can be rejected because it is not in agreement with the observed chemistry. If ClO_2^- were formed it would certainly lead to the formation in the system of ClO_2 or ClO_3^-. Furthermore, for this reaction also ΔH (= 41 kcal.) much exceeds the observed activation energy.

It appears that only if a strong oxygen to oxygen bond is maintained in the products (as is the case when O_2 is a product) will the value of ΔH be compatible with the activation energy. ΔH for reaction 1 is -18.9 kcal.

The observed activation energy does not preclude the possibility that the oxygen found in the rate determining step is left in an excited state. Thus for the reaction

$$Cl^- + O_3 \longrightarrow ClO^- + O_2{}^1\Delta$$

ΔH is 3.5 kcal. A formulation of this type ($^1\Sigma$ oxygen is another possibility) may in fact explain why the "a" has about the normal value, 1.4×10^{12}, although there is a spin change in the over-all reaction. The spin change may take place after the rate determining step by deactivation of the singlet oxygen. In a study recently published[10] the "a" factor in another reaction in which a spin change takes place

$$ClO^- + H_2O_2 \longrightarrow H_2O + O_2 + Cl^-$$

was also found to be normal. In this reaction also the activation energy is high enough so that the oxygen formed as product in the rate determining step may be in an excited singlet state, and the spin change may therefore take place after the rate determining step.

It may be of interest to note that the oxidation of bromine ion by ozone[11] at low hydrogen ion proceeds by a path similar to that of term 1 of equation III. As might be expected, the specific rate of the $Br^- + O_3$ reaction is much greater than that of the $Cl^- + O_3$ reaction, 1600 as compared to 0.28 at 0°.

It seems remarkable that hydrogen ion exerts a catalytic effect by enhancing the "a" factor rather than by lowering activation energy. The oxidation of halide ions by hydrogen peroxide is also governed by a rate law similar in form[12] to rate law III. Participation by hydrogen ion in these reactions leads to a decrease in activation energy amounting to 2,860 cal. in the reaction of hydrogen peroxide with chloride ion.

Catalysis of reaction A by cobaltous ion may be explained by the reaction of cobaltous ion with ozone to form cobaltic ion as the slow step. Cobaltic ion is known to react rapidly with chloride ion, thus the catalyst at the steady state will be present mainly in the lower oxidation state. This interpretation gives for the specific rate of the reaction $Co^{++} + O_3$ ($+H_2O$) the value of 39.3 l. mole^{-1} min.$^{-1}$. This reaction is important also in the decomposition of ozone catalyzed by cobaltous ion, and Hill[13] has measured the specific rate in the latter system as 37. Hill has suggested $CoOH^{++} + OH + O_2$ as the products formed in step 3. This formulation is consistent with the present work. HO at high Cl^- in acid is expected to react rapidly to produce Cl, Cl in turn is expected to react rapidly to form Co^{+++}. Thus, the net result of the interaction of one mole of ozone and one mole of cobaltous ion is the production of two moles of cobaltic ion, equivalent to one mole of chlorine. In the absence of chloride ion, each $Co^{++} + O_3 \rightarrow$ act accounts for the net destruction of two molecules of ozone.[6]

The data show that acceleration or inhibition of the reaction by cupric or ferric ions even at 0.01 M is inappreciable. It may therefore be concluded that the oxidation of these substances by ozone is very slow. Any catalytic effects to the magnetic moments of these substances are also very slight.

Acknowledgment.—The authors wish to express to Prof. E. R. VanArtsdalen their appreciation for the help he has given and interest he has taken in this work.

Summary

The rate law for the reaction of ozone with chloride ion in acid solution is

$$d(Cl_2)/dt = k_1(O_3)(Cl^-) + k_2(H)(Cl^-)(O_3)$$

At 0° and $\mu = 0.3$, k_1 is 0.0128 l. mole^{-1} min.$^{-1}$ and k_2 is 0.124 l.^{2} mole^{-2} min.$^{-1}$. The activation energies and "a" factors corresponding to the first and second terms are 17.6 and 17.5 kcal., 1.4×10^{12} and 1.2×10^{13}.

Cupric and ferric ions affect the rate of reaction only slightly, if at all. Cobaltous ion exerts a strong catalytic effect, expressible by adding the term k_3 (Co^{++}) (O_3) to the rate law. The value of k_3 is found to be 39.3 l. mole^{-1} min.$^{-1}$ in agreement with the value obtained by Hill in an independent system.

Mechanisms for the three reaction paths have been proposed.

RECEIVED APRIL 16, 1949

(10) Connick, THIS JOURNAL, **69**, 1514 (1947).
(11) Taube, *ibid.*, **64**, 2468 (1942).
(12) Mohammed and Liebhafsky, *ibid.*, **56**, 1680 (1934).
(13) Hill, THIS JOURNAL, **71**, 2434 (1949). The work published earlier (ref. 6) does not give the specific rate since the distribution of the catalyst between upper and lower oxidation states was not measured.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

The Rates of Reaction of Isocyanates with Alcohols. I. Phenyl Isocyanate with 1- and 2-Butanol[1]

BY ELIZABETH DYER, HUGH A. TAYLOR,[2] SHIRLEY J. MASON[3] AND JAN SAMSON[4]

In this Laboratory a program of investigating the factors influencing the reactivity of polymers both in solution and in solid form has been undertaken. In order to interpret the results it is desirable to secure information on lower molecular weight analogs of the polymers to be studied. Therefore, as a basis for understanding the reactivity of hydroxy-containing polymers with isocyanates, kinetic data have been secured on the interaction of normal and secondary butyl alcohols with phenyl isocyanate.

The first work on the kinetics of the action of alcohols with isocyanates was that of Davis and Farnum[5] who studied the relative reactivities of phenyl isocyanate with the lower aliphatic alcohols by allowing two alcohols to compete for a limited quantity of phenyl isocyanate and then determining the ratio of the two products from freezing points of the mixtures obtained. Tarbell, Mallatt and Wilson[6] showed the effect of certain acid and basic catalysts on the yields of urethans obtained from α-naphthyl isocyanate and phenols. A detailed investigation of the kinetics of the base-catalyzed reaction of various isocyanates with methanol was made by Baker and Holdsworth.[7] By the use of the Stagg[8] method of analysis for isocyanate groups, Baker and Holdsworth showed that the addition of the alcohol to the isocyanate follows second order kinetics in the presence of a constant concentration of a tertiary base. In subsequent papers Baker and Gaunt[9,10,11,12] have studied thoroughly both the base-catalyzed and "spontaneous" reactions of phenyl isocyanate with methyl, ethyl and isopropyl alcohols in di-*n*-butyl ether and in benzene solutions, and have secured kinetic evidence for the mechanism of these reactions.

In the present investigation a dilatometric method was developed for the determination of the reaction rates of *n*- and *s*-butyl alcohols with phenyl isocyanate. The correctness of the method was verified by chemical analyses.

(1) From the Master's theses of Hugh A. Taylor, September, 1947, Shirley J. Mason, June, 1948, and Jan Samson, June, 1949, University of Delaware. Presented before the Organic Division at the Chicago meeting of the American Chemical Society, April, 1948.

(2) Present address: General Electric Company, Pittsfield, Mass.

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(4) Present address: Shell Oil Company, Houston, Texas.

(5) Davis and Farnum, THIS JOURNAL, **56**, 883 (1934).

(6) Tarbell, Mallatt and Wilson, *ibid.*, **64**, 2229 (1942).

(7) Baker and Holdsworth, *J. Chem. Soc.*, 713 (1947).

(8) Stagg, *Analyst*, **71**, 557 (1946).

(9) Baker and Gaunt, *J. Chem. Soc.*, 9 (1949).

(10) Baker and Gaunt, *ibid.*, 19 (1949).

(11) Baker, Davies and Gaunt, *ibid.*, 24 (1949).

(12) Baker and Gaunt, *ibid.*, 27 (1949).

Experimental

Equipment.—The dilatometer was of the coil type in order to provide adequate surface for heat transfer. The coil, made from forty inches of Pyrex tubing, 10 mm. o. d., was sealed to two lengths of capillary tubing, 1.5 mm. i. d. The open ends of the capillaries were attached to stopcocks carrying calcium chloride tubes. The dilatometer was calibrated by the thermal expansion of water in order to make certain that there were no irregularities in the capillaries.

For the kinetic studies at 15, 25 and 35° the dilatometer was immersed in a stirred seven-gallon water-bath, the temperature of which was controlled by an "H-B Red Top Thermoregulator." Readings taken once a minute for twenty minutes showed a regular cycle of sharp rise and slow decline with an outside variation of 0.03 to 0.04°. This variation could be taken care of when necessary by applying a slight experimental correction of 0.009 scale unit per 0.01°. The reactions at 0° were carried out in a one-gallon thermos jug in which a mixture of ice and water was kept stirred. The temperature variation was found to be negligible by checking with a Beckmann thermometer.

Materials.—Xylene was a satisfactory solvent for the dilatometric work. Solvents such as benzene and dioxane could not be used because of their volatility.

Care was taken to remove water from all solvents and reagents. Xylene was distilled over sodium and fractionated. Acetone was dried over calcium chloride and distilled. Piperidine was fractionated after standing over solid potassium hydroxide. Phenyl isocyanate was distilled under reduced pressure, b. p. 58.2–59.5° at 18–20 mm. Normal and secondary butyl alcohols were purified by treatment with sodium followed by fractionation. A convenient test for the absence of moisture was to let a mixture of the alcohol, isocyanate and solvent stand for two days; if water was present crystals of the very insoluble diphenyl urea separated. Tertiary butyl alcohol was purified by refluxing over barium oxide, followed by several distillations from sodium. Alpha terpineol[13] was a redistilled sample, m. p. 34.5–35.5°.

Dilatometer Method.—Equal volumes of xylene solutions of alcohol and the isocyanate, of known concentration and previously brought to the bath temperature, were mixed quickly and introduced into the dilatometer by suction. Readings were made of time, accurate to ±1 second, and of the scale, accurate to ±0.01 unit, at periodic intervals until no further contraction occurred. In the initial work at least fifty readings were taken for each determination. For calculation of the velocity constants the customary second order expressions (1) and (3) were used in the form of equations (2) and (4) for equal and unequal reactant concentrations, respectively.[14]

$$(1)\quad k = \frac{1}{t}\,\frac{x}{a(a-x)}$$

(13) This material was furnished in pure condition through the courtesy of the Hercules Powder Company.

(14) A derivation of equations (1) and (4) and a discussion of errors in their use is given in the thesis of J. Samson, University of Delaware, June, 1949.

$$(2)\quad k = \frac{1}{t}\frac{R_0 - R_t}{a(R_t - R_\infty)}$$

$$(3)\quad k = \frac{1}{t}\frac{2.303}{a - b}\log\frac{b(a - x)}{a(b - x)}$$

$$(4)\quad k = \frac{1}{t}\frac{2.303}{a - b}\log\frac{a(R_0 - R_\infty) - b(R_0 - R_t)}{a(R_t - R_\infty)}$$

Where R_0, R_t and R_∞ are dilatometer readings at the times indicated.

The R_0 was found for equation (2) by extrapolating the plot of $1/(R_t - R_\infty)$ against time and for equation (4) by extrapolating the plot of log $(R_t - R_\infty)$ against time. The k values were determined graphically from data such as those shown in Figs. 1 and 2. At least fourteen points were plotted to obtain the slopes of the lines.

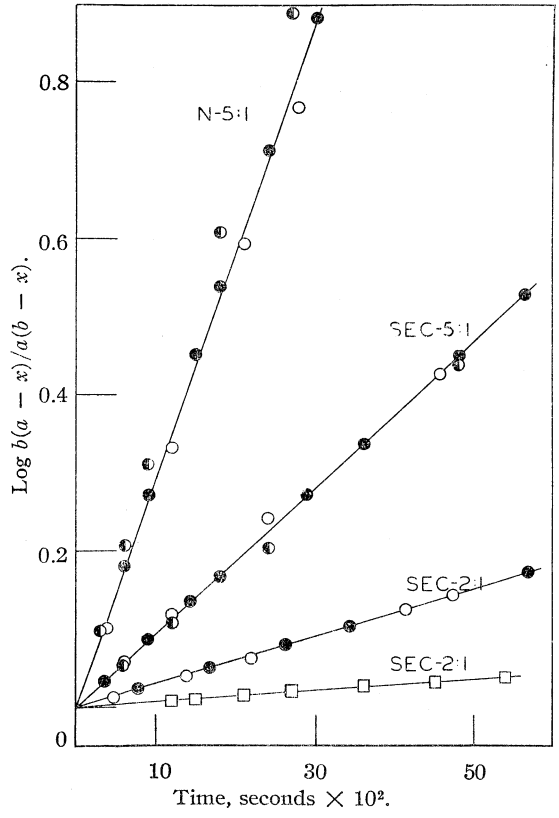

Fig. 1.—Second order curves for the reactions of *n*- and *s*-butyl alcohols with phenyl isocyanate in varying ratios of alcohol to isocyanate: O and ●, duplicate dilatometric analyses at 25°; ◐, chemical analysis at 25°; □, dilatometric analysis at 0°; a and b, initial concentrations of –OH and –NCO; x, –NCO reacted, moles/l.

Chemical Method.—Solutions of the alcohol and isocyanate of known concentrations were made up by weighing into volumetric flasks and diluting at constant temperature with xylene. Ten-milliliter samples of the alcohol solutions were transferred by pipet to each of several test-tubes to which were added at appropriate intervals ten-milliliter portions of the isocyanate solutions, and the mixtures were

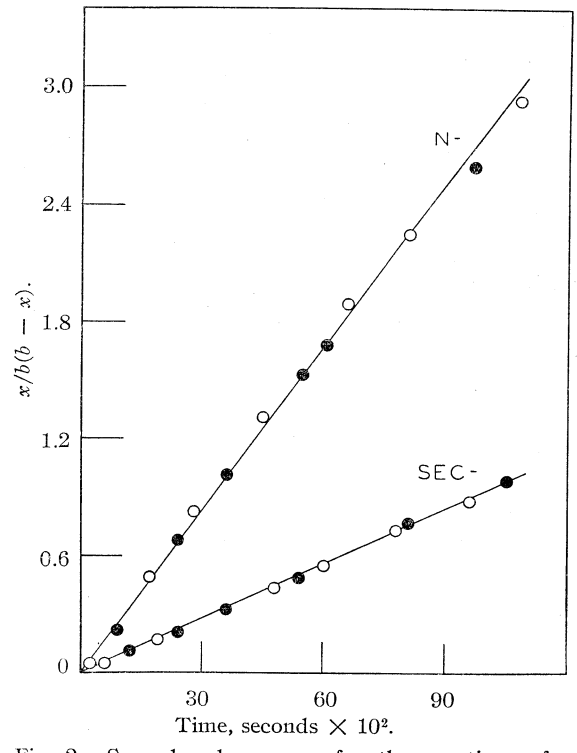

Fig. 2.—Second order curves for the reactions of *n*- and *s*-butyl alcohols with phenyl isocyanate in a 1:1 ratio at 25°: O and ●, duplicate dilatometric analyses; b, initial concn. of –NCO, moles/l.; x, –NCO reacted in time t.

allowed to stand in the constant temperature bath. At exactly the desired time each of the reactions was stopped by the addition of a known volume of a standard piperidine solution in xylene. After one-half hour the excess of piperidine was titrated with standard 0.1 *N* hydrochloric acid, using methyl red–methylene blue indicator. Blank determinations were always run on the piperidine and on the isocyanate. Thus the quantity of isocyanate which had reacted was determined by this modification of the Stagg method.[8] Analyses on known samples showed that the method had a precision of 3 parts per 1000 and an accuracy of 5 parts per 1000 or better. In work subsequent to that reported here the titration has been improved by the use of brom phenol blue as indicator and the addition of sufficient methanol-free acetone to give a one-phase system.

Determination of Volume Contraction.—The dilatometer was calibrated in terms of ml. per scale division by weighing water at constant temperature. From the calibration graph and the R_0 value for a given rate experiment the initial volume and hence the initial weight of isocyanate in the dilatometer was obtained. The total contraction, obtained from the value of $R_0 - R_\infty$, was used to find the contraction in ml. per mole of isocyanate reacted, shown in Table II.

Results and Discussion

A summary of the results obtained is given in Table I. All of the reactions studied were shown to follow the second order rate law to a high percentage of completion of reaction (see Figs. 1 and 2 and column 4 of Table I). The reactions at the lower reactant ratios are slow, but it was desirable to avoid the use of a catalyst so that in later work mixtures of polymers and reactants in films could be dried before appreciable reaction occurred.

The k values obtained by the chemical analysis were in the same general range as those from the dilatometric data, although in the 5:1 n-butyl alcohol–isocyanate reaction the points from the chemical plot are consistently slightly higher than those from the dilatometric one. In the other chemical run and in several not yet reported there is good agreement between dilatometric and titration data.

The second order k values for both the n- and s-butyl alcohols decreased with decreasing concentration of the alcohols. This is in accord with the behavior of methyl, ethyl and isopropyl alcohols with phenyl isocyanate as observed by Baker and Gaunt.[10] The explanation given by these investigators was that the alcohol acted as a catalyst through the formation of an intermediate complex with the isocyanate

$$C_6H_5NCO + ROH \rightleftharpoons C_6H_5N\overset{-}{C}O\ (\text{complex})$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad ROH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad +$$
$$\text{complex} + ROH \longrightarrow C_6H_5NHCOOR + ROH$$

The validity of this mechanism was established by the derivation of the following kinetic equation

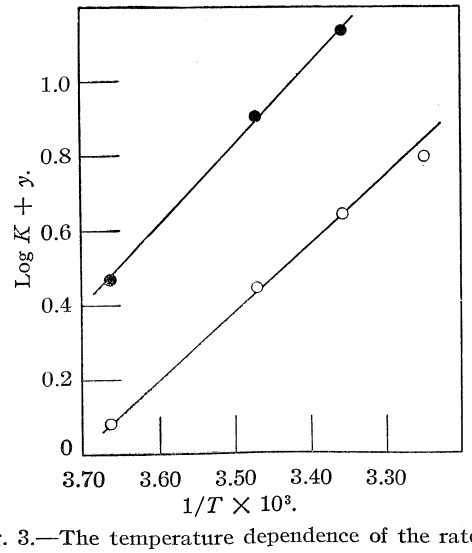

Fig. 3.—The temperature dependence of the rate constants for reactions of n- and s-butyl alcohol with C_6H_5-NCO (2:1 ratio): ○, n-; ●, sec-. The constant y was used for convenience in plotting; $y = 4$ for the n-, 5 for the s.

TABLE I

KINETICS OF THE INTERACTION OF n- AND s-BUTYL ALCOHOLS WITH PHENYL ISOCYANATE IN XYLENE SOLUTION

Ratio of concn. of OH:NCO	NCO concn., moles/l.	Temp., °C.	$k^a \times 10^4$ l. mole^{-1} sec.$^{-1}$	P,[b] %
n-Butyl Alcohol with Phenyl Isocyanate				
2:1	0.4948	35	6.27	68
2:1	.5386		6.34	
5:1	.3464	25	4.63	89
5:1	.3629		4.66	
5:1	.5004		4.53	
5:1	.4992		4.39	
5:1[c]	.3761		4.88	
2:1	.5004		4.38	71
2:1	.4978		4.46	
1:1	.3710		2.41	86
1:1	.3713		2.43	
2:1	.4985	15	2.78	51
2:1	.4960		2.80	
2:1	.4945	0	1.19	53
2:1	.4926		1.23	
s-Butyl Alcohol with Phenyl Isocyanate				
5:1	0.3699	25	1.60	87
5:1	.3696		1.54	
5:1	.4975		1.55	
5:1	.4978		1.48	
5:1[c]	.3815		1.39	
2:1	.5052		1.35	66
2:1	.5057		1.37	
1:1	.3715		1.01	59
1:1	.3667		0.95	
2:1	.5044	15	0.83	53
2:1	.5062		0.78	
2:1	.4967	0	0.295	31

[a] Second order rate constants. [b] P is the minimum per cent. completion of the reaction which follows the straight line slopes of the graphs, such as those in Figs. 1 and 2. [c] Chemical method; the others are dilatometric.

which could be tested graphically.

$$(ROH)/k_0 = k_2/k_1k_3 + (ROH)k_1$$

A similar test of the data from this investigation

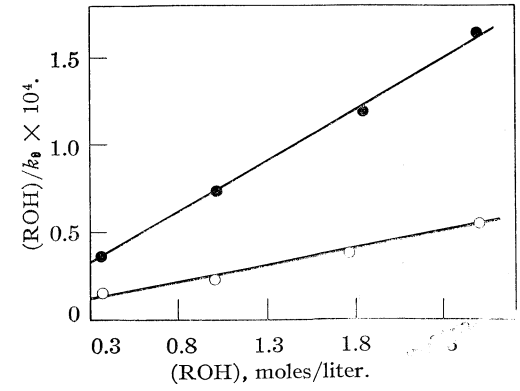

Fig. 4.—Effect of alcohol concentration on velocity constants: ○, n-butyl alcohol; ●, s-butyl alcohol, both with PhNCO in xylene solution at 25°. Each k_0 value is the average of those of approximately the same concentration from Table I.

is given in Fig. 4. The linearity of the plot of $(ROH)/k_0$ against (ROH) shows that the action of *n*- and *s*-butyl alcohols may be explained by the Baker and Gaunt mechanism.

It is of interest to compare the constants obtained in this work for the *n*- and *s*-butyl alcohols with the relative values reported by Davis and Farnum.[5] Their value for k_n/k_s is 3.03. In this investigation the value of k_n/k_s is 2.95 for the 5:1 ratio of reactants, and 3.24 for the 2:1 ratio of reactants, using in both cases the average of the dilatometric figures at 25°.

The rate of reaction of *t*-butyl alcohol with phenyl isocyanate to give a carbamate could not be determined because of the rapid formation of diphenyl urea. The reaction of α-terpineol with phenyl isocyanate in a 1:1 ratio at a concentration of 0.36 *M* for each reactant was followed by chemical analysis for a period of eight weeks. The data obtained were in accord with a second order reaction rate for the first five weeks; the velocity constant was 9×10^{-7} mole^{-1} l. sec.$^{-1}$. This may not be a correct value, however, because in this case also diphenyl urea was formed, although more slowly. It is not known whether the dehydration preceded or followed the interaction of the hydroxyl and isocyanate groups. Even with the *s*-butyl alcohol there was evidence of the same dehydration in the presence of phenyl isocyanate; at 35° an appreciable quantity of diphenyl urea was formed, although all reactants were anhydrous. At 25° or lower the *s*-butyl alcohol and phenyl isocyanate yielded traces of diphenyl urea, formed when 80% or more of the reaction had been completed. In the calculation of the velocity constants on the *s*-butyl alcohol experiments a possible source of error is the assumption that the R_∞ reading was not appreciably affected by the presence of traces of diphenyl urea crystals.

The effect of temperature on the rate constants for the action of *n*- and *s*-butyl alcohols with phenyl isocyanate at 2:1 reactant ratios is shown in Fig. 3. The slopes of the straight line graphs of log *k* against $1/T$ were determined by the method of least squares. The energy of activation, calculated by the Arrhenius equation, was 8100 cal./mole for the *n*- and 9900 cal./mole for the *s*-butyl alcohol.

The volume changes during the reactions, calculated as described in the experimental section, are given in Table II. It is apparent that the shrinkage per mole of isocyanate used is practically the same for various concentrations of the two different alcohols.

TABLE II

VOLUME CONTRACTION DURING REACTIONS AT 25°

Reactant ratios	Contraction, ml. of solution per mole C_6H_5NCO	
	n-BuOH	*s*-BuOH
5:1	18.7	19.8
2:1	21.1	20.0
1:1	19.9	20.2
Average	19.9	20.2

Work is in progress on the reactivity of difunctional isocyanates with simple alcohols, and also with polymeric alcohols in the film state.

Acknowledgment.—The authors are indebted to Dr. H. M. Spurlin of the Hercules Powder Company for suggesting this problem and giving valuable advice during the course of the work, to Dr. C. C. Lynch of the University of Delaware for helpful discussions, and to Mr. G. W. Creighton for making some of the measurements.

Summary

A dilatometric method has been developed for the measurement of the reaction rates of isocyanates with alcohols in solution. The velocity constants for the action of phenyl isocyanate with *n*- and *s*-butyl alcohols, respectively, in xylene at various temperatures are reported. It has been shown that these reactions follow closely second order kinetics, regardless of whether the ratio of alcohol to isocyanate is 5:1, 2:1 or 1:1. The value of the constant is somewhat higher, however, in the presence of an excess of the alcohol. The values for energy of activation are 8100 and 9900 cal./mole for the *n*- and *s*-butyl alcohols, respectively. The volume contraction during the reactions at 25° is approximately 20 ml. of solution per mole of isocyanate used.

NEWARK, DELAWARE RECEIVED JUNE 8, 1949

[CONTRIBUTION FROM THE CHEMICAL AND PHYSICAL RESEARCH LABORATORIES OF THE FIRESTONE TIRE & RUBBER COMPANY]

Infrared Studies of Hindered Phenols

BY WILLIAM C. SEARS AND LELAND J. KITCHEN

Infrared absorption measurements have proved[1] a useful method for studying the formation of hydrogen bonds between hydroxyl groups. Fox and Martin[2] observed the primary O–H bands for mono-, di- and triphenylcarbinols in the associated state at 2.97 μ, 2.89 μ and 2.87 μ, respectively. Each of these bands approached the value of 2.77 μ on extreme dilution in a non-polar solvent.

Coggeshall[3] used the wave length shift between the associated and unassociated states of the hydroxyl group as a measure of the strength of the hydrogen bond formed. He classed phenols containing ortho alkyl substituents as unhindered, partially hindered or hindered on the basis of wave length shifts $\Delta\lambda > 0.15$ μ, $0.04\mu < \Delta\lambda < 0.15$ μ or $\Delta\lambda < 0.04$ μ, respectively. On this basis phenols having no or small ortho substituents were classed as unhindered phenols.

In the present investigation the primary O–H bands of twenty-nine alkyl and alkoxy phenols were studied by the dilution method. Several of the phenols were unhindered; but the others contained one or two methyl, isobornyl, *t*-butyl or *tt*-octyl groups or a combination of one of these groups with methyl, as hindering ortho substituents. Relative hindrances imparted by these groups to the hydrogen bonding of the phenol hydroxyl were determined. A hydrogen bonding index was devised in order to compare the various groups in hindering power.

Several of the compounds reported by Coggeshall[3] were remeasured because he did not differentiate between the liquid and solid states. It is now found that there are large infrared shifts between the melt and solid states for several of these phenols, particularly for those without ortho substituents. Therefore a valid comparison of strengths of hydrogen bonds as determined by infrared shifts should be based on measurements on the liquid phase.

Experimental

Procedure.—Infrared bands were measured with an evacuable automatic recording spectrometer with a large sodium chloride prism, designed and constructed in the laboratories of The Firestone Tire & Rubber Co.

Wave length shifts were determined by comparing absorption bands of dilute solutions (0.07 molar solutions in carbon tetrachloride) with bands for concentrated solutions, for melts, and for crystalline solids. The concentrated solutions were prepared by wetting the phenols with just sufficient carbon tetrachloride to effect solution. Three phenols liquid at room temperature were measured without solvent. Several phenols were examined in the melted state at temperatures slightly above their melting points; then they were allowed to crystallize and the spectra were remeasured.

The melted and crystalline samples were 0.001 in. thick compared with 0.066 in. for the dilute solutions. Thickness of the concentrated solutions varied from 0.001 to 0.002 in.

Results are summarized in Table I. Conveniently the shift of the hydroxyl band from its wave length in dilute solution to the wave length in concentrated solution is defined as $\Delta\lambda_c$; the shift from dilute solution to melt as $\Delta\lambda_m$; and the shift to the solid state, $\Delta\lambda_s$.

Values for $\Delta\lambda$ are accurate within ± 0.004 μ, while the probable error in the determination of λ is ± 0.02 μ.

In comparison with values for $\Delta\lambda_s$ which are available in the literature, the present values are intermediate between those of Coggeshall[3] and those obtained by examination of the published curves of Richards and Thompson.[4] In making these comparisons it is assumed that Coggeshall measured 4-*t*-butylphenol, 4-*t*-amylphenol and 2-*t*-butyl-4-methylphenol in the solid state. Elsewhere agreement is good except for phenol.

Materials.—The solvent was C. P. carbon tetrachloride, which was found to have no absorption in the hydroxyl region.

Most of the phenols were of analytical purity (99.0–99.9%), having been purified by recrystallization and having melting points listed in Table I. The 2,4-dimethylphenol (Eastman Kodak Co. grade) and several other liquids—2,4-dimethyl-6-*t*-butylphenol, 2,4-dimethyl-6-*tt*-octylphenol and 2,6-di-*t*-butyl-4-*s*-butylphenol—which were not purified beyond fractional distillation were about 95% pure. The 2,6-diisobornyl-4-methylphenol, which was obtained as a solid resin of b. p. 254–276° (10 mm.) and could not be purified through recrystallization, was estimated to have a purity of 70–80%.

The 2,6-dimethylphenol, 3,4,5-trimethylphenol, 2,4,6-trimethylphenol, 2,3,6-trimethylphenol and 2,3,5,6-tetramethylphenol samples were supplied through the courtesy of Shell Development Company.

Alkyl phenols containing *t*-butyl groups in the ortho position were prepared by isobutylene alkylation.[5] The *tt*-octyl- or 1,1,3,3-tetramethylbutylphenols were prepared by alkylations with diisobutylene.[6] The isobornylphenols were the samples which have been described.[7] Phenol, 4-cresol, 4-*t*-amylphenol and 4-*tt*-octylphenol were obtained by recrystallization of commercial materials.

Discussion

Association in Crystalline State Compared with Liquid.—It is apparent from comparison of $\Delta\lambda_m$ and $\Delta\lambda_s$ values of Table I that the change in phase from liquid to solid cannot be neglected in

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(5) G. H. Stillson, D. W. Sawyer and C. K. Hunt, THIS JOURNAL, **67**, 303 (1945).

(6) L. J. Kitchen, *ibid.*, **70**, 1290 (1948); W. F. Hester, U. S. Patent 2,008,017, July 16, 1935.

(7) L. J. Kitchen, *ibid.*, **70**, 3608 (1948).

TABLE I

INFRARED MEASUREMENTS OF O–H BAND SHIFTS IN PHENOLS

Phenol	Melting point, °C.	λ of dil. soln., μ	Shift in O–H band in μ, dilute soln. *vs.* concd. soln. $\Delta\lambda_c$	Shift in O–H band in μ, dilute soln. *vs.* melt $\Delta\lambda_m$	Shift in O–H band in μ, dilute soln. *vs.* solid $\Delta\lambda_s$
Phenol		2.75	0.261[a]	0.249	0.365[b]
4-Cresol		2.74	.256	.277	.297
4-Methoxyphenol	54.6–56.2	2.74	.245	.243	.190
4-*t*-Butylphenol	99.2–99.8	2.75		.200	.388[c]
4-*t*-Amylphenol	93.7–94.1	2.76	.268	.237	.354[d]
4-*tt*-Octylphenol	85.2–85.6	2.75	.271		[e]
3,4,5-Trimethylphenol	104.6–105.7	2.75	.259		[f]
2,4-Dimethylphenol	20–22	2.76		.194	
2-*t*-Butyl-4-methylphenol	51.2–52.1	2.74		.081	.123[g]
2-*tt*-Octyl-4-methylphenol	47.0–47.8	2.75	.075	.080	.094
2-Isobornyl-4-methylphenol	71.8–72.5	2.72		.156	.260
2-Isobornylphenol	77.8–78.6	2.72		.152	.258
2,6-Dimethylphenol	45.2–45.8	2.75	.085	.094	.209[h]
2,3,6-Trimethylphenol	61.8–62.8	2.74	.053		
2,3,5,6-Tetramethylphenol	115.2–117.2	2.75	.027	.047	.154
2,4,6-Trimethylphenol	70.4–71.6	2.74	.080	.076	.235[i]
2,4-Dimethyl-6-*t*-butylphenol	16–21	2.73		.041	
2,4-Dimethyl-6-*tt*-octylphenol		2.74	.030		
2,4-Dimethyl-6-isobornylphenol	82.9–83.0	2.75	.023	.028	.330
Bis-(2-hydroxy-3,5-dimethylphenyl)-isopropylmethane	160.5–161.0	2.88	.046		
2-Methyl-4,6-di-*t*-butylphenol	51.6–52.6	2.72		.034	.049[j]
2,6-Di-*t*-butyl-4-methylphenol	69.8–70.5	2.72	.009	.007	.020[k]
2,6-Di-*tt*-octyl-4-methylphenol	51.6–52.2	2.73	.000	.000	.010
2,6-Diisobornyl-4-methylphenol		2.72	.013		
2,4,6-Tri-*t*-butylphenol	131.0–131.2	2.71	.003		
2,6-Di-*t*-butyl-4-*s*-butylphenol		2.72	.005		
2,6-Di-*t*-butyl-4-methoxyphenol	103.7–104.7	2.72	.009		
2,6-Di-*t*-butyl-4-ethoxyphenol	83.2–84.4	2.73	.007		
2,6-Di-*t*-butyl-4-chlorophenol	79.0–79.5	2.71	.004	.004	.022

[a] Literature value for $\Delta\lambda_c$, 0.181.[2] [b–l] Literature values for $\Delta\lambda_s$: [b] 0.264; [c] 0.45[3] and 0.354; [d] 0.40[3] and 0.334; [e] 0.334; [f] 0.324; [g] 0.123; [h] 0.184; [i] 0.224; [j] 0.063; [k] 0.023; [l] 0.01.[3]

comparing the hydrogen bonding of different phenols. Since $\Delta\lambda_s$ is greater than $\Delta\lambda_m$ for all phenols for which data were obtained, except 4-methoxyphenol, hydrogen bonding in the crystalline state appears to be stronger than in the liquid phase. On solidifying, the phenols crystallize into lattice structures in which force fields in addition to those from simple hydrogen bonding may affect the primary O–H force constant and the infrared shift. There could, for example, be a weak bond formed in crystals between the hydroxyl hydrogen atom and an aromatic carbon atom as suggested by Richards and Thompson[4] in the case of *o*-hydroxydiphenyl. Moreover, the packing coefficient of crystalline phenols would vary with substituents in the meta and para positions. The data appear to support these conclusions as evidenced by several anomalous effects. For example, among phenols with different para substituents the difference between $\Delta\lambda_s$ and $\Delta\lambda_m$ ranged from -0.053 μ to 0.188 μ. Unexpectedly the $\Delta\lambda_s$ value for 2,4-dimethyl-6-isobornylphenol was greater than the corresponding value for 2-isobornylphenol, although the former has methyl instead of hydrogen in the 2-position. However, the shifts within the liquid phase are in the expected order.

It is concluded that comparisons between different phenols of hydrogen bonding should be made on infrared shifts within the liquid phase. A study of corresponding $\Delta\lambda_c$ and $\Delta\lambda_m$ values in Table I reveals that they are essentially the same, the maximum deviation being 0.02 μ. This is of interest because the $\Delta\lambda_c$ values frequently are measured more readily than the $\Delta\lambda_m$ values on unknowns to determine the positions of substituent groups.

Hydrogen Bonding Index.—The phenols without ortho substituents, being unhindered, exhibited the greatest shifts. Among the seven para substituted phenols without ortho substituents included in Table I the maximum wave length shift is about 0.267 μ. The "hydrogen bonding index" is defined as the shift from dilute solution to the liquid state divided by 0.267 μ. This index can assume values only between 0 for complete hindrance to hydrogen bonding and 1 for unhindered phenol. The hydrogen bonding index calculations which follow were based on the average shift $(\Delta\lambda_c + \Delta\lambda_m)/2$.

Comparison of Homologous Series.—The six para substituted phenols of Table I containing the *t*-butyl group in both ortho positions were almost completely hindered with respect to hydrogen bonding. The various para substituents had only a slight effect on hydrogen bonding, since the bonding indices for the six phenols were within the range 0.01 to 0.03.

Hydrogen bonding indices for hindered 4-methylphenols are compared in Table II. One methyl group in the ortho position decreased hydrogen bonding slightly, bringing the index down to 0.73. When both ortho positions were occupied by methyl groups, the index was 0.29, about equivalent to one *t*-butyl group (0.30) or to a *tt*-octyl group (0.29).

TABLE II

HYDROGEN BONDING INDICES[a] OF HINDERED 4-METHYLPHENOLS

Ortho substituent in 2-position	Ortho substituent in 6-position				
	Hydrogen	Methyl	Isobornyl	*t*-Butyl	*tt*-Octyl
Hydrogen	1.00				
Methyl	0.73	0.29[b]			
Isobornyl	.59[c]	.10	0.05		
t-Butyl	.30	.15[d]		0.03	
tt-Octyl	.29	.11			0.00

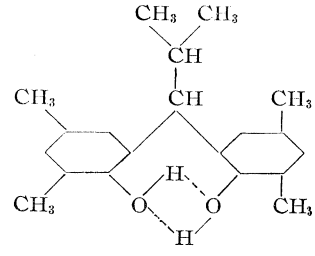
[a] Index is wave length shift of O–H band from dilute soln. to liquid state divided by 0.267 μ. [b] 2,6-Dimethylphenol had an index of 0.33. [c] 2-Isobornylphenol had an index of 0.57. [d] 2-Methyl-4,6-di-*t*-butylphenol had an index of 0.13.

An ortho isobornyl group, with an index of 0.59, was between methyl and *t*-alkyl in hindrance to hydrogen bonding. However, when the isobornyl group was combined with methyl in the other ortho position, the index was 0.10, which indicated less hydrogen bonding than with a combination of methyl and *t*-alkyl in the ortho positions. The apparently anomalous increase in hindrance may be due to the bicyclic structure of the isobornyl group.

With isobornyl or *t*-alkyl groups in both ortho positions, hydrogen bonding in liquid phase approached zero, the index being 0.00–0.05, contrasted with a value of about 1.00 for the para substituted phenols without ortho substituents.

Effect of meta Substitution.—It is well known that a meta methyl group, in itself, does not hinder the phenolic hydroxyl group. However, when both ortho and meta substituents are present on adjacent carbon atoms, the meta substituent can exert a hindering effect. For example, 2,3,5,6-tetramethylphenol had an index of only 0.14 compared with indices of 0.20, 0.29 and 0.33, respectively, for 2,3,6-trimethylphenol, 2,4,6-trimethylphenol and 2,6-dimethylphenol. Apparently a meta methyl group forces an adjacent ortho methyl group closer to the hydroxyl, increasing the hindrance.

Intramolecular Hydrogen Bonding.—Evidently intramolecular association occurs between the two O–H groups of bis-(2-hydroxy-3,5-dimethylphenyl)-isopropylmethane, indicated by the fact that its O–H absorption band did not shift all the way back to the non-associated state as a result of dilution. Therefore it is concluded to be associated



Structure of Isobornylphenol.—The preparation of a monoisobornylphenol of m. p. 77.8–78.6° was described previously.[7] Its hydrogen bonding index is 0.57, compared with 0.58 for 2-isobornyl-4-methylphenol; thus it is the ortho isomer, 2-isobornylphenol, rather than the para isomer, 4-isobornylphenol.

Acknowledgment.—The authors wish to express their appreciation to Dr. E. E. Hanson and Dr. G. E. P. Smith, Jr., for their advice and encouragement and to The Firestone Tire & Rubber Company for permission to publish this work. They wish to thank Mr. Harold C. Ransaw, to whom they are indebted for assistance in obtaining the data in this paper.

Summary

Twenty-nine phenols, twenty-two of which contained methyl, *t*-butyl, *tt*-octyl and isobornyl groups as ortho substituents, were examined for degrees of hydrogen bonding by means of infrared spectroscopy. Hydrogen bonding indices were assigned to the various phenols to indicate their tendencies to associate in liquid phase. It was found that the isobornyl group, a secondary alkyl group, hindered more than methyl but less than the tertiary alkyl groups, of which *tt*-octyl hindered to a slightly greater extent than *t*-butyl.

The effect of change of phase was investigated; O–H bands for the crystalline state included anomalies such that comparisons among phenols required measurements on the liquid phase.

Methyl groups in the meta position were found to increase the hindering action of adjacent ortho methyl substituents.

An example of intramolecular hydrogen bonding with formation of an eight-membered chelation ring is pointed out.

On the basis of its observed hydrogen bonding index, a monoisobornylphenol of m. p. 77.8–78.6° was found to be 2-isobornylphenol.

AKRON 17, OHIO RECEIVED JULY 5, 1949

[CONTRIBUTION NO. 724 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

X-Ray Diffraction Analysis of Vaccenic Acid[1]

BY JAMES H. BENEDICT AND B. F. DAUBERT

In a previous communication[2] from this Laboratory the *trans* configuration of natural vaccenic acid was confirmed by comparison of its infrared absorption data with those of oleic and elaidic acids. Subsequent to this work a comparison of the infrared data was made of a synthetic vaccenic acid submitted to us by Dr. F. M. Strong,[3] with the natural acid. On the basis of the comparative infrared results and mixed melting points it was concluded by Strong[3] that the synthetic vaccenic acid was of *trans* configuration and accordingly identical with the natural acid.

In order to provide further identification data, the natural and synthetic vaccenic acids were submitted to X-ray diffraction analysis, and the data compared with those for elaidic acid. Also, since the earlier X-ray diffraction data for elaidic acid[4] were very meager a more detailed analysis was made and is herewith reported.

The comparative X-ray data in Table I indicate that synthetic vaccenic and elaidic acids possess similar crystal structures since the two patterns have nearly identical long and short spacings. The dissimilarities in the diffraction pattern of natural vaccenic acid as compared to the patterns for synthetic vaccenic and elaidic acids may be attributed to differences in the angles of tilt in the crystals, and possibly to differences in the structure of the acids.

The exceedingly shorter long spacing for natural vaccenic acid as compared to elaidic acid could readily be explained by a greater angle of tilt in the natural vaccenic crystal structure since both acids are of *trans* configuration and differ only in the position of the double bond. It should also be noted that a vaccenic acid obtained as a product of the hydrogenation[5] of β-elaeostearic acid gave a pattern essentially identical to that obtained on the natural vaccenic acid.

Experimental

The elaidic acid was prepared by isomerization of highly purified oleic acid with nitrous acid according to the method of Lyutenberg.[6] It was recrystallized several times from ethyl ether and methyl alcohol; m. p. 44.5°, I. V. 89.9 (calcd. 89.9).

The vaccenic acid used in this study was a portion of the same acid, isolated from beef tallow, which was used in the infrared studies previously described.[2] The synthetic vaccenic acid was kindly furnished us by Dr. F. M. Strong of the University of Wisconsin and was prepared by methods described by Strong and co-workers.[3]

X-Ray Diffraction Analysis.—The X-ray diffraction patterns were obtained in a manner analogous to that previously described.[7] The solvent-crystallized acids were analyzed and the data are given in Table I.

TABLE I

X-RAY DIFFRACTION DATA, IN Å.

(*hkl*)	Elaidic acid	Vaccenic acid synthetic	Vaccenic acid natural
	Long Spacings		
001	48.9 VS	48.9 VS	39.8 VS
002	24.3 VW	24.4 W+	19.8 W
003	16.3 M	16.3 M	13.4 M+
004			
005	9.81 M	9.78 M	8.02 M
006			
007	6.97 W	7.00 W+	5.70 VW
008		6.12 VW	
009		5.42 VW	
0010	4.89 VW	4.88 VW	
Av. d	48.9	48.9	39.9
M. p.	44.5°	44.0°	42.5°
	Short Spacings		
	4.57 M−	4.56 M	4.64 M
	4.12 VS	4.12 VS	4.36 W+
	4.00 M	4.01 W+	4.16 VS
	3.74 S	3.71 S	4.02 W
	3.65 S	3.66 S	3.84 S
	3.47 W	3.47 M−	3.62 M−
	3.38 W	3.25 W	3.43 VW
	3.27 W	2.94 M+	3.35 M
	2.92 M+	2.68 W	3.03 M−
	2.75 W	2.62 W	2.89 W
	2.70 W	2.48 S−	2.78 W
	2.58 VW	2.34 M−	2.67 VW
	2.49 M+	2.26 M	2.46 M
	2.31 M−	2.23 S−	2.39 M−
	2.23 S−	2.18 M−	2.32 W
	2.20 M	2.13 W+	2.24 M
	2.15 W	1.92 W	2.19 M
	2.06 M−		2.06 W
	1.94 VW		1.88 VW
	1.86 VW		1.85 VW
	1.85 W		1.73 W
	1.77 VW		
	1.74 VW		

To determine the presence or absence of other polymorphic forms, the acids packed in nylon tubes were fused, cooled rapidly, and then stabilized by holding at −20° for four days. After X-ray exposure, melting points were determined. The fused samples under the experimental conditions indicated gave diffraction patterns similar to those obtained for the solvent-crystallized acids.

(1) A Research Fellowship grant of the Procter and Gamble Company in support of this investigation is gratefully acknowledged.

(2) Rao and Daubert, THIS JOURNAL, **70**, 1102 (1948).

(3) Ahmad, Bumpus and Strong, *ibid.*, **70**, 3391 (1948).

(4) Muller, *J. Chem. Soc.*, **123**, 2043 (1923); Muller and Shearer, *ibid.*, **123**, 3156 (1923).

(5) Woltemate and Daubert, unpublished results.

(6) Lyutenberg, *Fettchem. Umschau.*, **42**, 89 (1935).

(7) Daubert and Sidhu, THIS JOURNAL, **70**, 1884 (1948); **68**, 2603 (1946).

Summary

X-Ray data are reported for natural vaccenic acid, synthetic vaccenic acid and elaidic acid.

PITTSBURGH, PA. RECEIVED MAY 7, 1949

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STATE UNIVERSITY OF IOWA, IOWA CITY, IOWA]

On the Existence of the Higher Oxides of Neodymium[1]

BY ALEXANDER I. POPOV AND GEO. GLOCKLER

A literature survey showed that the question of the existence of the higher oxides of neodymium still remains unsettled. Earlier workers with the rare earth elements often claimed to have obtained NdO_2 and Nd_2O_5 either by heating the sesquioxide in air[2] or by heating the oxalate in oxygen.[3,4] Mark[5] claimed to have obtained excess of combined oxygen in a didymium–cerium mixture, which he attributed to the formation of neodymium "superoxide." Waegner[3] and Popovici[6] both claimed to have obtained Nd_2O_5 by fusion of the oxalate or the trifluoride with ammonium nitrate.

On the other hand Marsh[7] in 1946 repeated the work of Mark and failed to obtain any evidence for the formation of the higher oxides of neodymium. He also postulated that Waegner's and Brauner's results were due to the unusual stability of the basic neodymium oxide NdO(OH). This compound was first prepared by Joye and Garnier[8] in 1912 and seems to have the same reflection spectrum as Waegner's "superoxide." Pagel and Brinton[9] in 1929 attempted to oxidize the sesquioxide of neodymium by heating it to 350° with oxygen under 215-lb. pressure but found no evidence of oxidation.

Experimental Results

In an attempt to clarify this question the work of the earlier investigators was repeated. It was found that heating the sesquioxide in a current of oxygen at temperatures varying between 500 and 1000° did not result in any oxidation of the compound.

It was next decided to try the combustion of neodymium oxalate in a current of oxygen. The oxalate was obtained by precipitation of an acidified neodymium nitrate solution with oxalic acid and drying the precipitate at 120°. Weighed portions of the oxalate, in a porcelain boat, were introduced into an electrical combustion furnace. Dried commercial oxygen was passed while the furnace was progressively brought to the desired temperature. The period of heating was varied from one to two and a half hours. The resulting oxide was cooled in a current of dry nitrogen, weighed and dissolved in an acid potassium iodide solution. Liberated iodine was titrated with a standard sodium thiosulfate solution and the percentage of "active" oxygen calculated.

Seven experiments were made at 550, 700 and 950°. The average amount of "active" oxygen found in the product was 0.1%. No significant variation of this figure with temperature was observed. The active oxygen percentage in NdO_2 should be 4.54. The small amount of "active" oxygen found is probably due to traces of praseodymium, because the present sample of neodymium oxide was faintly grayish in color in comparison with a small sample of very pure neodymium oxide which originated in Professor Rolla's laboratory in Florence and which was at our disposal.

Neodymium oxalate which was heated to 550° was reintroduced into the combustion tube after being weighed and was heated again to 1000°. A tared drying tube was attached to the system and again a current of dry oxygen was passed. After heating the sample for one hour the boat was withdrawn and the weight of the drying tube redetermined. A blank was also run and gave negative results within the limits of experimental error (Table I).

TABLE I

DEHYDRATION OF BASIC NEODYMIUM OXIDE

	Sample, g.	Water obtained, mg.	Water calcd., mg.
Expt. 1	0.2412	13.0	12.2
Expt. 2	.2099	10.7	10.6
Expt. 3	.3714	19.0	18.9

It thus seems that the supposition of Marsh is correct and that by heating hydrated neodymium oxalate to 550° the basic oxide of the element is formed, which subsequently decomposes in the neighborhood of 1000° to the sesquioxide and water.

The fusion of neodymium oxalate, sesquioxide or the trifluoride with ammonium nitrate also failed to give any higher oxides.

As the fusion of praseodymium oxide with sodium chlorate yields praseodymium dioxide,[10]

(1) From a thesis presented by Alexander I. Popov to the Graduate College of the State University of Iowa in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) F. R. M. Hitchcock, THIS JOURNAL, **17**, 483 (1895).

(3) A. Waegner, *Z. anorg. allgem. Chem.*, **42**, 118 (1904).

(4) B. Brauner, *Coll. Czechoslov. Chem. Commun.*, **5**, 279 (1932).

(5) R. Mark, *Ber.*, **35**, 2370 (1902).

(6) J. Popovici, *ibid.*, **41**, 634 (1908).

(7) J. K. Marsh, *J. Chem. Soc.*, 20 (1946).

(8) P. Joye and C. Garnier, *Compt. rend.*, **154**, 510 (1912).

(9) H. A. Pagel and Paul H. Brinton, THIS JOURNAL, **51**, 42 (1929).

(10) W. Prandtl and K. Huttner, *Z. anorg. allgem. Chem.*, **149**, 235 (1925).

this method was tried for the oxidation of neodymium. Weighed portions of the sesquioxide were mixed intimately with about 20 times their weight of C. P. sodium chlorate and the mixture was fused for various lengths of time (thirty minutes to six hours and thirty minutes) at 250–300°. The melt was extracted with hot water, washed, dried and dissolved in acid potassium iodide solution. In all cases only traces of iodine were liberated.

Conclusions

The results obtained seem to indicate that the earlier reports of the existence of the higher oxides of neodymium were due to the use of impure compounds or to the mistaken identity of the basic oxide. It seems reasonable to conclude that the trivalent state of neodymium is the highest oxidation state of the element observed up to the present time.

Summary

1. A product claimed to be neodymium dioxide was identified as basic neodymium oxide NdO(OH).

2. The trivalent state of neodymium is the highest oxidation state observed so far.

IOWA CITY, IA. RECEIVED JULY 11, 1949

[CONTRIBUTION FROM THE PACIFIC EXPERIMENT STATION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

Heat Capacities at Low Temperatures and Entropies of Magnesium and Calcium Fluorides

BY S. S. TODD[1]

In an earlier paper[2] from this Laboratory, heat content and entropy-increment data were reported for magnesium and calcium fluorides, in the temperature range 298.16 to 1800°K. The present paper is a low-temperature calorimetric study of these compounds from 52 to 298°K. Throughout this temperature range, heat capacities of magnesium fluoride and calcium fluoride were obtained at regular intervals, and from the data their entropies were calculated. No previous similar data exist for magnesium fluoride. Eucken and Schwers[3] have investigated the heat capacity of calcium fluoride from 17 to 86°K. and Koref[4] has made two mean specific heat measurements at 136.4 and 236.5°K. However, from these data an entropy value[5] for calcium fluoride at 298.16°K. was derived which had an uncertainty of about 2.5%.

Materials

The magnesium fluoride used in these measurements was part of the material prepared for the heat content study of this substance by Naylor.[2] His method of preparation and analysis are repeated here. Baker C. P. Analyzed magnesium oxide, containing less than 0.3% Ca and 0.5% SO_4, was treated with hot 48% HF for sixteen hours and then dried at 400°. Analysis for magnesium by conversion to sulfate and weighing as magnesium sulfate gave 38.97% Mg (theoretical 39.02%).

The calcium fluoride sample was some large natural fluorite crystals, having a very faint purple color, which were coarsely ground in a diamond mortar and the iron removed with a magnet. Since Naylor[2] employed some of the same batch of fluorite, his analysis is given here. The ground fluorite when successively treated with hydrochloric and sulfuric acids and weighed as $CaSO_4$, gave 51.27% Ca (theoretical 51.33%).

Heat Capacities

The method and apparatus used in the heat capacity measurements have been described in

TABLE I

MOLAL HEAT CAPACITIES

T, °K.	C_p, cal./deg.	T, °K.	C_p, cal./deg.	T, °K.	C_p, cal./deg.
		MgF_2 (mol. wt., 62.32)			
54.22	1.577	114.54	6.380	216.7	12.37
58.05	1.836	124.76	7.169	226.4	12.74
62.12	2.131	135.83	8.007	236.2	13.06
66.64	2.467	146.10	8.707	246.1	13.38
71.12	2.818	155.72	9.339	256.2	13.73
75.72	3.188	166.02	9.951	266.3	13.98
80.20	3.552	176.0	10.51	276.2	14.23
83.62	3.852	186.0	11.02	286.5	14.47
94.70	4.754	196.0	11.49	296.5	14.67
104.30	5.547	206.3	11.94	(298.16)	(14.72)
		CaF_2 (mol. wt., 78.08)			
53.51	1.908	114.43	8.266	216.4	14.19
57.55	2.309	124.37	9.146	226.2	14.49
62.04	2.758	135.5	10.06	236.4	14.80
66.74	3.253	146.0	10.80	245.8	15.04
71.40	3.763	155.6	11.42	256.3	15.29
76.25	4.300	165.9	12.03	266.0	15.50
80.43	4.758	175.7	12.56	276.0	15.68
85.32	5.295	186.0	13.04	286.4	15.84
95.04	6.336	195.9	13.42	296.5	16.00
104.51	7.313	206.2	13.82	(298.16)	(16.02)

(1) Chemist, Pacific Experiment Station, Bureau of Mines. Article not copyrighted.

(2) B. F. Naylor, THIS JOURNAL, **67**, 150 (1945).

(3) A. Eucken and F. Schwers, *Ber. deut. physik. Ges.*, **15**, 578 (1913).

(4) F. Koref, *Ann. physik*, **36**, 49 (1911).

(5) K. K. Kelley, U. S. Bur. Mines Bull. 434 (1941).

detail by Kelley, Naylor and Shomate.[6] The conventional thermochemical calorie[7] (1 cal. = 4.1833 int. joules) is used throughout, and the ice-point is taken as 273.16°K. The calorimeter contained 102.01 g. and 252.02 g. *in vacuo* of magnesium and calcium fluorides, respectively.

All the experimental results are listed in Table I and shown graphically in Fig. 1.

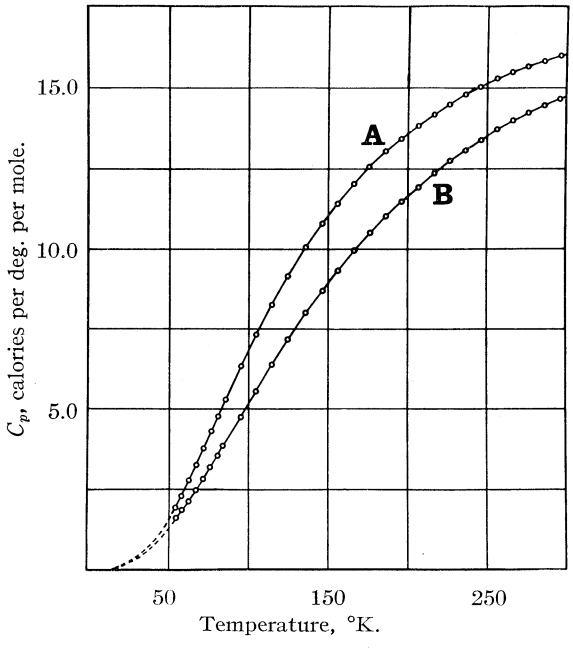


Fig. 1.—Heat capacities: A, CaF_2; B, MgF_2.

Also in Table I are extrapolated values of the heat capacity of each fluoride at 298.16°K. The molecular weights in Table I are taken from the 1947 table of international atomic weights.[8]

The heat capacity results are believed accurate on the average to within ±0.3% in the absolute sense and have a precision error under 0.1%. The early heat capacity measurements of Eucken and Schwers[3] on calcium fluoride from 17 to 86°K. have considerably less precision than the present work. In the overlapping temperature range, 53 to 86°K., their results run progressively higher than present values by amounts ranging from zero to 3%. At lower temperatures their values are below any reasonable extrapolation of the present results.

(6) K. K. Kelley, B. F. Naylor and C. H. Shomate, U. S. Bur. Mines Technical Paper 686 (1946).

(7) E. F. Mueller and F. D. Rossini, *Am. J. Phys.*, **12**, 1 (1944).

(8) G. P. Baxter, M. Guichard and R. Whytlaw-Gray, THIS JOURNAL, **69**, 731 (1947).

Entropies

The measured heat capacities were plotted against log T and the entropy increments between 51.00 and 298.16°K. (measured portion, Table II) were calculated by numerical integration. The entropy increments between 0 and 51.00°K. (extrapolated portion Table II) were obtained from the following combinations of Debye and Einstein functions fitted to all of the heat capacity results,[5] the average deviation between function sums and measurements being shown in parentheses.

$$MgF_2: \quad D\left(\frac{326}{T}\right) + 2E\left(\frac{553}{T}\right) \quad (1.0\%)$$

$$CaF_2: \quad D\left(\frac{308}{T}\right) + 2E\left(\frac{435}{T}\right) \quad (1.3\%)$$

TABLE II

MOLAL ENTROPIES, CAL./DEG.

	MgF_2	CaF_2
0–51.00°K. (extrap.)	0.54	0.64
51.00–298.16°K. (meas.)	13.14	15.82
$S^\circ_{298.16}$	13.68 ± 0.07	16.46 ± 0.08

The extrapolated entropy values, 0.54 for magnesium fluoride and 0.64 for calcium fluoride, constitute less than 4% of their entropies at 298.16°K. as given in Table II. The previously accepted entropy value,[5] 16.4 ± 0.4 at 298.1°K., for calcium fluoride has not been changed materially by the present work but its uncertainty has been reduced sharply in magnitude.

Summary

The heat capacities of magnesium fluoride and calcium fluoride have been measured throughout the temperature range 52 to 298°K.

Their entropies at 298.16°K. have been calculated to be 13.68 ± 0.07 and 16.46 ± 0.08 cal./deg./mole, respectively.

BERKELEY, CALIFORNIA RECEIVED AUGUST 3, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF GEOLOGY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Effects of Radioactivity on Oleic Acid[1,2]

BY VIRGINIA L. BURTON

In initial research[3,4] pertaining to the role of radioactivity in petroleum genesis, it was shown that paraffinic components of petroleum could be produced by the irradiation with alpha particles or deuterons of certain fatty acids known to occur in source sediments. Likewise, a cycloparaffin has been produced from a naphthenic acid.

In all these early bombardments hydrogen was usually the major component of the gaseous products. However, since hydrogen is found only in minute quantities in the natural gases associated with petroleum, the theory that radioactivity plays a part in petroleum genesis has been subject to some criticism. Although it had been proposed that hydrogen could disappear to the atmosphere by diffusion through the cap rock, it seemed likely that the unsaturated compounds in source sediments might be hydrogenated under the influence of radioactivity and thus absorb at least part of the hydrogen produced.

Benzoic acid was the first unsaturated compound to be bombarded with deuterons in an effort to determine if the hydrogen usually produced during a bombardment would saturate the double bonds of the ring. That is, an effort was made to determine if hydrogen produced by the decomposition of one molecule would, under the influence of radiation, enter the ring of another molecule. The volume of gas produced was very small; it consisted of 85% of carbon dioxide and only 1.8% of hydrogen. No evidence has been found for the formation of the saturated compounds, hexahydrobenzoic acid or cyclohexane, and attempts to identify the infusible reaction product have been unsuccessful.

Because considerable data were available concerning the effects of radioactivity on the fatty acids, a carefully purified sample of oleic acid was bombarded in the M. I. T. cyclotron. Bombardment techniques and equipment have been described elsewhere.[5]

Results

Gaseous products were analyzed and found to consist mainly of carbon dioxide and hydrogen. Table I shows the complete analysis. The data from a preliminary alpha bombardment are given for comparison. The columns under "deuteron" represent analyses of the gas sample collected during each thirty-minute period of the two-hour bombardment. There appears to be a consistent increase in hydrogen production and decrease in carbon dioxide formation during the irradiation.

TABLE I

GASEOUS BOMBARDMENT PRODUCTS FROM OLEIC ACID

Component	Volume % Deuteron[a] Cut 1	Cut 2	Cut 3	Cut 4	Alpha[b]
H_2	41.2	44.0	55.1	56.4	50.0
CO_2	41.4	42.6	32.2	28.8	41.0
CO	5.8	4.5	2.9	6.8	6.0
H_2O	3.5	2.9	4.8	0.7	..
CH_4	3.9	0.4	0.5	4.2	
C_2H_6	0.4	1.2	1.0	1.1	
C_2H_4	3.9	0.4	1.1	1.9	
C_3H_8		1.5	0.5		
C_4H_{10}		1.6	.9		
C_4H_8		0.6	..		1.8
C_5H_{12}		0.4	.2		
C_5H_{10}		0.4	.1		
C_6H_{12}			.3		
C_7H_{16}			.1		
C_7H_{14}			.1		

[a] Mass spectrometric analyses. [b] Low temperature omit combustion analysis.

The acid changed during the bombardment from a light colorless liquid to an amber, fluorescent, highly viscous material resembling heavy motor oil. Thirty-one per cent. of the original oleic acid remained after bombardment. Of the material converted, 10% was recovered as non-saponifiable material, 52.5% as polymerized acid and an estimated 1.7% as stearic acid.

Thirty per cent. of the non-saponifiable material was separated as a light colorless hydrocarbon (3% of the original oleic acid).[6]

A second product from the bombardment was a viscous material remaining in the flask following the saponification. This material, which was insoluble in the alcoholic solution and in ether, went into soapy solution in water. After hydrolysis, these polymerized acids, which were now ether-soluble, weighed 10.5 g. (52.5% of the total oleic acid bombarded). Although an infrared analysis has been run, no further data have been obtained. It appears that polymerization occurs as a result of unsaturation since no polymerized acidic material had been recovered in earlier bombardments of saturated fatty acids.

After the stearic acid was isolated, it was purified and mixed with an authentic sample of the compound. The stearic acid recovered from the bombarded oleic acid had a melting point of 69.5° and the mixed melting point was 70°. No stearic

(1) This paper is a contribution from American Petroleum Institute Research Project 43 C located at the Massachusetts Institute of Technology: W. L. Whitehead, Director; Clark Goodman, Physical Director.

(2) Presented before the Division of Organic Chemistry at the 112th meeting of the American Chemical Society, New York, N. Y., Sept. 18, 1947.

(3) Sheppard and Burton, THIS JOURNAL, **68**, 1636 (1946).

(4) Breger and Burton, *ibid.*, **68**, 1639 (1946).

(5) Honig, *Rev. Sci. Instruments*, **18**, 389 (1947).

(6) Burton and Breger, submitted for publication.

acid could be detected in the original unbombarded oleic acid proving that hydrogenation had taken place under the influence of the deuteron beam.

The following material balance was drawn up for the bombardment:

	Mole
Reactant	
Oleic acid	0.201
Products	
(Total moles liberated during bombardment)	
Oleic acid (recovered after bombardment)	0.063
Carbon dioxide	0.043
Hydrogen	0.066
Other gaseous products	0.019
Heptadecene	0.007
Stearic acid	0.003
Polymeric acids (52.5%) and uninvestigated non-saponifiables (7%)	...
Total	0.201

The moles of polymeric acids formed could not be calculated because of the difficulty in determining the molecular weight of the material. These acids were insoluble in the solvents commonly used for this purpose and a high molecular weight is therefore inferred.

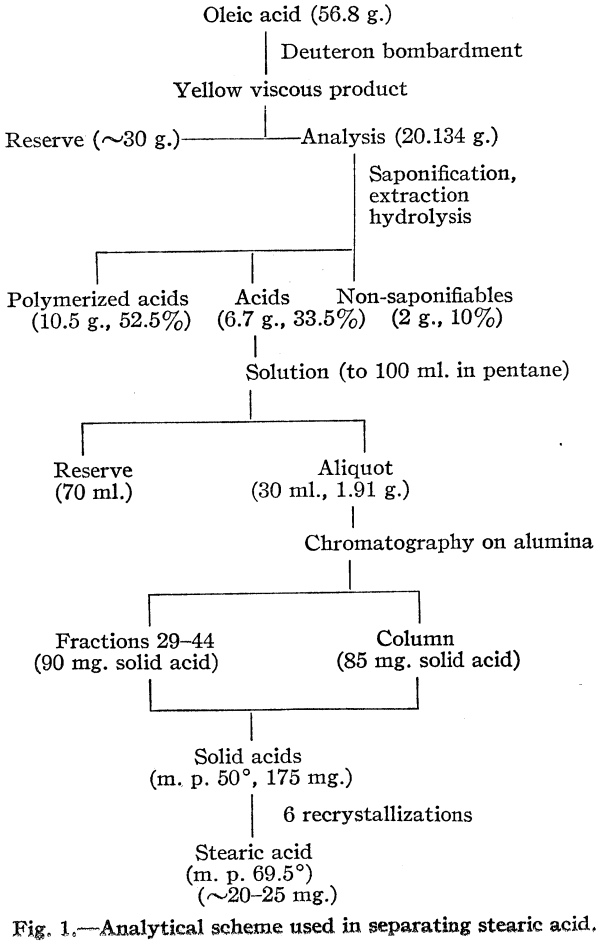


Fig. 1.—Analytical scheme used in separating stearic acid.

The number of molecules of oleic acid converted per one hundred electron volts of energy input was 2.16. Likewise, the number of molecules of stearic acid formed was 0.047. This indicates that approximately 2.5 molecules of stearic acid were formed for every one hundred molecules of oleic acid that were converted.

Experimental

Several methods for the purification of oleic acid were attempted, but a modification of the procedure of Wheeler and Riemenschneider[7] was used. This method consisted of the fractional distillation and crystallization of the methyl esters followed by hydrolysis and distillation of the acid.

Technical oleic acid (2 l.) obtained from the Eastman Kodak Company, Rochester, New York, was converted to the methyl ester by refluxing with 2 l. of methanol and 75 ml. of sulfuric acid for three hours. The methyl ester was then fractionated under 1–2 mm. of mercury in a two-foot jacketed Vigreux column to give 1765 ml. of product.

To simplify handling, all crystallizations were carried out batchwise. The ester (1320 ml.) was dissolved in 16.8 l. of acetone and cooled to −60° with stirring to remove the linoleic and linolenic acids. The heavy white precipitate of methyl oleate was rapidly filtered on a Büchner funnel maintained at the crystallization temperature by a Dry Ice–acetone jacket.

The crystals were allowed to melt, and the material was then dissolved in acetone (10 ml. per g.) and crystallized at −37° to remove palmitic and stearic acids. The precipitate was filtered on a Büchner funnel as before. This procedure was repeated twice and was then followed by another −60° crystallization; yield, 480 ml. Unlike the method of Wheeler and Riemenschneider, which included a second distillation of the methyl esters followed by two crystallizations at −65°, the methyl oleate was next hydrolyzed with alcoholic potassium hydroxide. The soap formed was carefully neutralized with hydrochloric acid to remove the pure acid and this was then fractionated under 1 mm. of mercury to yield 75 ml. of oleic acid, b. p. 220–221° (1.5 mm.), $n^{20}D$ 1.4592, freezing point (from curve) 5.74°–8.92°. Small percentages of linoleic and linolenic acids were probably still present in the final product. These compounds were of little importance to the object of this work.

The purified oleic acid (56.8 g.) was bombarded for two hours with an average beam intensity of 9 microamperes using the gold plated chamber described by Honig.[5] After the bombardment, 20 g. of the thick viscous product was saponified by refluxing for three hours with 50 ml. of 10% sodium hydroxide and 100 ml. of alcohol. The amber-colored solution was decanted from the insoluble polymerized acids and was then extracted with ether, enough water being added to yield two phases. A small amount of hexane was added to cut down the solubility of the water in ether.

The sodium hydroxide solution was acidified with excess hydrochloric acid and was extracted with ether which was then dried over sodium sulfate and evaporated on a steam-bath. The residue was made up to 100 ml. with pentane in a volumetric flask (6.7 g., 33.5% of the oleic acid bombarded). To a 30-ml. aliquot was added 70 ml. of pentane, 15 ml. of ether, and 2 ml. of benzene to obtain a clear solution which was then passed through a 12 × 800 mm. column packed with a mixture of five parts of J. T. Baker alumina to one part of Celite 545. The filtrate was collected in 10-ml. portions in a running chromatogram and the column was washed with 175 ml. of the pentane–ether–benzene solution, 50 ml. of pentane containing 10% methanol, and 120 ml. of pentane containing 20% methanol. A total of 44 cuts was collected.

(7) Wheeler and Riemenschneider, *Oil and Soap*, **16**, 207 (1939).

Fractions 29–44 contained an infusible solid in each flask after the solvent was evaporated. When ether was added the precipitate swelled and became very gelatinous. Following hydrolysis of several of the above cuts with hydrochloric acid, extraction with ether, and evaporation of the solvent, an oily residue remained indicating that the acids had come through the column as aluminum salts. Since a solid residue was recovered from cut 44 after hydrolysis, cuts 29–44 inclusive were combined, hydrolyzed, extracted with ether and dried over sodium sulfate. After the ether was evaporated on a steam-bath, 90 mg. of solid material was separated from the above cuts by crystallization from acetone at −20°.

The chromatographic column was next cut into four sections each of which was eluted with methanol. The three lower sections contained gelatinous precipitates which, after hydrolysis, yielded solid residues. One hundred and seventy-five milligrams of solid material (m. p. 50°) was separated from the column and the filtrates. By means of six crystallizations from acetone at −20° in a centrifuge tube, the melting point of this solid was raised from 50 to 69.5°. A mixed melting point with authentic stearic acid was 70° (stearic acid, m. p. 70°). All melting points were taken on a microscope hot stage. The analytical scheme to this point is shown in Fig. 1.

Because the loss of stearic acid during recrystallization was so great, it was necessary to use an indirect method to estimate the amount present. A blank chromatogram containing 3% of stearic acid (42 mg.) in the purified oleic acid was next run. Seventy-four milligrams of solid acid (m. p. 50°) was separated as above. From melting point curves for mixtures of oleic and stearic acids,[8,9] it was established that the isolated material contained 25% of stearic acid, a recovery of 18.5 mg. or 44%.

The solid separated from the bombarded oleic acid (175 mg.) also contained 25% stearic acid (43.8 mg.) as indicated by its melting point of 50°. After correcting for the 44% recovery by chromatography, as indicated above, it was found that the stearic acid isolated (100 mg.) amounted to 5.3% of the non-polymerized saponifiable material. On the basis of the original acid bombarded this figure becomes 1.7%.

Since the stearic acid isolated had been concentrated by a factor of nearly three upon the removal of the polymeric acids and the non-saponifiable material (62.5%), it was necessary to determine if the acid (1.7%) represented original impurity which was below the limit of chromatographic detection using the unbombarded acid. A sample of the purified oleic acid to which was added 1% of stearic acid was, therefore, chromatographed by the above procedure and the stearic acid was easily detectable. No stearic acid could be isolated when the oleic acid itself was chromatographed.

This work indicated that the original oleic acid contained less than 1% of stearic acid and the bombarded oleic acid contained approximately 1.7%, both values being determined by the same analytical technique. It was thus shown that oleic acid was hydrogenated to stearic acid.

Acknowledgments.—The author wishes to thank Prof. Clark Goodman and Prof. W. L. Whitehead for their encouragement and counsel. Considerable advice and assistance was given by I. A. Breger. Mass spectrometric analyses were obtained by Earle C. Farmer and through the courtesy of R. E. Honig of the Socony–Vacuum Company. The bombardment was made possible through the coöperation of Mr. Farmer, Dr. Eric Clarke and the M. I. T. cyclotron crew.

Summary

Purified oleic acid has been bombarded with deuterons in the M. I. T. cyclotron. Analysis of the irradiated material has revealed the formation of stearic acid, heptadecene, and polymerized acids.

It has been shown that the hydrogen produced by decomposition of an organic molecule under the influence of radioactivity can enter the double bond of a neighboring molecule. It has thus been demonstrated that hydrogen which may be produced by the effects of radioactivity on the organic constituents of a petroleum source sediment could, in part, be removed from the gas phase by reaction with unsaturated components of the sediments.

RECEIVED[10] AUGUST 1, 1949

(8) Smith, *J. Chem. Soc.*, 974 (1939).

(9) Markley, "Fatty Acids," Interscience Publishers, New York, N. Y., 1947, p. 124.

(10) Original manuscript received January 28, 1948.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Metal–Salt Interactions at High Temperatures: the Cerium–Cerium Chloride System[1]

BY DANIEL CUBICCIOTTI[2]

The properties of alkali halide crystals containing excess metal have been the subject of extensive investigation by Pohl and co-workers.[3] Their study has led to an explanation of the ability of an alkali halide to dissolve excess metal and to the development of the theory of lattice defect points in crystals.[4] For divalent halides, studies of the miscibility of metal and salt have been made[5]; however, few other data have been accumulated on such systems. Only one report of metal–salt equilibria for trihalide salts is known to this author. The bismuth–bismuth trichloride and bismuth–bismuth tribromide phase diagrams are reported by Eggink.[6] These systems appear to be similar to those recently reported for divalent halides.[5]

To extend the data in the field of metal–salt equilibria the present study on a trivalent halide was made. The system cerium–cerium chloride was chosen because the melting point of cerium

(1) This work was conducted under the direction of the late Professor E. D. Eastman and sponsored by the Manhattan Project.

(2) Present address: Department of Chemistry, Illinois Institute of Technology, Chicago.

(3) Pohl, *Proc. Physical Soc. (London)*, **49**, extra part, p. 3 (1937).

(4) For a discussion see: Mott and Gurney "Electronic Processes in Ionic Crystals," The Oxford Press, London, 1940.

(5) Cubicciotti and Thurmond, THIS JOURNAL, **71**, 2149 (1949).

(6) Eggink, *Z. physik. Chem.*, **64**, 493 (1908).

is very near that of cerium chloride and thus no elaborate containers were necessary for the materials.

Experimental

Method.—The methods used in this work were the same as those reported in a previous paper.[5] Since cerium metal dissolves iron, however, it was impossible to use iron containers or thermocouple wells. The containers used were molybdenum crucibles formed from sheet metal and welded under a helium atmosphere. The end of the thermocouple well was a molybdenum test-tube of 0.01-inch wall thickness and 4 inches long. This end was machined from a solid rod of metal. It was threaded and screwed into an iron tube to give the thermocouple well sufficient length.

Materials.—Cerium metal and anhydrous cerium trichloride were supplied by Dr. F. H. Spedding of Iowa State College. The trichloride was found to contain 3 weight % other rare earths and less than 0.1 weight % insoluble matter (oxide or oxychloride). The metal had been prepared by the chemical reduction of its chloride and contained 0.4 mole % of chloride. The metal was found to freeze at 770° as compared to a m. p. of 775° given by Kelley.[7] The trichloride froze at 802° as compared to a melting range of 790 to 810° given by Jantsch and Wien.[8]

Results

Some of the cooling curves obtained are shown in Fig. 1 as illustrations of the magnitude of the thermal effects observed. Figure 1, a, b, c, gives curves obtained on the pure salt and salt-rich mixtures. The humped character of the first break indicates some supercooling of the mixture before the solid salt phase separated. The temperatures of the break in such cases was taken as the temperature at the top of the hump.

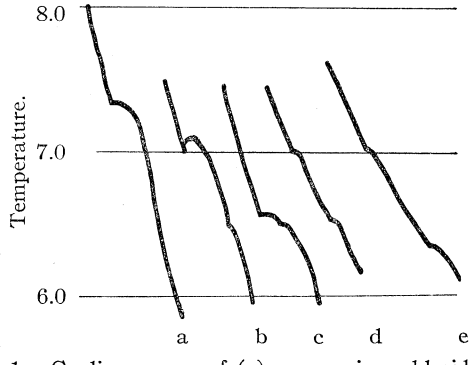


Fig. 1.—Cooling curves of (a) pure cerium chloride, (b) cerium chloride with 10 mole % cerium, (c) cerium chloride with 29 mole % cerium, (d) cerium metal, and (e) cerium metal with 14 mole % cerium chloride (temperature scale in millivolts from a Pt–Pt 10% Rh thermocouple).

In Figure 1, d, e the cooling curves obtained on the metal and a metal-rich mixture are given. In both of these curves there are two breaks detectable. The higher temperature breaks occurred at the same temperature, while the temperatures of the lower breaks are only approximately the same. The higher-temperature breaks for both the metal and the mixture must have been the invariant temperature corresponding to two liquid plus one solid equilibrium. Apparently, the 0.4 mole per cent. of cerium chloride impurity in the metal was sufficient to lower the freezing point of the metal to the temperature of the three-phase invariant. The lower temperature breaks of these metal-rich mixtures are assumed to correspond to the eutectic break. The temperatures of the lower breaks are below the eutectic break, as observed in the salt-rich region, presumably because the mixture super-cooled.

At one temperature (810°) the compositions of the two liquids in equilibrium were measured. A mixture of salt and metal was equilibrated at that temperature and then quenched by immersing the bottom of the crucible in water.[9] When cold, the metal phase was found on the bottom of the crucible. It had all the appearances of the original metal. The salt-rich phase was an intensely black, friable solid that reacted vigorously with dilute acid.

The temperature–composition diagram for the solid–liquid equilibria of the cerium–cerium chloride system is shown in Fig. 2. Since the cerium metal used was not pure, a literature value for the f. p. of pure cerium is included in the diagram. The point at 775° and 100% cerium is the m. p. of pure cerium as given by Kelley.[7] The shapes of the curves outlining the miscibility gap were assumed to be similar to those observed in other metal–salt systems,[5] and were drawn in through the observed points.

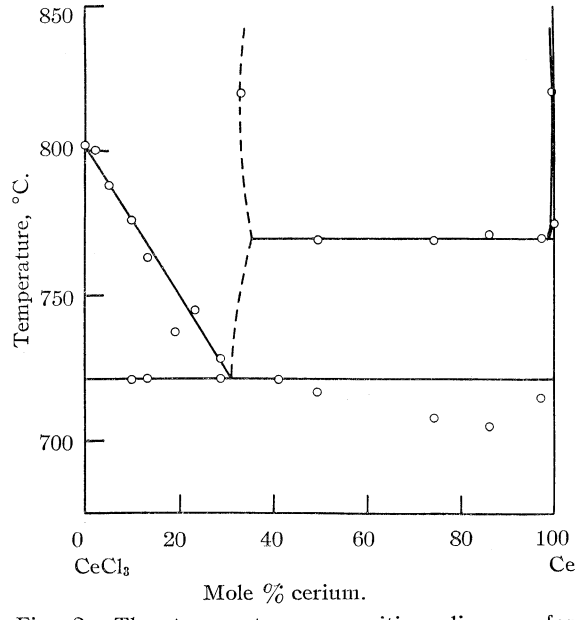


Fig. 2.—The temperature–composition diagram for solid–liquid equilibria in the cerium chloride–cerium system.

Discussion

A comparison of the solubility of cerium in its chloride with the solubilities of other metals in

(7) Kelley, "Contributions to the Data on Theoretical Metallurgy," Bur. Mines Bull. No. 393.

(8) Jantsch and Wien, *Monatsh.*, **69**, 16 (1936).

(9) See ref. (5) for experimental details.

their salts is made in Table I which gives the concentration of metal in the salt phase of the two-phase equilibrium between liquid metal and liquid salt. The metals chosen for the comparison are those whose cationic radii are approximately equal because it has been shown that for divalent systems the solubility depends on the cationic radius.[5]

TABLE I

Metal	Solubility in mole %	Cationic radius[a] in Å.
K	1[b]	1.33
Sr	20[c]	1.13
Ce	33	1.15[d]

[a] Radii from Pauling "The Nature of the Chemical Bond." [b] Estimated from the data of Mollwo, *Z. Physik*, **85**, 56 (1933), on the solubility of potassium in its solid halides and Rogener, *Ann. Phys. Leipzig*, [5] 29, 386 (1937), on the solubility of potassium in liquid potassium bromide. [c] Estimated from data on other alkaline earth systems, see ref. (5). [d] The radius of trivalent cerium is assumed to be the same as that for trivalent lanthanum.

From Table I it appears that the solubility of a molten metal in its chloride depends upon the charge of the cation of the pure salt. However, this dependence may be a dependence of the solubility upon some property related to the cationic charge. Thus, the significant property may be the ratio of number of cations to number of anions in the salt, which, for a given anion, is proportional to the cationic charge. Additional data would be required to select the property upon which the solubility truly depends.

Summary

The temperature–composition diagram has been determined for the liquid–solid equilibria in the cerium–cerium chloride system. The diagram is similar to those previously reported for some alkaline earth metal–halide systems.

BERKELEY, CALIFORNIA RECEIVED MAY 28, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Quantitative Determination of Amino Acids on Filter Paper Chromatograms by Direct Photometry[1]

BY LOUIS B. ROCKLAND AND MAX S. DUNN

The following types of procedures have been suggested for the determination of amino acids on filter paper chromatograms: (A) elution of the spots before or after staining with a chromogenic agent (such as ninhydrin) and analysis of the elutes,[2–8] (B) modified isotope dilution analysis of the spots with the aid of radioactive tracer amino acids,[9] (C) visual comparison of the color intensities of standard and test sample chromatograms stained with ninhydrin,[2] and (D) direct comparison of spot sizes or color intensities of ninhydrin-stained standard and test-sample chromatograms.[10–14] Amino acid test mixtures have been analyzed by Bull, *et al.*,[11] and Woiwod[3] and protein hydrolyzates by Polson, *et al.*,[2] Martin and Mittlemann,[4] Keston, *et al.*,[9] and Block.[13]

Alanine and glycine have been determined in silk fibroin in the present study by a rapid, direct photometric analysis of color intensities of filter paper chromatograms stained with ninhydrin.

Experimental

Filter paper chromatograms were prepared by the capillary ascent test-tube method of Rockland and Dunn.[15] Ten dilutions, 2×10^{-4} ml. each, of standard containing from 0.625 to 6.250 mg. per ml. of DL-alanine and of glycine were placed on eight replicate strips ($10 \times 18 \times 140$ mm.) of Whatman No. 1 filter paper with the aid of a 0.01 ml. total displacement Gilmont ultramicroburet.[16] Similarly, seven dilutions of an acid hydrolysate[17] containing from 3.010 to 12.040 mg. per ml. of silk fibroin (moisture- and ash-free basis) were placed on three replicate strips of the filter paper. The chromatograms were developed simultaneously for three hours at room temperature in 8-inch test tubes containing water saturated phenol, dried for 5 minutes at 100°, sprayed lightly eight times on each side with 0.25% ninhydrin solution in water saturated butanol and heated for five minutes at 100°. The alanine was resolved completely at the seven levels but glycine only at the two lowest levels.

In order to determine the concentrations of the amino acids, the filter paper strips were placed in a special sample holder containing an opening of a size just sufficient to enclose the entire area of the colored spot and the color intensities were read directly with the aid of a photoelectric colorimeter.[19] The alanine and glycine content of silk fibroin were estimated by interpolation from the standard curves drawn from plots of per cent. transmission against concentration of amino acid on coördinate paper.

(1) Paper 61. For Paper 60, see Murphy and Dunn, *Proc. Soc. Exp. Biol. Med.*, **71**, 241 (1949). This work has been aided by a grant from the National Institutes of Health of the United States Public Health Service. The described chromatographic procedures were presented in a symposium before the Division of Chemical Education at the San Francisco, California, meeting of the American Chemical Society, March 30, 1949. The authors are indebted to Jeremiah C. Blatt for technical assistance.

(2) Polson, Mosley and Wyckoff, *Science*, **105**, 603 (1947).

(3) Woiwod, *Biochem. J.*, **42**, xxviii (1948).

(4) Martin and Mittlemann, *ibid.*, **43**, 23 (1948).

(5) Woiwod, *Nature*, **161**, 169 (1948).

(6) Naftalin, *ibid.*, **161**, 763 (1948).

(7) Awapara, *Archiv. Biochem.*, **19**, 172 (1948).

(8) Awapara, *J. Biol. Chem.*, **178**, 113 (1949).

(9) Keston, Udenfriend and Levy, THIS JOURNAL, **69**, 3151 (1947).

(10) Fischer, Parsons and Morrison, *Nature*, **161**, 764 (1948).

(11) Bull, Hahn and Baptist, THIS JOURNAL, **71**, 550 (1949).

(12) Block, *Science*, **108**, 608 (1948).

(13) Block, *Fed. Proc.*, **8**, 185 (1949).

(14) Fosdick and Blackwell, *Science*, **109**, 313 (1949).

(15) Rockland and Dunn, *ibid.*, **109**, 539 (1949).

(16) Emil Greiner Company, 161 6th Avenue, New York City.

(17) Prepared by Dr. M. N. Camien from the silk fibroin described by Dunn, *et al.*[18]

(18) Dunn, Camien, Rockland, Shankman and Goldberg, *J. Biol. Chem.*, **155**, 591 (1944).

(19) Lumetron, Model 402 EF, manufactured by the Photovolt Corporation, 95 Madison Avenue, New York City.

TABLE I

PERCENTAGES OF ALANINE AND GLYCINE IN SILK FIBROIN[a]

Amino acid		Alanine	Glycine
Analysis of filter paper chromatograms	Indirect photometric, Polson *et al.*[2]	37.6	39.9
	Direct: Visual Polson, *et al.*[2]	34.0	42.4
	Direct: Photometric, authors	34.9	43.4
Selective pptn., Bergmann and Niemann,[21]		26.4	43.8
Microbiological, Shankman, *et al.*[20]		..	43.6

[a] Corrected for moisture and ash.

The data obtained for glycine and alanine in silk fibroin are given in Table I. It may be noted that the value (43.4%) found for glycine in silk fibroin is in good agreement with the values (39.9 to 43.8%) reported by earlier workers who used microbiological,[20] selective precipitation[21] and analogous photometric-chromatographic[2] procedures. Although the value 34.9% found for alanine is in good agreement with the values, 34.0 and 37.6%, reported by Polson, *et al.*,[2] it is much higher than the value of 26.4%, obtained by Bergmann and Niemann.[21]

Summary

A method has been described for the quantitative determination of amino acids on filter paper chromatograms by direct photometry. It has been found by this method that silk fibroin contained 43.4 per cent. of glycine and 34.9 per cent. of alanine. These values are in good agreement with others given in the literature.

(20) Shankman, Camien and Dunn, *J. Biol. Chem.*, **168**, 51 (1947).
(21) Bergmann and Niemann, *ibid.*, **122**, 577 (1937–1938).

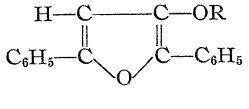
RECEIVED MAY 4, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Transetherification of 3-Alkoxy-2,5-diphenylfurans[1]

BY PHILIP S. BAILEY AND JOHN D. CHRISTIAN

The conversions of 3-methoxy- and 3-ethoxy-2,5-diphenylfurans (I), one into the other, in solutions of the opposite alcohol, triethylamine hydrochloride and a trace of hydrogen chloride was reported in an earlier paper.[2] In the present paper is described a further study of this reaction which might be termed a transetherification[1b] by comparison to the corresponding transesterification reaction which esters undergo. Both employ an acid catalyst and both involve the displacement of an alkoxy group directly attached to an unsaturated grouping.



I (a) R = CH_3
(b) R = C_2H_5
(c) R = C_3H_7-*n*
(d) R = C_4H_9-*n*
(e) R = C_4H_9-*i*
(f) R = $-C(=O)-CH_3$

Concerning the minimal conditions necessary for the reaction, it was found in the study that the hydrogen chloride was essential, whereas the amine hydrochloride was not. No conversion was observed in the absence of the hydrogen chloride even though the amine hydrochloride was present. Under the opposite conditions, conversion did occur, but in poorer yield than when both reagents were present. In all subsequent runs, therefore, both reagents were used.

The reaction using 3-methoxy-2,5-diphenylfuran was found to occur with ethanol, *n*-propyl alcohol, *n*-butyl alcohol and isobutyl alcohol. The yields varied from 68 to 55%. Isopropyl alcohol and *t*-butyl alcohol gave no reaction, and *s*-butyl alcohol, *n*-amyl alcohol and isoamyl alcohol gave principally non-crystalline products which are assumed to be of a different nature, since the corresponding alkoxyfurans should be crystalline by comparison to the others known.[3] Transetherifications of alkoxyfurans of higher molecular weight to alkoxyfurans of lower molecular weight were also carried out.

The alcoholysis reaction was extended also to 3-acetoxy-2,5-diphenylfuran, using methanol and *n*-propanol. Isopropyl alcohol, *n*-butyl alcohol and isobutyl alcohol reacted differently to yield oils plus a dimolecular oxidation product, 2,2′-bis-(2,5-diphenylfuranone-3).[4] The reaction failed with 3-(4-morpholinyl)-2,5-diphenylfuran (II) and, as reported earlier,[2] with 3-chloro-2,5-diphenylfuran. All of the above described transformations are listed in Table I.

From the viewpoint of synthesis of alkoxyfurans, the alcoholysis of 3-methoxy-(or 3-ethoxy-) and 3-acetoxy-2,5-diphenylfurans is of limited value. However, since only 3-methoxy- and 3-ethoxy-2,5-diphenylfurans can be made from 1,2-dibenzoyl-1,2-dibromoethane,[2,5,6] these transfor-

(1) (a) From the M. A. Thesis of J. D. Christian, January, 1949. (b) Since the paper was accepted for publication, similar transetherification reactions have been reported with different systems; see Croxall, Van Hook and Luckenbaugh, THIS JOURNAL, **71**, 2736 (1949), and Ogata and Okano, *ibid.*, **71**, 3211 (1949).
(2) Bailey and Kelly, THIS JOURNAL, **70**, 3442 (1948).
(3) Melting points: Me, 114–115°, Et, 94–95°, Pr, 86–87°, iso-Pr, 87–88°, Bu, 60–61°, iso-Bu, 71–72°.
(4) Previously reported by Lutz, McGinn and Bailey, THIS JOURNAL, **65**,843 (1943); and Kohler and Woodward, *ibid.*, **58**, 1933 (1936).
(5) Bailey and Lutz, *ibid.*, **69**, 498 (1947).
(6) Conant and Lutz, *ibid.*, **47**, 881 (1925).

mations constitute the best known method for the cases applicable. Very poor yields are obtained from the addition of alcohols to 1,2-dibenzoylethylene.[2,5]

It is interesting to note that under the conditions of the transetherification reaction the purely aliphatic, unsaturated alkyl vinyl ethers undergo addition[7] and the purely aromatic anisole (III) gives no reaction. Other alkoxyunsaturates, in between these two extremes as far as stability of the unsaturated nucleus is concerned, should, like the alkoxydiphenylfurans (I), react by displacement. This displacement perhaps occurs by an addition mechanism similar to that of the transesterification reaction. Such a mechanism has previously been suggested for the etherification of β-naphthol by alcoholic hydrogen chloride.[8]

The similarity between the alkoxyfurans (I) and esters does not extend too well to other reactions. No reaction was observed between 3-methoxy-2,5-diphenylfuran and ammonia (in methanolic solution) or hot morpholine. Hydrolysis occurred, however, when the methoxyfuran was refluxed with 6 *N* hydrochloric acid. The product was 2,2′-bis-(2,5-diphenylfuranone-3)[4] (IV), presumably formed by the oxidation of 3-hydroxy-2,5-diphenylfuran.

The characteristic nitric acid oxidation of Lutz and Wilder[9] has been carried over to several 3-alkoxy-2,5-diphenylfurans in order to facilitate identification.

Experimental[10]

Typical Experiment. Reaction of 3-Methoxy-2,5-diphenylfuran with Ethanol.—A solution of 1 g. of 3-methoxy-2,5-diphenylfuran, 1 g. of triethylamine hydrochloride, 30 ml. of ethanol (distilled from sodium ethoxide) and enough ethanolic hydrogen chloride to give an indicated *p*H of 2 (*p*-Hydrion paper) was refluxed for thirty hours, during which time the *p*H was maintained at 2–3. The solution was evaporated to dryness, the residue was extracted with ether and the ether extract was washed and evaporated. Crystallization of the residue from ethanol gave 0.7 g. (66% yield) of 3-ethoxy-2,5-diphenylfuran (m. p. 90.5–92.5°; identified by a mixture melting point with an authentic sample).[5] A red viscous oil remained.

When the triethylamine hydrochloride was omitted, everything else remaining the same, only a 33% yield of the ethoxyfuran was obtained. No reaction was obtained when the hydrogen chloride was omitted and the triethylamine hydrochloride was present (80% recovery of methoxyfuran plus an intractable oil) nor when both the hydrogen chloride and triethylamine hydrochloride were omitted (96% recovery of methoxyfuran).

Attempted reaction of 3-methoxy-2,5-diphenylfuran with morpholine (1 g. of furan and 40 ml. of morpholine for thirty hours at 70°) gave a 87% recovery of the methoxyfuran (m. p. 112–114°, identified by a mixture melting point) and a red oil. A similar reaction with a saturated methanolic solution of ammonia (1 g. furan, 80 ml. solution) was attempted for eight days at room temperature. The recovery of methoxyfuran was 99%.

Acid Hydrolysis of 3-Methoxy-2,5-diphenylfuran.—A mixture of 1 g. of the 3-methoxyfuran and 50 ml. of 6 *N* hydrochloric acid was refluxed with stirring for thirty hours. The mixture was evaporated to dryness by a stream of air, the residue was treated with ether, and the resulting mixture was filtered. On the filter paper was obtained 0.33 g. (34% yield) of 2,2′-bis-(2,5-diphenylfuranone-3) which melted at 243–246° and was identified by a mixture melting point with an authentic sample.[4] Evaporation of the ether extract gave an oil which resisted crystallization.

The nitric acid oxidation of 3-methoxy-2,5-diphenylfuran was carried out by the general method of Lutz and Wilder[9] in acetic acid medium at room temperature. The yield of known 1,2-dibenzoyl-1-methoxyethylene, which, incidentally, must be the *cis* isomer,[9] was 14% (m. p. 103–106°, identified by a mixture melting point with a known sample[6]). A red oil also was obtained.

The nitric acid oxidation[9] of 3-ethoxy-2,5-diphenylfuran was carried out in propionic acid at 0° for ten minutes. The yield of *cis*-1,2-dibenzoyl-1-ethoxyethylene (m. p. 97–100°, identified by a mixture melting point with an authentic sample[6]) was 78%. The lower temperature apparently accounts for the improved yield over that of the preceding experiment.

TABLE I

Reactants[a]	Products	Yield, %
Ia + ethanol	Ib	66
Ia + *n*-propyl alcohol	Ic	55[b]
Ia + *n*-butyl alcohol	Id	67[c]
Ia + isobutyl alcohol	Ie	68[d]
Ia + isopropyl alcohol	Ia	95
Ia + *s*-butyl alcohol	Ia	33[e]
Ia + *t*-butyl alcohol	Ia	96
Ia + *n*-amyl alcohol[f]	Oil[e]	...
Ia + 3-methyl-1-butanol[f]	Ia	10[e]
Id + ethanol	Ib	84[g]
Ie + methanol	Ia	76[h]
If[i] + methanol	Ia	96
If + *n*-propyl alcohol[f]	Ic	55[e,j]
If + isopropyl alcohol	IV[k]	20[e]
If + *n*-butyl alcohol[f]	IV[k]	20[e]
If + isobutyl alcohol[f]	IV[k]	10[e]
III[l] + ethanol	III[l]	56[m]
II[n] + ethanol	II[n]	85[e]

[a] Conditions were as described in the typical experiment. The reaction time was always thirty hours, the corresponding alcoholic hydrogen chloride solution was used and triethylamine hydrochloride was present. The alcohols were made anhydrous by distillation from the corresponding sodium alkoxide. Temperatures were the reflux temperature except where otherwise indicated. The reactions were worked up as described in the typical experiment. All products were identified by mixture melting points with authentic samples. [b] M. p. 83–84°, see ref. 2. [c] Recryst. from isopropyl alcohol and from ethanol, m. p. 60–61°. *Anal.* Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.07, H, 7.09. [d] M. p. 70–72°, see ref. 2. [e] A red viscous residue remained which resisted all crystallization efforts. [f] The temperature was 85–95°. [g] A 14% recovery of the *n*-butoxyfuran also was obtained. [h] A 20% recovery of the isobutoxyfuran also was obtained. [i] Prepared by the method of Lutz.[11] [j] A 6% yield of 2,2′-bis-(2,5-diphenylfuranone-3) (IV) also was obtained. See reference 4. [k] 2,2′-Bis-(2,5-diphenylfuranone-3), m. p. 245–250°; see reference 4. [l] Anisole. [m] Identified through the sulfonamide (m. p. 108–109°; no sulfonamide of phenetole (m. p. 149–150°) was isolated).[12] [n] 3-(4-Morpholinyl)-2,5-diphenyl-furan.

(7) For a review of the chemistry of alkyl vinyl ethers see Schildknecht, Zoss and McKinley, *Ind. Eng. Chem.*, **39**, 180 (1947).

(8) (a) Davis, *J. Chem. Soc.*, **77**, 33 (1900); (b) Fieser and Lothrop, THIS JOURNAL, **57**, 1459 (1935).

(9) Lutz and Wilder, *ibid.*, **56**, 978 (1934).

(10) All melting points are corrected.

(11) Lutz, THIS JOURNAL, **48**, 2916 (1926).

(12) See Procedures I and A of Huntress and Carten, *ibid.*, **62**, 511, 603 (1940), for directions for preparation of the sulfonamides.

cis-**1,2-Dibenzoyl-1-*n*-propoxyethylene** was prepared from 2,5-diphenyl-3-*n*-propoxyfuran by the general method[9] described in the experiment just preceding. After several recrystallizations from ethanol and isopropyl alcohol the material melted at 72–73°; the yield was 77%.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.17. Found: C, 77.18; H, 6.16.

The propoxyethylene was converted back to the furan by reduction with zinc and acetic acid.[6]

cis-**1,2-Dibenzoyl-1-isopropoxyethylene** was prepared from 2,5-diphenyl-3-isopropoxyfuran[5] in propionic acid at 0° by the general method[9] described above. The yield of material melting at 108–109° after recrystallization from isopropyl alcohol was 78%.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.17. Found: C, 77.74; H, 6.44.

Zinc and acetic acid reduction[6] converted the material back to the furan from which it was made.

The difference in melting points between 1,2-dibenzoyl-1-*n*-propoxyethylene and 1,2-dibenzoyl-1-isopropoxyethylene makes them easily distinguished. Thus the corresponding furans can easily be distinguished through these derivatives. They are otherwise difficult to differentiate between, since the isopropoxyfuran melts at 87–88°, the *n*-propoxyfuran at 86–87° and the mixture melting point between the two is 82–85°.

Acknowledgments.—The authors wish to thank the Research Corporation, New York, N. Y., for a grant-in-aid which helped make this work possible. They also wish to thank Mr. Elias E. Kawas for carrying out three of the alcoholysis experiments.

Summary

1. 3-Alkoxy-2,5-diphenylfurans have been found to undergo alcoholysis, termed transetherification, under acidic conditions.

2. A comparison is made of transetherification, transesterification and the addition of alcohols to alkyl vinyl ethers.

3. The nitric acid oxidation of 2,5-diarylfurans to *cis*-1,2-diaroylethylenes has been extended to 3-alkoxy-2,5-diphenylfurans.

AUSTIN, TEXAS RECEIVED APRIL 25, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

A Glyco-lipide Produced by *Pseudomonas Aeruginosa*[1]

BY F. G. JARVIS[2] AND M. J. JOHNSON

Several crystalline compounds[3,4,5,6,7] and at least two partially purified oils[8,9] have been isolated from *Pseudomonas aeruginosa* cultures. These materials have been primarily investigated with respect to their antibacterial activity. With the exception of pyocyanin,[3,4] none of these metabolic products have been fully characterized. The isolation and investigation of the structure of an acidic, crystalline glyco-lipide produced by *P. aeruginosa* is described in this paper. The compound contains the same structural units (L-rhamnose and *l*-β-hydroxydecanoic acid) as the oil isolated by Bergström, *et al.*,[9] but has a higher molecular weight and a higher rhamnose–hydroxy-acid ratio. It is quite possible that the compound is identical to the crystalline material isolated by Birch-Hirschfeld[6] but insufficient data are available for suitable comparison. Our compound was found to be bacteriostatic to *Mycobacterium tuberculosis* H37 Rv in a concentration of about 0.5 mg. per ml. of culture medium. Five mg. given introperitoneally to mice killed in about sixteen hours.[10]

Isolation.—The organism was grown on a 4% Difco peptone–3% glycerol broth at 30° on a reciprocating shaker. Cultures were harvested after from four to five days growth. The acid was produced by each of three strains of *P. aeruginosa* tested (University of Washington strains no. 141, 142, 261). The one strain of *P. florescens* tested failed to produce the compound. Yields as high as 2.5 g. per liter were obtained. The crystalline acid was not produced (or could not be isolated by our procedure) when the peptone was replaced by tryptone or the glycerol replaced by glucose in the growth medium.

The compound was obtained in crystalline form by acidifying the whole culture to *p*H 2 with sulfuric acid and refrigerating for two or three days. The crystals were collected on very coarse filter paper, taken up in a small volume of ethyl ether (insoluble residues discarded) and precipitated by addition of petroleum ether. After the removal of solvent by decantation and evaporation, the precipitate was dissolved in dioxane and crystallized by adding water and chilling. The material could be recrystallized in the cold by acidifying water solutions of its sodium salt or by adding water to dioxane or acetone solutions of the free acid.

Properties.—The compound crystallizes in the form of thin, colorless rectangular platelets. It is very soluble in ether, ethyl alcohol, acetone, dioxane and dilute sodium bicarbonate solution. It is nearly insoluble in water and petroleum ether. The compound (m. p. 86°, α_D = −84°, 3% in chloroform) has a neutral equivalent of about 665. Molecular weight determinations by the Rast method gave a value of about 650.

Anal.[11] Calcd. for $C_{32}H_{58}O_{14}$: C, 57.64; H, 8.77. Found: C, 57.62; H, 8.74.

Other data (see below) indicate that the true formula is $C_{32}H_{60}O_{14}$. Quantitative acetylation of the material showed 4.3 hydroxyl groups per mole; however, chromatographic analysis of the acetylated material gave three acidic bands indicating either incomplete acetylation or decomposition during the reaction. The chromatographic

(1) Published with the approval of the Director of the Wisconsin Experiment Station.

(2) National Institute of Health Predoctorate Research Fellow.

(3) F. Wrede and E. Strack, *Ber.*, **62B**, 2051 (1929).

(4) H. Hillemann, *ibid.*, **71B**, 46 (1938).

(5) S. Hosoya, *Compt. rend. soc. biol.*, **99**, 771 (1928).

(6) L. Birch-Hirschfeld, *Z. Hyg. Infektionsrank.*, **116**, 304 (1935).

(7) E. E. Hays, *et al.*, *J. Biol. Chem.*, **159**, 725 (1945).

(8) R. Schoental, *Brit. J. Exp. Path.*, **22**, 137 (1941).

(9) S. Bergström, H. Theorell and H. Davide, *Arkiv Kemi Mineral. Geol.*, **23A**, No. 13 (1947).

(10) The authors are indebted to Dr. Russell S. Weiser, University of Washington, for the antibiotic and mouse toxicity tests.

(11) The carbon–hydrogen analyses were performed by the Clarke Microanalytical Laboratory, Urbana, Illinois.

procedure of Ramsey and Patterson[12] was employed, modified to the extent that Celite 545 was used as the supporting phase in place of silica gel. Tests for other active groups were negative. The compound undergoes acid hydrolysis. Periodate oxidation resulted in the uptake of 2 atoms of oxygen per mole of compound. The compound gives a positive Molisch test but does not reduce Fehling solution. A loss of weight equivalent to 1 water molecule per mole of acid occurs upon heating under reduced pressure to 60° for twenty-four hours. The weight loss is more rapid at higher temperatures. The resultant product (m. p. 60–64°) could not be crystallized from dry solvents. When crystallized from aqueous solutions, the original acid (m. p. 86°) was obtained.

Degradation.—The water-soluble fraction obtained by acid hydrolysis (1 *N* hydrochloric acid in 50% redistilled dioxane for two hours at reflux temperature) was obtained in pure crystalline form by neutralization to *p*H 7, removal of solvent by distillation under reduced pressure, extraction of the residue with absolute ethyl alcohol, and crystallization from acetone–ethanol or acetone–water mixtures. The crystalline material gave the usual qualitative tests for an aldose-type monosaccharide.

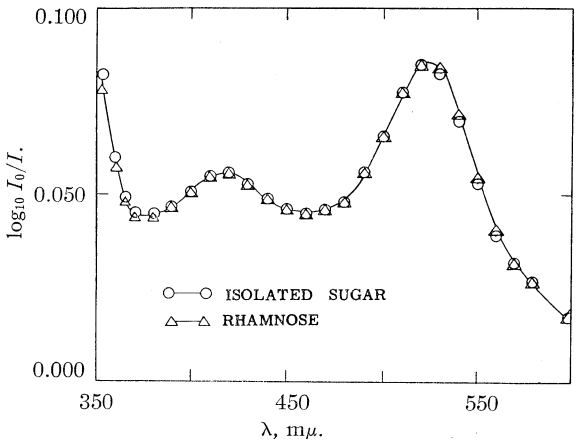


Fig. 1.—Absorption spectra of carbazole–sugar reaction mixtures. Sugar concentrations were 15γ/ml. of reaction mixture: O—O, isolated sugar; △—△, rhamnose.

The absorption spectrum of its carbazole reaction product in sulfuric acid[13,14,15] was determined (Beckman photometer model A, 1-cm. Corex cell and tungsten filament lamp), and found to be identical with that for L-rhamnose (Fig. 1). Although the efficacy of this method has been questioned,[15] we have found that the differences in the absorption spectra (340–600 mμ) of the sugars tested (glucose, galactose, mannose, arabinose, xylose and rhamnose) are more than sufficient for the qualitative indentification of pure sugars if suitably controlled conditions are employed. The sugar (α_D = +8.4°, 5% solution in water) crystallized in two forms, the usual hydrated form (m. p. 92–93°) and the anhydrous form (m. p. 121–123°). A phenylosazone was also prepared (m. p. 179–180°).

Anal. (hydrated form). Calcd. for $C_6H_{14}O_6$: C, 39.56; H, 7.75. Found: C, 39.75; H, 7.69.

All of these data indicate that the sugar is L-rhamnose.

Two moles of reducing sugar were shown to be present in each mole of original acid by quantitative measurement of of hydrolysis (Fig. 2). Quantitative sugar analyses were made by the Shaffer and Somogyi method[16] with their reagent 50 with 5 g. of potassium iodide. Titrations were referred to a standard rhamnose curve. The rates of release of the two reducing groups were quite different, the first being released much more readily than the second. When hydrolysis was halted after the release of the first mole of sugar and the reaction mixture extracted with petroleum ether, the second mole of sugar (unhydrolyzed) was found in the petroleum ether fraction. The sugar present in each fraction was found to be L-rhamnose after isolation.

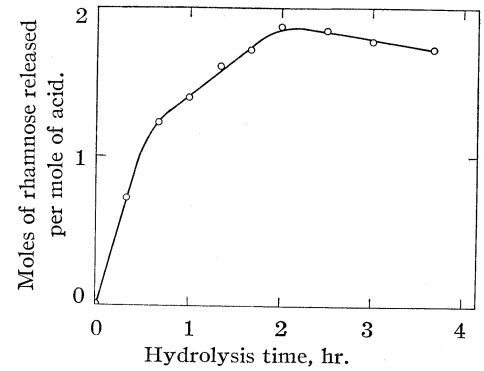


Fig. 2.—Acid hydrolysis of isolated crystalline acid: the reaction mixture contained 200 mg. of isolated acid in 50 ml. of 1 *N* hydrochloric acid in 50% redistilled dioxane at zero hours. Hydrolysis was conducted at reflux temperature and 1 atm.

No other water-soluble compound could be found in appreciable quantity after complete hydrolysis.

The ether-soluble fraction from a two-hour acid hydrolysis was examined by chromatography.[12] Two major acidic fractions were isolated, one of which passed through the column very rapidly and the other much more slowly. The slow component, after separation from small amounts of two closely related impurities by chromatography, was recrystallized from petroleum ether.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.93; H, 10.52.

The acid was shown to contain one hydroxyl group per mole by quantitative acetylation followed by chromatography. Two acids were recovered from the column, one with a neutral equivalent of 232 (acetylated acid) and one with a neutral equivalent of 170 (probably dehydrated acid). Titration of the acetylated material produced corresponded closely to theory for the amount of acetic anhydride used. The isolated acid (α_D = −21°, 2.5% solution in chloroform) melted at 47–48°. The S-benzylthiouronium salt melted at 129–130°. Upon oxidation by chromic acid by the method used by Bergström, *et al.*,[9] a volatile, optically inactive liquid acid (neut. equiv. 145) was obtained which was chromatographically identical to *n*-caprylic acid. The chromatographic method employed[12] was found to be sufficiently efficient to positively differentiate between *n*-pelargonic, *n*-caprylic and *n*-enanthic acids. The amide of the oxidized acid was prepared (m. p. 105–106°). A mixed melting point with *n*-caprylamide showed no depression.

Anal. Calcd. for $C_8H_{17}ON$: N, 9.78. Found (Kjeldahl): N, 9.85.

These data indicate that the isolated acid is normal *l*-β-hydroxydecanoic acid although the possibility of its being a branched chain isomer has not been rigorously excluded.

The other major component of the ether-sol-

(12) L. L. Ramsey and W. I. Patterson, *J. Assn. Official Agr. Chem.*, **31**, 139 (1948).

(13) S. Gurin and D. B. Hood, *J. Biol. Chem.*, **131**, 211 (1939).

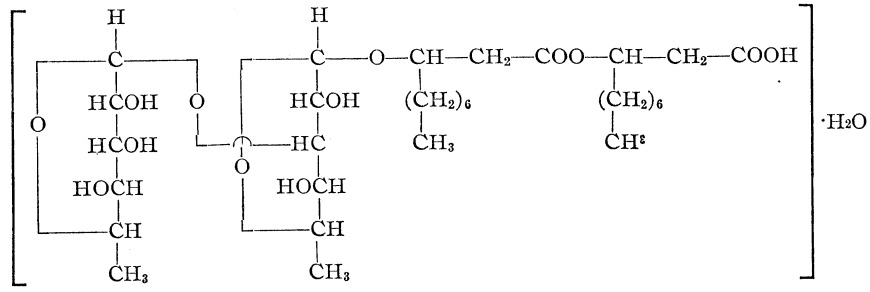
(14) S. Gurin and D. B. Hood, *ibid.*, **139**, 775 (1941).

(15) G. Holzman, R. V. MacAllister and C. Niemann, *ibid.*, **171**, 27 (1947).

(16) P. A. Shaffer and M. Somogyi, *J. Biol. Chem.*, **100**, 695 (1933).

uble hydrolytic fraction could not be obtained in crystalline form. It proved to have a neutral equivalent of about 360 and yielded two moles of β-hydroxydecanoic acid upon saponification. As no such ester is formed by the conditions employed during hydrolysis, and as the proportion of this compound decreases with hydrolysis time, it was concluded that two moles of *l*-β-hydroxydecanoic acid exist in esterified form in the original acidic compound.

The following formula is presented as being most compatible with the accumulated data. The 1,3-linkage shown is, of course, largely speculative as the only pertinent data obtained were the uptake of only two atoms of oxygen per mole of compound by periodate oxidation. Assuming a pyranoside-type ring, either the 1,2- or 1,4-linkages would result in a structure which would normally take up three oxygen atoms. No direct evidence for the type of sugar linkages involved (α or β) was obtained.



Summary

A crystalline, acidic glyco-lipide was produced by three strains of *Pseudomonas aeruginosa* on peptone–glycerol broth.

This compound was found to contain two units each of L-rhamnose and normal *l*-β-hydroxydecanoic acid.

The most likely formula on the basis of the available data is proposed.

MADISON 6, WIS. RECEIVED JULY 18, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, JEFFERSON MEDICAL COLLEGE]

The Preparation of 3,4,5-d_3-Lithocholic Acid[1]

BY W. H. PEARLMAN, M. R. J. PEARLMAN AND S. ELSEY

Schoenheimer and Berliner[2] described a procedure whereby deuteriolithocholic acid might be obtained by reduction of methyl $\Delta^{4,5}$-3-ketocholenate in ethanol–ether solution in the presence of platinum oxide; the isotopically labelled bile acid should prove useful for metabolic study. However, their work was carried out with hydrogen and not with deuterium. On repeating their procedure but using deuterium, we obtained lithocholic acid containing only 0.35 atom % excess deuterium whereas the theoretical value for 3,4,5-d_3-lithocholic acid is 7.50. This result is not altogether surprising in view of the observation by Anderson and MacNaughton[3] that deuterium is exchanged for the hydroxyl hydrogen of alcohols such as isopropyl alcohol in the presence of catalysts; evidence was obtained, however, that exchange did not occur with isopropyl alcohol as long as any acetone was present. When absolute ether was substituted for ethanol–ether in the catalytic reduction, lithocholic acid was obtained containing 1.92 atom % excess deuterium. Further investigation of optimal conditions for catalytic deuteration of methyl $\Delta^{4,5}$-3-ketocholenate appeared to be desirable; the results of such an investigation are summarized in Table I. The most satisfactory procedure found was the following. Reduction of methyl $\Delta^{4,5}$-3-ketocholenate in ether using a 5% palladium on charcoal catalyst gave a mixture consisting principally of methyl 3-ketocholanate and some methyl 3-ketoallocholanate; the mixture contained 3.59 atom % excess deuterium. Deuteration of this mixture in ether in the presence of platinum oxide yielded lithocholic acid with a slightly higher value, 3.72 atom % excess deuterium. Another run was made under identical conditions starting with methyl $\Delta^{4,5}$-3-ketocholenate; lithocholic acid was obtained containing 3.89 atom % excess deuterium. Thus, it appears that two step deuteration of methyl $\Delta^{4,5}$-3-ketocholenate furnishes lithocholic acid with twice as much deuterium as that obtained in the single step procedure; yet, theoretically three deuterium atoms should enter the steroid molecule in either procedure.[4] By way of comparison, it is interesting that Schoenheimer,

(1) This investigation was supported by a grant-in-aid from the United States Public Health Service, under the National Cancer Institute Act.

(2) R. Schoenheimer and F. Berliner, *J. Biol. Chem.*, **115**, 19 (1936).

(3) L. C. Anderson and N. W. MacNaughton, THIS JOURNAL, **64**, 1456 (1942).

(4) Since there are 40 hydrogen atoms per molecule, the value corresponding to a content of three deuterium atoms is 7.5 atom% excess deuterium. A fourth deuterium atom is introduced but, being an hydroxyl deuterium, it is readily exchanged in subsequent manipulation.

et al.,[5] obtained 4,5-d_2-coprostanone-3, which is identical in structure with methyl 3-ketocholanate with respect to rings A and B, by deuteration of $\Delta^{4,5}$-cholestenone-3 in dry ether in the presence of palladium and that this product contained 3.44 atom % deuterium (theoretical value 4.35). However, the 3,4,5-d_3-coprosterol described by Anchel and Schoenheimer[6] contained only 2.32 atom % deuterium (theoretical value 6.25); unfortunately, the mode of preparation of this compound was not described.

Further study of the mechanism of catalytic reduction of α,β-unsaturated ketones might afford an explanation of the results described here; Anderson and MacNaughton[3] studied the mechanism of catalytic reduction of some carbonyl compounds with the aid of deuterium.

Of incidental interest is the observation that the proportion of non-digitonin precipitable products (chiefly if not entirely lithocholic acid) formed on complete reduction of methyl $\Delta^{4,5}$-3-ketocholenate is dependent on the nature of the solvent used (see Table I). In addition to lithocholic acid and 3(β)-hydroxyallocholanic acid previously[2] described, a small amount of 3(β)-hydroxycholanic acid was isolated.

TABLE I

CATALYTIC DEUTERATION OF METHYL $\Delta^{4,5}$-3-KETOCHOLENATE

Reduction procedure (in D_2 at atm. pressure)	Non-digitonin pptble. fraction (as % of total reduction products)	Reduction product analyzed	Analysis[a] (atom % excess deuterium)
PtO_2; ethanol–ether; 25°	67	Lithocholic acid	0.35
PtO_2; ether; 5°	67	Reduction[b] mixt.	2.07
		Lithocholic acid	1.92
PtO_2; ethanol; 25°	36	Reduction mixt.[c]	0.32
PtO_2; acetic acid; 25°	36	Digitonin-pptble. fraction	0.34
Pd–charcoal; ether; 5°	..	Reduction mixt.	3.59
PtO_2; ether; 5° (using reduction mixture from preceding run)	66	Lithocholic acid	3.72
Pd–charcoal; ether; 5° followed by PtO_2; ether; 5°	64	Lithocholic acid	3.89
Pd–ZrO_2; ethyl acetate followed by PtO_2; acetic acid; 25°	34	3(β)Hydroxycholanic acid	3.22

[a] The "falling-drop method" was employed as described by A. S. Keston, D. Rittenberg and R. Schoenheimer, *J. Biol. Chem.*, **122**, 227 (1937–1938), and modified by M. Cohn in "Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, Michigan, 1947. [b] Similarly, deuteration of methyl $\Delta^{4,5}$-3-keto,12(α)-hydroxycholenate gave a reduction mixture containing 1.80 atom % excess deuterium; 74% of this mixture was non-digitonin precipitable. [c] Similarly, deuteration of $\Delta^{4,5}$-cholestenone-3 gave a reduction mixture containing 0.98 atom % excess deuterium.

(5) R. Schoenheimer, D. Rittenberg, B. J. Bergman and L. Rousselot, *J. Biol. Chem.*, **115**, 635 (1936).

(6) M. Anchel and R. Schoenheimer, *ibid.*, **125**, 23 (1935).

Experimental[7]

3,4,5-d_3-Lithocholic Acid.—8.56 g. of methyl $\Delta^{4,5}$-3-ketocholenate, m. p. 124–125°, obtained by Oppenauer oxidation[2] of methyl $\Delta^{5,6}$-3(β)-hydroxycholenate,[8] was dissolved in 400 ml. of absolute ether and shaken in deuterium at atmospheric pressure at 5° in the presence of 3.5 g. of 5% palladium on charcoal catalyst (previously treated with deuterium) until there was no further uptake of gas. The reduction product appeared to consist chiefly of methyl 3-ketocholanate and some methyl-3-ketoallocholanate. This mixture was dissolved in 400 ml. of absolute ether and deuterated under the same conditions as above but in the presence of 4.0 g. of platinum oxide. The final reduction mixture was separated into digitonin and non-digitonin fractions in a manner essentially that described by Schoenheimer and Berliner.[2] The latter fraction weighed 5.51 g. It was dissolved in 3 ml. of benzene plus 21 ml. of petroleum ether, b. p. 35–45°, adsorbed on a column containing 40 g. of aluminum oxide (Harshaw), and eluted with mixtures of benzene (5–100%)–petroleum ether. The eluates were worked up individually, yielding from aqueous methanol, a total of 3.51 g. of crystals with melting points ranging from 120 to 125°. This material was refluxed for two hours with 5% potassium hydroxide in 90% methanol; the solution was poured into water, acidified and extracted with ether. The product after two recrystallizations from ethyl acetate yielded 2.71 g. of lithocholic acid, m. p. 186–187°, containing 3.89 atom % excess deuterium; an additional 0.34 g. of crystals, m. p. 185–185.5° were obtained from the mother liquors.

The digitonin-precipitable material weighed 2.96 g. It yielded on treatment with ether–petroleum ether 740 mg. of crystals, m. p. 139–144°. The material in the mother liquor gave crystalline mixtures and hence was dissolved in 1.6 ml. of benzene plus 8 ml. of petroleum ether, adsorbed on a column containing 25 g. of aluminum oxide (Harshaw) and eluted with benzene (10–100%)–petroleum ether and finally with methanol. The benzene (10–20%)–petroleum ether eluates gave on repeated crystallization from aqueous methanol 380 mg., m. p. 108.5–110.5°. This material was hydrolyzed as above and crystallized from ethanol to furnish 359 mg. of 3(β)-hydroxycholanic acid,[9] m. p. 176–177.5°. The benzene (50–100%)–petroleum ether eluates were worked up individually furnishing, from aqueous methanol, a total of 224 mg. of crystals with melting points ranging from 141 to 148°. This material was combined with 740 mg. of the aforementioned product, m. p. 139–144°, and hydrolyzed as before; on repeated crystallization from ethanol, 604 mg. of 3(β)-hydroxyallocholanic acid, m. p. 219–220°, was obtained.

Summary

3,4,5-d_3-Lithocholic acid, containing 3.89 atom % excess deuterium, has been prepared by catalytic deuteration of methyl $\Delta^{4,5}$-3-ketocholenate in two steps. In addition, 3(β)-hydroxyallocholanic acid and 3(β)-hydroxycholanic acid were obtained.

PHILADELPHIA, PA. RECEIVED JUNE 9, 1949

(7) All melting points determined by the authors are corrected.

(8) Generously furnished by the Ciba Pharmaceutical Products, Inc., Summit, New Jersey, and by the Schering Corporation, Bloomfield, New Jersey.

(9) Melting points cited by H. Sobotka in "Chemistry of the Sterids," Williams and Wilkins Company, 1937, are 177–178° and 113–114.5°, 115–116° for this compound and its methyl ester respectively.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

A New Reaction of Nitriles. III. Amides from Dinitriles[1]

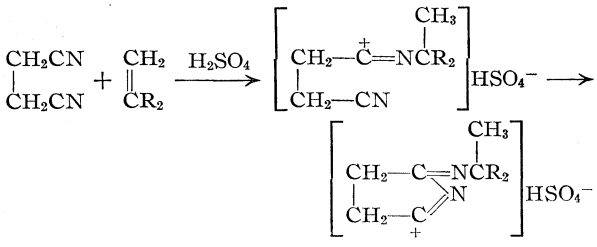
BY FREDERIC R. BENSON[2] WITH JOHN J. RITTER

The previous publications in this series have described the interaction of mononitriles and olefins to form N-substituted amides,[3] and the application of this reaction to the synthesis of *t*-carbinamines.[4] The use of dinitriles in this substituted amide synthesis, as well as a description of a variation of the reaction in which alcohols are used in place of olefins, form the subject matter of the present report.

Reaction of one mole of malononitrile, succinonitrile or glutaronitrile with two moles of an olefin such as isobutene, 2-methylbutene-2, camphene or diisobutene was carried out according to the previously described procedure.[3] In most instances the anticipated N,N′-disubstituted diamides were obtained (Table I). The reaction of succinonitrile with isobutene, diisobutene or camphene, however, under the same conditions resulted in the formation of N-monosubstituted succinamides, the second cyanide group of the dinitrile hydrolyzing in the usual manner. This anomalous behavior of succinonitrile

$$CH_2{=}C(CH_3)CH_3 + NCCH_2CH_2CN \xrightarrow[(2)\ H_2O]{(1)\ H_2SO_4} (CH_3)_3CNHCOCH_2CH_2CONH_2$$

possibly involves a cyclic mechanism according to the scheme



Subsequent hydrolytic reactions of the above intermediate would give rise to the monosubstituted amide. There is no immediately obvious explanation for the fact that 2-methylbutene-2-reacts with succinonitrile to yield the N,N′-diamide.

In view of the requirement of a strongly acid medium for the conduct of the reaction, it seems probable that a carbonium ion is an essential intermediate. Consideration of other possible sources of carbonium ions, besides the alkene–acid combination, led to the idea that alcohols might also function in this synthesis.[5] Accordingly, succinonitrile and *t*-butanol were subjected to reaction in the acetic acid–sulfuric acid solvent found suitable for use with olefins. The product isolated was found to be N-mono-*t*-butyl succinamide, identical with that obtained using isobutene. By means of this modification, it was found possible to utilize cyanogen in the synthesis of a diamide. Although preliminary work had failed to develop a means of effecting reaction between cyanogen and diisobutene, when *t*-butanol was employed, N,N′-di-*t*-butyloxamide was obtained, having the same properties described by Brander.[6]

The use of a secondary alcohol was investigated next. While reaction of secondary alcohols and nitriles in the acetic acid–sulfuric acid solvent could not be effected, concentrated sulfuric acid alone proved to be satisfactory for this purpose. Isopropyl alcohol and malononitrile produced N,N′-diisopropylmalonamide which has previously been prepared by conventional means.[7] Efforts to utilize a primary alcohol in the reaction proved fruitless; expedients such as the use of elevated temperatures, prolonged heating or the employment of fuming sulfuric acid were unsuccessful in the production of N-primary alkyl amides.

Comparison of the yields (Table I) of the products from dinitriles and olefins or alcohols, reveals that fumaronitrile is appreciably more active than any of the saturated dinitriles in the formation of substituted amides. It is evident that the reactivity of the cyanide groups is enhanced by the presence of the double bond.

Experimental

The following specific directions will serve to illustrate the methods followed in the preparation of the N-alkyl diamides. Recrystallizations of most of the succinamides and glutaramides were performed using benzene to which a small quantity of alcohol had been added. N,N′-Di-isopropyl and *t*-butyl malonamides were recrystallized from hexane, while for N,N′-di-*t*-octylmalonamide, di-*t*-butyloxamide, and di-*t*-butylfumaramide an alcohol–water mixture was used. Glacial acetic acid was required for N,N′-dicyclohexylfumaramide.

The carbon, hydrogen and Kjeldahl nitrogen determinations were performed in the Laboratory of Microchemistry at New York University.

N,N′-Di-*t*-amylglutaramide.—A mixture of 50 ml. of glacial acetic acid, 10.2 g. (0.1 mole) of concentrated sulfuric acid and 4.7 g. (0.05 mole) of glutaronitrile was prepared at room temperature. To this solution was added 7.0 g. of 2-methylbutene-2 which dissolved immediately. The temperature of the reaction rose to 50° and was kept below this point by periodic cooling with water. After remaining overnight, the reaction mixture was poured into 250 ml. of water; white crystals separated quickly from

(1) Based upon the thesis submitted by Frederic R. Benson in February, 1947, to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Remington Rand, Inc., South Norwalk, Conn.

(3) J. J. Ritter and P. P. Minieri, THIS JOURNAL, **70**, 4045 (1948).

(4) J. J. Ritter and J. Kalish, *ibid.*, **70**, 4048 (1948).

(5) The use of alcohols was developed with the collaboration of Robert M. Lusskin, Ph.D. research in progress.

(6) M. Brander, *Rec. trav. chim.*, **37**, 67 (1917).

(7) R. W. West, *J. Chem. Soc.*, **127**, 750 (1925).

TABLE I

N-ALKYL DIAMIDES

RNHCOYCONHR′; from NCYCN + alkenes or alcohols

Alkene or alcohol	R, R′[a]	Y	M. p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
t-Butanol	$(CH_3)_3C$—	.....	176	20	$C_{10}H_{20}O_2N_2$	..	..
Isopropanol	$(CH_3)_2CH$—	—CH_2—	115	40	$C_9H_{18}O_2N_2$	15.0	15.1
Isobutene	$(CH_3)_3C$—	—CH_2—	115	50	$C_{11}H_{22}O_2N_2$	13.1	12.9
Diisobutene	C_8H_{17}-(*t*-octyl)	—CH_2—	108	30	$C_{19}H_{38}O_2N_2$	8.6	8.6
t-Butanol[e]	R=$(CH_3)_3C$—						
	R′=H	—$(CH_2)_2$—	149	25	$C_8H_{16}O_2N_2$	16.3	16.2
2-Methylbutene-2	$C_2H_5(CH_3)_2C$—	—$(CH_2)_2$—	164	40	$C_{14}H_{28}O_2N_2$	10.9	10.8
Diisobutene	R=C_8H_{17}-(*t*-octyl)						
	R′=H	—$(CH_2)_2$—	150	50	$C_{12}H_{24}O_2N_2$	12.3	12.8
Camphene	R=$C_{10}H_{17}$-(isobornyl)						
	R′=H	—$(CH_2)_2$—	130	24	$C_{14}H_{24}O_2N_2$	11.1	11.0
Isopropanol	$(CH_3)_2CH$—	—CH=CH—	320d	80	$C_{10}H_{18}O_2N_2$	14.1	14.2[b]
t-Butanol	$(CH_3)_3C$—	—CH=CH—	310d	88	$C_{12}H_{22}O_2N_2$	..	..[c]
Cyclohexanol	C_6H_{11}—	—CH=CH—	320d	87	$C_{16}H_{26}O_2N_2$	10.1	9.8[d]
Isobutene	$(CH_3)_3C$—	—$(CH_2)_3$—	196	25	$C_{13}H_{26}O_2N_2$	11.5	11.4
2-Methylbutene-2	$C_2H_5(CH_3)_2C$—	—$(CH_2)_3$—	147	35	$C_{15}H_{30}O_2N_2$	10.3	10.4

[a] R = R′ except where otherwise noted. [b] Calcd.: C, 60.6; H, 9.1. Found: C, 60.9; H, 8.9. [c] Calcd.: C, 63.7; H, 9.8. Found: C, 63.6; H, 9.3. [d] Calcd.: C, 69.0; H, 9.4. Found: C, 68.9; H, 9.2. [e] Or isobutene.

the solution. These were filtered, slurried with 50 ml. of dilute sodium carbonate solution, washed with 50 ml. of water and recrystallized from water. A further crop of crystals was obtained by neutralizing the acid filtrate with sodium carbonate. This batch of crystals was also recrystallized from water. On twice recrystallizing the combined yield from a mixture of benzene and hexane, 5.0 g. of the compound with a constant melting point of 147° was obtained.

N-Mono-*t*-butylsuccinamide: (1) **From Isobutene.**—Isobutene was passed for two and one-half hours into a solution of 16 g. (0.2 mole) of succinonitrile in 100 ml. of glacial acetic acid and 40.8 g. of concentrated sulfuric acid until 25 g. (0.45 mole) was absorbed. The mixture was allowed to stand overnight and was worked up as described above.

(2) **From *t*-Butanol.**—To a mixture of 10.2 g. of concentrated sulfuric acid, 50 ml. of glacial acetic acid and 4.0 g. of succinonitrile was added 7.4 g. (0.1 mole) of *t*-butanol. The temperature of the reaction mixture rose spontaneously to 50°, and was maintained below this point by occasional cooling. After standing overnight, the product was separated and worked up as described above. Its melting point, alone and mixed with the product from isobutene, was 149°.

N,N′-Di-*t*-butyloxamide.—Cyanogen, generated from 40 g. of sodium cyanide, was passed into a mixture of 40 ml. of glacial acetic acid, 10.2 g. of concentrated sulfuric acid and 7.5 g. of *t*-butanol. The temperature rose from 20 to 26°. Isolation and purification of the product was accomplished as indicated above immediately after stopping the flow of cyanogen.

N,N′-Diisopropylfumaramide.—To 3.9 g. of fumaronitrile dissolved at room temperature in 20 ml. of concentrated sulfuric acid, was added, over a period of twenty minutes, 6.0 g. (0.1 mole) of isopropyl alcohol, the temperature being kept below 45° by means of an ice-bath. After two hours the reaction mixture was treated as described to separate and purify the product. Both the recrystallized and unrecrystallized material melted with decomposition at 320°, after beginning to darken at 225°. The substance decolorizes aqueous potassium permanganate in the cold. The following qualitative solubilities were noted: insoluble in water, benzene, acetone, ethyl acetate; soluble in ethanol and hot methanol.

Summary

A series of dinitriles have been converted to N-substituted diamides by means of the reaction with olefins. Use of tertiary and secondary alcohols instead of alkenes in this reaction also leads to N-substituted amides.

WASHINGTON SQUARE
NEW YORK, N. Y.

RECEIVED JUNE 30, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

A New Reaction of Nitriles. IV. Synthesis of N-Benzoylamino Acids[1]

BY LAWRENCE W. HARTZEL[2] WITH JOHN J. RITTER

Previous work in this Laboratory[3] has shown that nitriles interact with certain alkenes and alcohols in the presence of sulfuric acid to form substituted amides. In order to extend the scope of this reaction, the reaction of benzonitrile with a number of unsaturated acids and esters, and hydroxy esters, has now been investigated. This paper describes the preparation of N-benzoylamino acids by this novel procedure. Table I lists the reactants used and the products obtained, together with yields, melting points and analyses.

It was found that only certain of the acids and esters examined would undergo reaction with benzonitrile under the conditions of these experiments; compounds of the general types

$$R_1CCR_2R_2COOR_1 \text{ (OH)} \quad \text{and} \quad R_1C{=}CR_2COOR_2$$

where R_1 = alkyl and R_2 = H or alkyl

were found to be very reactive, while certain other types showed less reactivity. Among the compounds which failed to react with benzonitrile under a variety of conditions were methyl acrylate, methyl methacrylate, methyl crotonate, ethyl lactate, vinyl acetic acid, allyl acetic acid, maleic acid, diethyl fumarate and citraconic acid.

Two of the products obtained, β-benzoylamino-β-methylbutyric acid and β-benzoylamino-β-phenylpropionic acid, have been prepared previously by conventional methods.[4] A comparison of the physical properties found with those recorded in the literature established their identity. Hydrolysis of β-benzoylamino-α-ethyl-β-methylbutyric acid and β-benzoylamino-β-methylbutyric acid yielded β-amino-α-ethyl-β-methylbutyric acid and β-valine, respectively. The latter compound has been described by Slimmer.[4a] No attempt has been made to determine the position of the benzoylamino group on benzoylaminohendecanoic acid.

Experimental

Certain of the unsaturated and hydroxy esters were prepared by means of the Reformatsky reaction; two of the hydroxy esters, ethyl β-hydroxy-β-methylcaprylate and ethyl β-hydroxy-β-methyl-γ-phenylbutyrate have not been previously described.

All reactions were carried out in concentrated sulfuric acid with no other solvent. The same general procedure was followed in most cases; detailed directions are given for only a few typical preparations. Most of the products were recrystallized from benzene; in a few cases mixed solvents were used.

Analyses were performed in the Laboratory of Microchemistry at New York University. Nitrogen determinations were carried out by the Kjeldahl method.

Ethyl β-Hydroxy-β-methylcaprylate.—Reaction of methyl *n*-amyl ketone and ethyl bromoacetate in the presence of zinc using the Natelson and Gottfried[5] modification of the Reformatsky reaction gave a colorless oil in 71% yield; b. p. 93–95° (3 mm.), $n^{22}D$ 1.4350, d^{22}_{22} 0.941.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.3; H, 11.0. Found: C, 65.4; H, 11.1.

Ethyl β-Hydroxy-β-methyl-γ-phenylbutyrate.—Reaction of methyl benzyl ketone and ethyl bromoacetate as described above gave a viscous oil in 61% yield; b. p. 118–119° (2 mm.), $n^{22}D$ 1.5041, d^{22}_{22} 1.051.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.3; H, 8.2. Found: C, 70.9; H, 8.2.

Reaction of Benzonitrile with Unsaturated and Hydroxy Esters.—The following procedure is typical of that used throughout the work. A mixture of 14.6 g. (0.1 mole) of ethyl β-hydroxy-β-methylbutyrate and 10.3 g. (0.1 mole) of benzonitrile was cooled in an ice-bath and 20 ml. of concentrated sulfuric acid was added with stirring so that the temperature remained below 20°. When all the acid had been added, the temperature was allowed to rise to 40–45° until the exothermic reaction subsided. The mixture was allowed to stand at room temperature overnight and was then poured into 200 ml. of ice-water. The crude ester so precipitated was hydrolyzed to the benzoylamino acid by refluxing for two hours with 50 ml. of ethanol and 10 ml. of 50% aqueous potassium hydroxide solution. The hydrolysis mixture was poured into 400 ml. of water, non-acidic impurities were removed by extraction with ether; the free acid was precipitated by acidification with hydrochloric acid and recrystallized from benzene. The data on this compound and on the others prepared in this work are given on Table I.

β-Valine.—A mixture of 3.0 g. (0.0135 mole) of β-benzoylamino-β-methylbutyric acid, 20 g. (approximately 0.1 mole) of dried C. P. barium hydroxide and 180 ml. of distilled water was refluxed for one hundred and twenty hours, the condenser being fitted with a soda lime tube to exclude carbon dioxide. The hot solution was filtered, acidified with dilute sulfuric acid, and allowed to stand overnight. The heavy barium sulfate precipitate was filtered and washed thoroughly with distilled water. The filtrate and washings, approximately 400 ml. in all, were combined and made slightly alkaline with aqueous barium hydroxide. After standing overnight the mixture was filtered and washed. The filtrate and washings were combined and evaporated on a water-bath to a 50-ml. volume. This solution was again acidified with dilute sulfuric acid and allowed to stand overnight. The precipitate was filtered and washed. The filtrate and washings were combined and extracted with four 30-ml. portions of hexane. The aqueous solution was then shaken for ten minutes with 10 g. of Amberlite IR-4B[6] resin, which had previously been purified by shaking for ten minutes with six successive portions of distilled water. The mixture was filtered and washed. The filtrate was treated with further portions of resin until the *p*H of the solution no longer changed (approximately 5.9–6.1 as measured by indicator paper). The clear filtrate was heated with charcoal on a water-bath, filtered, and evap-

(1) Based upon the thesis submitted by Lawrence W. Hartzel in February, 1948, to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) Ritter and Minieri, THIS JOURNAL, **70**, 4045 (1948); Benson with Ritter, *ibid.*, **70**, 4128 (1949).

(4) (a) Slimmer, *Ber.*, **35**, 400 (1902); (b) Posner, *Ber.*, **38**, 2322 (1905).

(5) Natelson and Gottfried, THIS JOURNAL, **61**, 970 (1939).

(6) This material was kindly supplied by the Resinous Products Division, Rohm and Haas Company.

TABLE I

N-BENZOYLAMINO ACIDS FROM BENZONITRILE AND UNSATURATED ACIDS AND ESTERS, AND HYDROXY ESTERS

Starting compound	Formula of product	M. p., °C.[a]	Yield, %	Nitrogen, % Calcd.	Found
β,β-Dimethylacrylic acid	$C_{12}H_{15}O_3N$	141–142[b]	72	6.33	6.49
Ethyl β-hydroxy-β-methylbutyrate	$C_{12}H_{15}O_3N$	141–142.5	62	..	..
Ethyl β-hydroxy-β-methylvalerate	$C_{13}H_{17}O_3N$	103–104.5	76.5	5.99	5.82
Ethyl β-hydroxy-β-methylcaproate	$C_{14}H_{19}O_3N$	76–78	72	5.62	5.77
Ethyl β-hydroxy-β-methylcaprylate	$C_{17}H_{25}O_3N$[c]	113.5–114	67	4.81	4.49
Ethyl β-ethyl-β-hydroxyvalerate	$C_{14}H_{19}O_3N$	125–126.5	78	5.62	5.66
Ethyl α-ethyl-β-methylbutenoate	$C_{14}H_{19}O_3N$	108–109.5	72	5.62	5.70
Ethyl β-hydroxy-α-isopropyl-β-methylbutyrate	$C_{17}H_{25}O_3N$[d]	99–100	62	4.81	4.65
Ethyl β-hydroxy-α,α,β-trimethylbutyrate	$C_{14}H_{19}O_3N$	150–152	80	5.62	5.47
Ethyl 1-hydroxycyclopentylacetate	$C_{14}H_{17}O_3N$	185–187	40	5.66	5.51
Ethyl α-(1-hydroxycyclopentyl)-propionate	$C_{15}H_{19}O_3N$	133–134	44	5.36	5.47
Ethyl 1-hydroxycyclohexylacetate	$C_{15}H_{19}O_3N$	167–168	65	5.36	5.37
Ethyl α-(1-hydroxycyclohexyl)-propionate	$C_{16}H_{21}O_3N$	160–161.5	58	5.09[e]	4.94
Ethyl β-hydroxy-β-methyl-γ-phenylbutyrate	$C_{18}H_{19}O_3N$[f]	179–181	9	4.71	4.32
Ethyl cinnamate	$C_{16}H_{15}O_3N$[g]	195–196	26	5.20	5.23
Methyl undecylenate	$C_{18}H_{27}O_3N$[h]	103–105	16	4.59	4.56

[a] All melting points uncorrected. [b] Slimmer[4a] reported m. p. 141.5°. [c] *p*-Tolunitrile used in place of benzonitrile in this experiment. Calcd.: C, 70.1; H, 8.7. Found: C, 70.6; H, 8.7. [d] Isolated as the ethyl ester since standard alkaline hydrolysis failed. Calcd.: C, 70.1; H, 8.7. Found: C, 70.3; H, 8.9. [e] Calcd.: C, 69.8; H, 7.7. Found: C, 69.7; H, 7.6. [f] Crude acid dissolved in benzene and reprecipitated with hexane. Recrystallized from benzene–ethanol. Calcd.: C, 72.7; H, 6.4. Found: C, 72.7; H, 6.6. [g] Posner[4b] reported m. p. 194–196°. Excess cinnamic acid removed by dissolving in hot benzene. Residue dissolved in alkali, reprecipitated with acid and recrystallized from water. [h] Saponification mixture acidified with acetic acid; crude acid recrystallized twice from diisopropyl ether–acetone and finally from benzene. Calcd.: C, 70.8; H, 8.9. Found: C, 70.9; H, 8.7.

orated to dryness under reduced pressure. The residue was washed from the flask with 30 ml. of absolute ethanol and allowed to stand overnight. The mixture was filtered and the precipitate dried for two weeks under vacuum, then two hours at 110°; yield 0.50 g. (32%), m. p. 215–217°. Slimmer[4a] reported the melting point of β-valine to be 217° (cor.).

Anal. Calcd. for $C_5H_{11}O_2N$: N, 12.0. Found: N, 12.0.

The absolute alcohol filtrate was diluted with 200 ml. of ether, allowed to stand overnight and filtered. The white solid obtained after drying and heating melted at 205–207° and weighed 0.47 g.

β-Amino-α-ethyl-β-methylbutyric Acid.—This material was obtained from 3.0 g. (0.0120 mole) of β-benzoylamino-α-ethyl-β-methylbutyric acid by hydrolysis with barium hydroxide as described above; yield, 0.40 g. (23%), m. p. 228–229°.

Anal. Calcd. for $C_7H_{15}O_2N$: N, 9.65. Found: N, 9.41.

Summary

The preparation of a number of benzoylamino acids by the interaction of benzonitrile with certain unsaturated acids and esters and hydroxy esters, has been described.

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[CONTRIBUTION FROM THE P. R. INDUSTRIAL DEVELOPMENT LABORATORY AT THE UNIVERSITY OF PUERTO RICO]

Nitric Acid Oxidation of 2,4:3,5-Dimethylene-D-gluconic Acid; Some Derivatives of 2,4-Methylene-D-glucarolactone-3,6

BY I. A. COLÓN, R. FERNÁNDEZ-GARCÍA, LUIS AMORÓS AND HILDA BLAY

In a previous communication[1] from this Laboratory a modification of Zief and Scattergood's preparation of 2,4:3,5-dimethylene-D-gluconic acid was recorded. This paper deals with the nitric acid oxidation of dimethylene-D-gluconic acid as well as with the preparation and properties of derivatives of monomethylene glucarolactone, the oxidation product.

The oxidation of 2,4:3,5-dimethylene-D-gluconic acid was carried out with concentrated nitric acid. No spontaneous reaction could be noticed when dilute nitric acid was used at room temperature. Using the minimum amount of concentrated nitric acid required to dissolve all the dimethylene gluconic acid, a yield of 56% of the theoretical amount was obtained. A higher proportion of concentrated nitric acid led to slightly higher yields (67%).

The oxidation product crystallized directly from the reaction solution on cooling. The physical properties of this substance and of its monoethyl ester, dimethyl ester, monomethyl ester and diamide agreed with the values reported[2,3] for 2,4-methylene-D-glucarolactone-3,6 and its corresponding derivatives.

The stability of the 2,4-methylene acetal ring

(1) Colón, Fernández, Amorós and Blay, THIS JOURNAL, 71, 1493 (1949).

(2) Henneberg and Tollens, *Ann.*, **292**, 40 (1896).

(3) Haworth and Jones, *J. Chem. Soc.*, 66 (1944).

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR THE N,N′-SUBSTITUTED 2,4-METHYLENE-D-GLUCARODIAMIDES

Amide	Yield, %	M. p., °C.	$[\alpha]_D$	Temp., °C.	c	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Diamide	77	226 (dec.)	+52.0	30.4	2.16	$C_7H_{12}N_2O_6$	..	..	...	...	12.7	12.4
Methyl	69	224 (dec.)	+59.2	29.2	1.22	$C_9H_{16}N_2O_6$	43.5	43.5	6.4	6.4	11.3	11.0
Ethyl[a]	87	177.2–177.8	+54.1	26.8	1.78	$C_{11}H_{22}N_2O_7$	44.9	44.7	7.5	7.1	9.5	9.4
Isopropyl	73	213.4–214.6	+49.7	27.2	1.24	$C_{13}H_{24}N_2O_6$	51.2	51.3	7.9	8.0	9.2	9.0
Butyl[b]	48	202.8–203.4	+48.1	30.6	0.90	$C_{15}H_{30}N_2O_7$	51.4	51.7	8.6	8.3	8.0	8.1
Isobutyl	37	227.2–229.4	+51.5	27.2	0.80	$C_{15}H_{28}N_2O_6$	54.2	54.4	8.4	8.2	8.4	8.1
Allyl	68	169.5–170.0	+43.5	28.2	1.97	$C_{13}H_{20}N_2O_6$	52.0	51.7	6.7	6.5	9.0	8.9
β-Hydroxyethyl	68	163.0–164.6	+53.7	29.2	2.53	$C_{11}H_{20}N_2O_8$	42.9	42.5	6.5	6.6	9.1	8.5
Cyclohexyl	40	243.2–244.4	+49.7	27.4	0.55	$C_{19}H_{32}N_2O_6$	59.4	59.3	8.3	8.2	7.3	7.5

[a] A sample of 80.42 mg. lost on heating *in vacuo* at 100°, 4.96 mg.; calculated for such sample of $C_{11}H_{20}N_2O_6 \cdot H_2O$, 4.87 mg. [b] A sample of 87.93 mg. lost on heating *in vacuo* at 100°, 4.52 mg.; calculated for such sample of $C_{15}H_{28}N_2O_6 \cdot H_2O$, 4.52 mg.

in boiling concentrated nitric acid was surprising even though the limited acetolysis of methyl 2,4:3,5-dimethylene-D-gluconate has been shown[4] to result in the cleavage of only the 3,5-methylene acetal ring. The acetolysis reaction was tried on methyl 2,4-methylene-D-glucarolactone-3,6 and on dimethyl 2,4-methylene-D-glucarate at 0° for forty-five minutes. The monomethyl ester was subjected to a similar treatment with propionic acid–propionic anhydride mixture. The 2,4-methylene acetal ring was not cleaved in any of the three cases as shown by the formation of N,N′-dimethyl-2,4-methylene-D-glucarodiamide.

Some N,N′-disubstituted 2,4-methylene-D-glucarodiamides have been prepared which appear to be new; their properties are listed in Table I.

Experimental

Oxidation of 2,4:3,5-Dimethylene-D-gluconic Acid.—The reaction was carried out in a fume hood. In a 1.5-l. beaker 408 g. (1.86 moles) of dimethylenegluconic acid[1] was placed and 650 ml. of concentrated nitric acid added. After ten–fifteen minutes the mixture started to react and the temperature increased steadily to about 100°; a violent evolution of oxides of nitrogen was produced. The solid did not dissolve completely and the temperature started to decrease; 70 ml. of concentrated nitric acid was added and after a few minutes the solid dissolved so that a clear solution was obtained at the end of the reaction (one hour). On cooling a white crystalline precipitate was formed. The crude product was filtered, washed with 100 ml. of cold water, and dried under reduced pressure; m. p. 170–172°. The yield of the partially hydrated substance was (232 g.) 56% of the theoretical amount. The acid was recrystallized from methanol and dried *in vacuo* at 100°; m. p. 177.6–178.2; neutral equivalent found 201, calculated for $C_7H_8O_7$: 204; $[\alpha]^{28.6}D$ + 121 (c, 2.22; water), in close agreement with the values reported by Henneberg and Tollens[2] and by Haworth and Jones[3] for 2,4-methylene-D-glucarolactone-3,6. The monoethyl, monomethyl and dimethyl esters were prepared and their physical properties found to be in close agreement with the values reported.[3] The diamide was obtained from the ethyl ester.

Anal. Calcd. for $C_7H_{12}O_6N_2$: N, 12.7. Found: N, 12.4.

Using essentially the same procedure, 440 g. of dimethylenegluconic acid treated with 1260 ml. of concentrated nitric acid produced 297 g. (67%) of monomethylene glucarolactone.

N,N′-Disubstituted 2,4-Methylene-D-glucarodiamides.—Through a suspension of 0.02 mole of ethyl ester of monomethylene glucarolactone in methanol at 0° was passed enough of the freshly distilled amine to dissolve the ester. Any undissolved residue was filtered out and the solution allowed to stand at 5–10° for twenty-four hours. The first crop of crystalline amide was filtered out and washed with ether; on adding ether to the mother liquor further crops were obtained. The crude amides were recrystallized from methanol–ether except the N,N′-di-β-hydroxyethyl amide which was recrystallized from methanol. Specific rotations were determined in methanol as solvent for all the diamides except the unsubstituted diamide and N,N′-di-β-hydroxyethyl amide in which cases water was used as solvent. The specific rotations as well as concentrations and temperatures are indicated in Table I. All the diamides were found to be insoluble in benzene and ether but soluble in methanol except the unsubstituted diamide and N,N′-di-β-hydroxyethyl amide. All were found to be insoluble in water except N,N′-di-β-hydroxyethyl amide. The N,N′-diethyl and N,N′-dibutyl amides were obtained as hydrates.

Dimethyl 3,5-Diacetyl-2,4-methylene-D-glucarate.—To an ice-cold mixture of 35 ml. of acetic anhydride, 15 ml. of glacial acetic acid and 1 ml. of concentrated sulfuric acid, 4.7 g. (0.019 mole) of dimethyl 2,4-methylene-D-glucarate[3] was added. The mixture was shaken for forty-five minutes at 0°. It dissolved completely when shaken at room temperature for fifteen minutes. The solution was poured into a beaker containing 400 g. of ice. Seventy grams of sodium bicarbonate was added to nearly neutralize the solution; the precipitate was filtered and upon recrystallizing from benzene–petroleum ether it melted at 87.8–89.2°. The solid was soluble in benzene in which it showed a specific rotation $[\alpha]^{25.6}D$ −15.5° (c, 2.67; benzene). The yield was (2.8 g.) 44% of the theoretical amount.

Anal. Calcd. for $C_{13}H_{18}O_{10}$: C, 46.7; H, 5.4. Found: C, 47.1; H, 5.4.

N,N′-Dimethyl-2,4-methylene-D-glucarodiamide from Dimethyl 3,5-Diacetyl-2,4-methylene-D-glucarate.—Methylamine was bubbled through a solution of 0.5 g. of dimethyl 3,5-diacetyl-2,4-methylene-D-glucarate in 25 ml. of methanol at 0° until the theoretical amount had dissolved. The solution was left overnight at 5–10°. A white precipitate was formed when ether was added; m. p. 219–220° (dec.) and a specific rotation $[\alpha]^{28.2}D$ + 62.3 in methanol (c, 1.13), these data being in agreement with those previously found for the N,N′-dimethyl-2,4-methylene-D-glucarodiamide obtained by the action of methylamine on ethyl ester of monomethyleneglucarolactone. A mixed melting point determination with N,N′-dimethyl-2,4-methylene-D-glucarodiamide from this source showed no depression.

(4) Mehltretter, Mellies and Rist, THIS JOURNAL, 70, 1064 (1948).

Methyl-5-acetyl-2,4-methylene-D-glucarolactone-3,6.—To an ice-cold mixture of 20 ml. of acetic anhydride, 8 ml. of glacial acetic acid and 0.5 ml. of concentrated sulfuric acid, 2.6 g. (0.012 mole) of methyl 2,4-methylene-D-glucarolactone-3,6[3] was added. The mixture was shaken for forty-five minutes at 0°. The solid dissolved and almost immediately a white precipitate was formed. It was filtered, washed with water and recrystallized from hot water. The yield was (2.1 g.) 68% of the theoretical amount; m. p. 190.6°–192°; $[\alpha]^{27.2}D$ + 133 (*c*, 1.99; acetone).

Anal. Calcd. for $C_{10}H_{12}O_8$: C, 46.1; H, 4.6. Found: C, 46.1; H, 4.7.

N,N'-Dimethyl-2,4-methylene-D-glucarodiamide from Methyl-5-acetyl-2,4-methylene-D-glucarolactone-3,6.—In 30 ml. of ice-cold methanol 2.1 g. (0.008 mole) of methyl-5-acetyl-2,4-methylene-D-glucarolactone-3,6 was suspended. Methylamine was passed through the mixture until the solid dissolved. The solution was allowed to stand at 5–10° overnight. A white precipitate (0.5 g.) was formed; m. p. 217–218° (dec.). The filtrate was evaporated to dryness and crude product was recrystallized from methanol–ether. The yield was (2.1 g.) 95% of the theoretical amount; m. p. 223–224° (dec.) and a specific rotation $[\alpha]^{26.6}D$ + 60.0° in methanol (*c*, 0.69), these data being in agreement with those previously found for the N,N'-dimethyl-2,4-methylene-D-glucarodiamide obtained by the action of methylamine on ethyl ester of monomethyleneglucarolactone. A mixed melting point determination with N,N'-dimethyl-2,4-methylene-D-glucarodiamide from this source showed no depression.

Methyl-5-propionyl-2,4-methylene-D-glucarolactone-3,6.—To an ice-cold mixture of 35 ml. of propionic anhydride, 15 ml. of propionic acid and 1 ml. of concentrated sulfuric acid, 5.0 g. (0.023 mole) of methyl 2,4-methylene-D-glucarolactone-3,6 was added. The mixture was shaken for forty-five minutes at 0°. The solid dissolved and almost immediately a white precipitate was formed. It was filtered, washed with water and ether and recrystallized from hot water. The yield was (5.0 g.) 79% of the theoretical amount; m. p. 164.6–165.8°; $[\alpha]^{28.6}D$ + 153° (*c*, 2.06; chloroform).

Anal. Calcd. for $C_{11}H_{14}O_8$: C, 48.2; H, 5.1. Found: C, 48.2; H, 5.3.

N,N'-Dimethyl-2,4-methylene-D-glucarodiamide from Methyl-5-propionyl-2,4-methylene-D-glucarolactone-3,6.—In 15 ml. of ice-cold methanol 0.6 g. of methyl 5-propionyl-2,4-methylene-D-glucarolactone-3,6 was suspended. Methylamine was passed through the mixture until the solid dissolved and the solution allowed to stand at 5–10° overnight. A white precipitate was formed; m. p. 223° (dec.). The crude product was recrystallized from methanol–ether and the specific rotation determined in methanol $[\alpha]^{27.2}D$ + 61.7° (*c*, 1.03); these data are in agreement with those previously found for the N,N'-dimethyl-2,4-methylene-D-glucarodiamide obtained by the action of methylamine on ethyl ester of monomethyleneglucarolactone. A mixed melting point determination with N,N'-dimethyl-2,4-methylene-D-glucarodiamide from this source showed no depression.

Summary

1. The nitric acid oxidation of 2,4:3,5-dimethylene-D-gluconic acid has been shown to yield 2,4-methylene-D-glucarolactone-3,6 in 67% yield.

2. An attempted controlled acetolysis of dimethyl-2,4-methylene-D-glucarate and of methyl 2,4-methylene-D-glucarolactone-3,6 did not remove the 2,4-methylene acetal ring.

3. Some N,N'-disubstituted-2,4-methylene-D-glucarodiamides have been prepared which appear to be new.

RIO PIEDRAS, PUERTO RICO RECEIVED APRIL 7, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE]

Some N-Aminophenylarsanilic Acids

BY ROBERT L. MCGEACHIN

Since it was found recently that Melarsen,[1,2] a diamino triazino derivative of *p*-arsanilic acid, is an effective trypanocidal agent, it was decided to study the preparation of some N-aminophenylarsanilic acids.

Barber[3] condensed 3-nitro-4-chlorophenylarsonic acid with certain aromatic amines to give N-phenylarsanilic acids but no studies on the condensation of dinitrochlorobenzene with *p*-arsanilic acid have been made. However, Linke[4] condensed dinitrochlorobenzene with *p*-aminobenzoic acid and Kogan, Voronov and Lyubiteleva[5] condensed dinitrochlorobenzene with *p*-aminophenol-3,5-disulfonic acid.

Heating *p*-arsanilic acid and 2,4-dinitrochlorobenzene in 5% aqueous sodium hydroxide for seven hours proved to be an unsatisfactory method since excessive hydrolysis of the 2,4-dinitrochlorobenzene to 2,4-dinitrophenol occurred under these conditions. Sodium acetate and calcium carbonate (in aqueous alcohol medium) were found to be satisfactory condensing agents, however, with the latter the better of the two since it produced less by-products than the sodium acetate and gave better yields of N-2,4-dinitrophenylarsanilic acid. N-2,4-Diaminophenylarsanilic acid was prepared from this dinitro compound.

It was found that 3-nitro-4-chlorophenylarsonic acid would react with *p*-aminodimethylaniline and *p*-aminodiethylaniline under conditions outlined by Barber[3] to give N-4-dimethylaminophenyl-3-nitroarsanilic acid and N-4-diethylaminophenyl-3-nitroarsanilic acid. Attempts to reduce the nitro groups in these compounds to amino groups were unsuccessful, however, presumably due to the instability of the products formed.

(1) Friedheim, THIS JOURNAL, **66**, 1775 (1944).
(2) Banks, *et al.*, *ibid.*, **66**, 1771 (1944).
(3) Barber, *J. Chem. Soc.*, 471 (1929).
(4) Linke, *J. prakt. Chem.*, **91**, 202 (1915).
(5) Kogan, Voronov and Lyubiteleva, *Anilinokrasochnaya Prom.*, **3**, 153 (1933).

Experimental

N-2,4-Dinitrophenylarsanilic Acid (I). A.—Six grams of *p*-arsanilic acid, 5 g. of 2,4-dinitrochlorobenzene and

0.5 g. of calcium carbonate were added to 100 ml. of 50% aqueous ethyl alcohol and the mixture heated under reflux on a steam-bath for eight hours. The reaction mixture was cooled, diluted with 50 ml. of water and filtered. The residue was dissolved in 10% sodium hydroxide (the solution was deep blood-red in color), treated with 0.5 g. of activated charcoal and the solution filtered. On acidification of the solution to congo red with concd. hydrochloric acid, a canary-yellow solid precipitated. After allowing the acidified mixture to stand overnight in the ice-box, the product was filtered off and dried at 130° for twelve hours giving a yield of 3.8 g. (41%). This compound did not melt below 250°.

Anal.[6] Calcd. for $C_{12}H_{10}O_7N_3As$: As, 19.58. Found: As, 19.44.

B.—I was also prepared from *p*-arsanilic acid and 2,4-dinitrochlorobenzene using sodium acetate as the condensing agent. In this reaction a considerable quantity of a red-orange solid was formed as a by-product. The product was isolated and purified, the same procedure used in method A giving a yield of 30%.

Anal. Calcd. for $C_{12}H_{10}O_7N_3As$: As, 19.58. Found: As, 19.16.

N-2,4-Diaminophenylarsanilic Acid.—One gram of I was reduced using 10.1 g. of ferrous sulfate in the method of Jacobs, Heidelberger and Rolf.[7] The product was a dark-red solid which rapidly turned black in the presence of air. The yield was 0.3 g. (36%).

Anal. Calcd. for $C_{12}H_{14}O_3N_3As$: As, 23.22. Found: As, 23.10.

(6) Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

(7) Jacobs, Heidelberger and Rolf, *ibid.*, **40**, 1581 (1918).

N-4-Dimethylaminophenyl-3-nitroarsanilic Acid.—Four grams of 3-nitro-4-chlorophenylarsonic acid was dissolved in 10 ml. of 10% sodium hydroxide and 8 ml. of water, 3 ml. of *p*-aminodimethylaniline added and the mixture heated under reflux in an oil-bath at 140° for eight hours. On addition of concd. hydrochloric acid to the neutral point, a sticky dark-brown solid precipitated. This product was purified by twice redissolving in 5% sodium hydroxide, charcoaling the solution, filtering and reacidifying. The red-brown solid was filtered off, washed well with water and alcohol and dried at 100° for twenty-four hours to yield 3 g. of product (56%).

Anal. Calcd. for $C_{14}H_{16}O_5N_3As$: As, 19.40. Found: As, 19.29.

N-4-Diethylaminophenyl-3-nitroarsanilic Acid.—This product was prepared by the same method used for the dimethylamino compound. It was a red-brown solid. The yield was 3.5 g. (60%).

Anal. Calcd. for $C_{16}H_{20}O_5N_3As$: As, 18.32. Found: As, 18.36.

Summary

The reaction of *p*-arsanilic acid with 2,4-dinitrochlorobenzene to form N-2,4-dinitrophenylarsanilic acid has been studied. N-2,4-Diaminophenylarsanilic acid has been prepared.

N-4-Dimethylaminophenyl-3-nitroarsanilic acid and N-4-diethylaminophenyl-3-nitroarsanilic acid have been prepared.

LOUISVILLE, KY. RECEIVED AUGUST 3, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

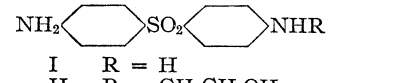
Monosubstituted Diaminodiphenyl Sulfones

BY JOHN WEIJLARD AND EDWARD SWANEZY

The antistreptococcal and antitubercular efficacy of substituted 4,4′-diaminodiphenyl sulfones appears to be increased if one amino group is free; consequently a number of monosubstituted diaminodiphenyl sulfones have been reported upon recently.[1,2] These compounds have generally been prepared either by reducing 4-nitro-4′-halodiphenyl sulfone followed by reaction of the resultant 4-amino-4′-halodiphenyl sulfone with the requisite amine,[1] or by alkylation of 4-nitro-4′-aminodiphenyl sulfone followed by reduction of the nitro group.[2] In either case the methods are laborious, the replacement reactions are often sluggish and the yields poor. This is particularly noticeable when 4-nitro-4′-aminodiphenyl sulfone is subjected to hydroxyethylation with compounds such as ethylene bromohydrin.[2]

A simple and rapid method has now been found for these compounds consisting of treating the readily available 4-acetylaminobenzene sulfonyl chloride with monochlorobenzene in presence of aluminum chloride to give 4-acetylamino-4′-chlorodiphenyl sulfone in 88% yield and of reacting the latter with, for instance, ethanolamine or isopropanolamine in presence of copper to yield the corresponding 4-amino-4′-(β-hydroxyethylamino)- or (β-hydroxypropylamino)-diphenyl sulfone, respectively, in 70 to 85% yields. Other amines, such as N-aminoethylmorpholine, reacted readily to give 4-amino-4′-(β-morpholineëthylamino)-diphenyl sulfone in high yield. With ammonia water, 4,4′-diaminodiphenyl sulfone was obtained in good yield. It is noteworthy that deacetylation takes place simultaneously with the alkylations.

A simplified method for the preparation of the parent substance, 4,4′-diaminodiphenyl sulfone, is thus available, and in addition a general method for preparing a large number of monosubstituted diaminodiphenyl sulfones, by selecting the proper amine and catalyst. The preparation of four compounds in this class is described.



I R = H
II R = CH_2CH_2OH
III R = CH_2CHCH_3 (OH)
IV R = CH_2CH_2N (morpholine)

(1) Amstutz, Fehnel and Woods, THIS JOURNAL, **69**, 1922 (1947).

(2) Jackson, *ibid.*, **70**, 680 (1948).

The new compounds, III and IV, show activity *in vitro* against *M. Tuberculosis;* compound III has also been found to be active against *D. pneumoniae* and *Staph. aureus.*[3] Compound II is being investigated elsewhere.

Experimental

4-Acetylamino-4′-chlorodiphenyl Sulfone.[4]—Four hundred sixty-seven grams of 4-acetylaminobenzene sulfonyl chloride (2 moles) was mixed with 1500 cc. of monochlorobenzene and warmed to 50°; 533 g. of anhydrous aluminum chloride (4 moles) was added in portions over a period of one hour at 55–65° with rapid stirring. The mixture was stirred at 70–80° for an additional three hours, then the excess monochlorobenzene was distilled *in vacuo.* The hot residual sirup was poured into a mixture of 2 kg. of crushed ice and 400 cc. of concentrated hydrochloric acid and stirred till completely disintegrated. The product was collected, washed with liberal quantities of water, then alcohol, and dried at 50°; yield 544 g. (88%), m. p. 194°.

Anal. Calcd. for $C_{14}H_{12}O_3NSCl$: N, 4.57. Found: N, 4.87.

4,4′-Diaminodiphenyl Sulfone.—Thirty-one grams of 4-acetylamino-4′-chlorodiphenyl sulfone (0.1 mole) was mixed with 100 cc. of concentrated ammonia water containing 0.5 g. of cuprous chloride, and the mixture was held in a mechanically agitated steel bomb at 180–190° for twelve hours. The cooled reaction mixture was filtered, washed with water and dried; yield 22 g. of crude sulfone (89%). The crude product was dissolved in 400 cc. of hot 50% methanol, the copper was precipitated with hydrogen sulfide, 2 g. of decolorizing black was added, and the solution was filtered through a heated filter. The clear filtrate was poured into 1400 cc. of water containing a trace of hydrosulfite, and the precipitated sulfone was filtered and washed with water; yield 18.6 g. (84.5%) of white sulfone, m. p. 172°.

Anal. Calcd. for $C_{12}H_{12}O_2N_2S$: C, 58.06; H, 4.87; N, 11.30. Found: C, 57.78; H, 4.84; N, 10.99.

4-Amino-4′-(β-hydroxyethylamino)-diphenyl Sulfone.—Thirty-one grams of 4-acetylamino-4′-chlorodiphenyl sulfone (0.1 mole) was mixed with 37 g. of ethanolamine (0.6 mole) and 0.5 g. of cuprous chloride, and the mixture was stirred and refluxed at 160–168° for twenty-two hours. The cooled reaction mixture was diluted with 400 cc. of water and cooled in ice overnight. The mother liquor was decanted and the gummy residue was dissolved in 180 cc. of hot 50% ethanol. The solution was treated with hydrogen sulfide and 2 g. of decolorizing black, filtered, scratched until crystallization was well under way, then chilled at 0° for forty-eight hours. The crystals were collected, washed with iced 50% ethanol and dried *in vacuo;* yield 21.0 g. (73%), m. p. 128–131°. After recrystallization in absolute alcohol the product melted at 131–132°.[5]

Anal. Calcd. for $C_{14}H_{16}O_3N_2S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.55; H, 5.31; N, 9.73.

The X-ray diffraction pattern was identical with that from the sulfone made by the Jackson method,[2] and the solubility analysis indicated a purity of over 95%.[6]

4-Amino-4′-(β-hydroxypropylamino)-diphenyl Sulfone.—One-tenth of a mole of 4-amino-4′-chlorodiphenyl sulfone was mixed with 45 g. of isopropanolamine (0.6 mole) and 0.5 g. of cuprous chloride, and the mixture was stirred and refluxed at 165–175° for fifteen hours. The reaction mixture was worked up essentially as above, except that the crude product was dissolved in a hot mixture of 200 cc. of alcohol and 100 cc. of acetone. After removal of the copper and treatment with Darco, the solution was diluted with two volumes of water and cooled overnight in ice; yield 26.0 g. (85%), m. p. 183–186°. After recrystallization in absolute alcohol, the m. p. rose to 190–192°.

Anal. Calcd. for $C_{15}H_{18}O_3N_2S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.87; H, 5.88; N, 9.22.

4-Amino-4′-(β-morpholineethylamino)-diphenyl Sulfone.—One-tenth of a mole of 4-amino-4′-chlorodiphenyl sulfone, 65 g. of N-aminoethylmorpholine (0.5 mole), and 0.5 g. of cuprous chloride were mixed and held at 200° for fifteen hours with stirring. The reaction mixture was diluted with 600 cc. of water and the precipitated product was separated by decantation and dissolved in 250 cc. of hot alcohol. The copper was removed with hydrogen sulfide, the clear filtrate was concentrated *in vacuo,* and during the concentration the sulfone crystallized suddenly. The crystals were filtered, washed with cold alcohol and dried at 50°; yield 30.1 g. (83%), m. p. 204–205°.

Anal. Calcd. for $C_{18}H_{23}O_3N_3S$: N, 11.63. Found: N, 11.54.

Acknowledgment.—We are indebted to Dr. Max Tishler for his interest and valuable suggestions.

Summary

A new and rapid method for the preparation of monosubstituted diaminodiphenyl sulfones is described. Two new sulfones have been prepared.

RAHWAY, N. J. RECEIVED JULY 2, 1949

(3) The study of the chemotherapeutic activity of these compounds is being carried out by Dr. Morris Solotorovsky and Miss Bettina M. Frost of the Merck Institute for Therapeutic Research.

(4) Heymann and Fieser, *ibid.*, **67**, 1979 (1945), isolated the 4-amino-4′-chlorodiphenyl sulfone from a mixture of incompletely ammonolyzed 4,4′-dichlorodiphenyl sulfone.

(5) Two forms of this compound have been observed, one of m. p. 145–146°, the other of m. p. 131–132°. The form of lower m. p. appears to be the more stable.

(6) We are indebted to Mr. F. A. Bacher of the Research Laboratories of Merck and Co., Inc., for carrying out these measurements.

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

Synthesis of 1′-Dehydro-β-ionone

BY HARRY SOBOTKA AND J. D. CHANLEY

In a recent publication[1] we have indicated the role of 2,2,6-trimethyl-1-ethynylcyclohexanol[2] as a useful intermediate in the synthesis of vitamin A. We have accomplished the dehydration of this carbinol (III) by the use of thionyl chloride and pyridine to 2,2,6-trimethyl-1-ethynylcyclohexene-1 (IV), a compound which takes a central position in a projected total synthesis of vitamin A.[1] The physical properties of this hydrocarbon and the successful synthesis of tetrahydroionone therefrom in high yield confirms its structure. The physical properties of hydrocarbon fractions, previously described[3] as 2,2,6-trimethyl-1-ethynylcyclohexene-1, differ considerably. One of us[4] had previously referred to the dehydration of the carbinol over an alumina catalyst in analogy to the dehydration of the simple 1-ethynylcyclohexanol. Subsequent studies, however, had thrown doubt on the nature of the dehydration product. As will be reported in a subsequent paper,[5] dehydration over alumina is accompanied by methyl migration and by migration of hydrogen from the ring into the side chain, leading to aromatization. Besides the resulting benzenoid hydrocarbon, there is found in small amounts an acetylenic fraction of which an insignificant portion, in turn, may be the desired 2,2,6-trimethyl-1-ethynylcyclohexene-1. The major part of the acetylenic fraction, however, lacks the conjugation of the double bond with the triple bond.

Condensation of acetic anhydride with the Grignard derivative of the true acetylenic hydrocarbon yielded 1′-dehydro-β-ionone (V). This compound shows the typical spectral qualities expected from a conjugated system so closely related to β-ionone; its λ_{max} is 288 mμ with an extinction of ϵ_{max} 11,800, and its refractive index is $n^{20}D$ 1.5205. It was subsequently hydrogenated and yielded a tetrahydroionone (VI) whose semicarbazone was found to be identical with that of an authentic sample of tetrahydroionone to which Prelog[6] assigns the *cis*-configuration.

The Grignard derivative of 2,2,6-trimethyl-1-ethynylcyclohexene-1 was condensed with acetaldehyde; the resulting DL-dehydro-β-ionol (VII) was catalytically hydrogenated to DL-tetrahydroionol (VIII); this, in its turn, was oxidized to a saturated ketone (VI) characterized by three derivatives, which were again identical with those obtained from tetrahydroionone prepared from β-ionone.

The dehydration of 1-ethynylcyclohexanol to ethynylcyclohexene over alumina proceeds with relative ease. The difficulty encountered in the instance of the trimethyl compound is due, not merely to the fact that only one, instead of four hydrogen atoms, is available, but also to steric considerations[7] and to the further complication that a neopentyl alcohol type system is present.[8] It is generally believed that elimination of the elements of water is predicated upon the *trans*-position of hydrogen and hydroxyl with respect to each other. Two diastereomeric racemates are possible for 2,2,6-trimethyl-1-ethynylcyclohexanol-1, only one of which may be expected to dehydrate without rearrangement, namely, that carbinol which carries the ortho hydrogen atom *trans* to the hydroxyl group. The reaction of sodium acetylide with trimethylcyclohexanone (I) may be anticipated to yield a mixture of both forms.[9] From the negative outcome of dehydration experiments, one is led to assume that the *cis*-diastereomer prevails in the reaction mixture. Thus, we set out to replace the hydroxyl group by a group X in a reaction which probably proceeds with racemization at carbon atom 1. This should lead to a product containing a higher percentage of the *trans*-compound. Removal of HX from the resulting mixture should then lead to the proper hydrocarbon. As the carbinol did not react with dry hydrogen chloride, thionyl chloride in excess pyridine was employed. This did not lead to a simple replacement of hydroxyl by chlorine, but the proper hydrocarbon was isolated in 15% yield. The major reaction product (60%) was a chloro compound of the elementary composition $C_{11}H_{17}Cl$. This substance still contained the —C≡CH grouping as it formed a silver salt, which speaks against the formation of an allene.[10] The chlorine atom is easily removable, rendering unlikely the formulation of this compound as a vinyl chloride derivative.[11] Replacement of chlorine by hy-

(1) Sobotka and Chanley, THIS JOURNAL, **70**, 3914 (1948).

(2) Sobotka, Progress Reports 1942–1944, Final Report 1944 to OSRD, distributed by Office of Production Board, Nos. 77, 214–215 (1947).

(3) *Cf.* Milas, MacDonald and Black, THIS JOURNAL, **70**, 1829 (1948).

(4) See ref. 2, Progress Reports of October 28, 1943 and February 25, 1944.

(5) Chanley and Sobotka, THIS JOURNAL, **71**, 4140 (1949).

(6) Prelog and Frick, *Helv. Chim. Acta*, **31**, 417 (1948).

(7) Bartlett and Pockel, THIS JOURNAL, **59**, 820 (1937); Bartlett and Bavley, *ibid.*, **60**, 2416 (1938); Price, *ibid.*, **61**, 1847 (1939); Price and Karabinos, *ibid.*, **62**, 1159 (1940).

(8) Dostrovsky, Hughes and Ingold, *J. Chem. Soc.*, 179, esp. 188, 192–194 (1946); see also Dostrovsky and Hughes, *ibid.*, 157, 161, 164, 166, 169 (1946).

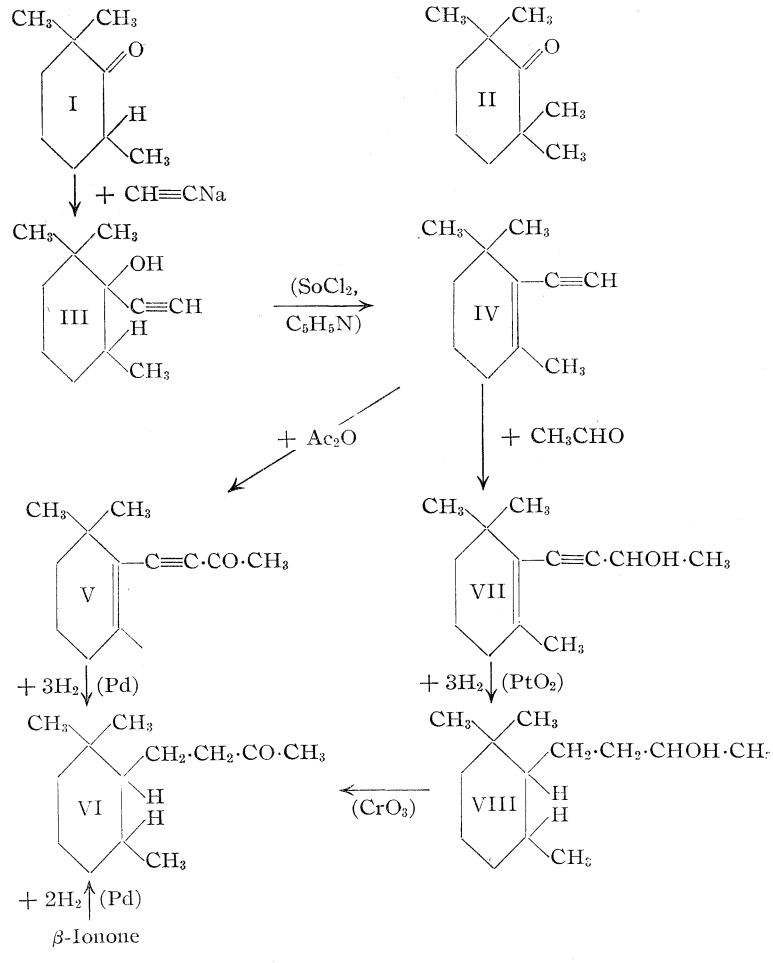
(9) Wang and Hu, *J. Chin. Chem. Soc.*, **10**, 1 (1943); *cf.* ref. 5. Careful fractional distillation of the carbinol did not afford any separation; the carbinol boiled over a range of 1° and the various portions collected did not differ from one another in their refractive index.

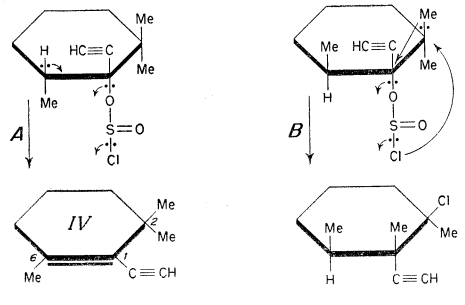
(10) A. W. Johnson, "Chemistry of Acetylenic Compounds," Arnold and Co., London, 1946, pp. 62, 71.

(11) Hurd and Jones, THIS JOURNAL, **56**, 1924 (1934), have shown that the action of thionyl chloride–pyridine on 1-ethynylcyclohex-

droxyl did not regenerate the original carbinol, but gave rise to a new carbinol, presumably with an altered carbon skeleton. The chloro compound, when treated with reagents used for dehydrohalogenation, did not yield the desired hydrocarbon.

The chloro compound can be derived from the *cis*-carbinol under the following assumption: Since no simple elimination reaction is possible in this stereomer of the hypothetical –OSOCl intermediate (B), the latter may react in two other ways, namely, by formation of the corresponding chloro compound, with loss of sulfur dioxide, or by rearrangement and subsequent addition of the chloride ion to another part of the molecule. The latter presumably occurs according to a reaction exemplified by scheme B. Contraction of the ring is not excluded nor migration of the methyl group on carbon atom 6, rather than that on carbon atom 2. The *trans*-form reacts according to scheme A which involves the loss of a proton from carbon atom 6 and the simultaneous loss of sulfur dioxide and chloride ion, leading to the formation of the "ene–yne" system. An alternative explanation, equally compatible with the results, is that scission of the C–O bond in the intermediate addition product results in the generation of a carbonium ion, which assumes a planar configuration, implying racemization at carbon atom 1. From this carbonium ion both reactions may proceed in proportion to their respective reaction rates, and lead to the products isolated. This mechanism appears to be less likely.[12] We consider it most probable that the modest yield of the correct hydrocarbon in the thionyl chloride–pyridine reaction originated from the *trans*-form present in the carbinol. Work is in progress to establish the structure of the chloro compound.





Experimental

The ultraviolet absorption spectra were obtained with a Beckman spectrophotometer Model DU using 95% ethanol as solvent except as otherwise noted. We are indebted for the microanalyses to the late Dr. Gertrude Oppenheimer and her associates, Microchemical Laboratory, California Institute of Technology, Pasadena, California.

***o*-Methylcyclohexanone** was prepared for us by Givaudan–Delawanna, Inc., Delawanna, N. J., through the courtesy of Drs. Luthy and Fiori by the catalytic hydrogenation of purest *o*-cresol and subsequent oxidation of the resulting 2-methylcyclohexanol with dichromate.

Preparation of 2,2,6-Trimethyl-1-cyclohexanone (I) and 2,2,6,6-Tetramethyl-1-cyclohexanone (II).[12a]—The introduction of one methyl group into *o*-methylcyclohexanone has been described by one of us.[13] The crude dimethylcyclohexanone fraction of b. p. 169–173° was further methylated in two to three mole batches by the use of sodamide and methyl iodide under the same conditions as in the preparation of the dimethyl compound. The reaction was brought to conclusion by refluxing the mixture for seven hours. After decomposition of the reaction mixture with 10% sulfuric acid, the organic layer was

anol produced some 1-ethynylcyclohexene, but for the most part 1-(α-chlorovinyl)-cyclohexene-1. Such a conjugated diene system, carrying a chlorine atom, would show λ_{max} around 230–235 mμ; *cf.* Bowden, Brauder and Jones, *J. Chem. Soc.*, 948 (1946). Our product showed no absorption in the ultraviolet.

(12) *Cf.* Bartlett and Brown, THIS JOURNAL, **62**, 2927 (1940).

(12a) We are greatly indebted to Givaudan-Delawanna, Inc., whose Mr. Kaiser prepared for us considerable quantities of trimethylcyclohexanone and the corresponding ethynylcarbinol by the methods here described.

(13) J. D. Chanley, THIS JOURNAL, **70**, 244 (1948).

dried and carefully fractionated in a packed column of 15 theoretical plates. Two main fractions boiling from 171–176° and from 176–183°, respectively, were collected. In order to achieve further purification, we resorted to fractional crystallization of the semicarbazones.

Semicarbazones of Fraction b. p. 171–176°.—To 100 g. of this fraction dissolved in 1000 ml. of 95% ethyl alcohol, 84 g. of semicarbazide hydrochloride and 126 g. of sodium acetate trihydrate, dissolved in 1000 ml. of water, were added with stirring over a period of twenty minutes. After standing an additional ten minutes, the crude semicarbazone of 2,2-dimethylcyclohexanone separated; yield, 37 g.; m. p. 190–193°. The filtrate was then allowed to stand for three hours in the ice-box, where a mixture of di- and trimethylcyclohexanone crystallized. The filtrate from the second crop was then refluxed for a few hours and eventually 850 ml. of ethanol was distilled off. The resulting mixture was left in the ice-box overnight. The next day the crude semicarbazone of trimethylcyclohexanone was collected.

Semicarbazone of Fraction b. p. 176–183°.—This fraction contained an inconsequential amount of the dimethyl compound, but was contaminated with the tetramethyl compound, which does not form a semicarbazone. It was, therefore, worked up differently. One hundred grams of the crude ketones was dissolved in 1000 ml. of 95% ethanol and the same quantities of semicarbazide hydrochloride and sodium acetate in water were added as above. After refluxing for ninety minutes, the mixture was allowed to stand in the ice-box overnight. The crude semicarbazone was collected the next day. Its yield was 50% of the theoretical for this fraction. The combined impure semicarbazones (from fractions of b. p. 171–176° and 176–183°) were twice recrystallized from absolute ethanol; m. p. 207–209°; reported 220°.[14] The yield of the semicarbazone, calculated on the methylcyclohexanone, from which we had started, was 25–30%.

Anal. Calcd. for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.70; N, 21.31. Found: C, 60.93; H, 9.95; N, 21.72.

Two hundred and fifty-six grams of the combined purified semicarbazone were mixed with 220 g. of phthalic anhydride and steam distilled until one liter of distillate was collected. The oily layer was separated, dried over sodium sulfate and distilled through a packed column of 15 theoretical plates; yield, 165 g. (91%) of pure trimethylcyclohexanone; b. p. 178.7–179° at 767 mm.; $n^{20}D$ 1.4480, $n^{25}D$ 1.4460, d^{25}_4 0.8983, *MR*, calcd. 41.59. Found: *M R* 41.62; reported,[3] 177–178.5° (758 mm.), $n^{25}D$ 1.4465.

Anal. Calcd. for $C_9H_{16}O$: C, 77.08; H, 11.50. Found: C, 76.97; H, 11.79.

The oxime prepared from this ketone melted at 103°; reported,[15] 104–105°.

The 2,4-dinitrophenylhydrazone melted at 141°.

Anal. Calcd. for $C_{15}H_{20}N_4O_4$: N, 17.5. Found: N, 17.8.

Tetramethylcyclohexanone (II), which does not form a semicarbazone had remained behind in the mother liquor and because of its high volatility was also found in the ethanol distillates. The ketone was purified by distillation. It boiled at 183.5–184° (772 mm.), m. p. 15°; $n^{20}D$ 1.4473; reported,[15] b. p. 182–184° (753 mm.), $n^{15.6}D$ 1.4484.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.44; H, 11.74.

2,2,6-Trimethyl-1-ethynylcyclohexanol-1 (III) was prepared in half-mole batches from the pure ketone with sodium acetylide in liquid ammonia following the procedure of Campbell.[16] The compound was obtained in 71% yield; b. p. 121–121.5° (49–50 mm.), 93° (13–14 mm.), $n^{20}D$ 1.4791, $n^{25}D$ 1.4770; reported,[3] b. p. 88–90° (20 mm.) $n^{25}D$ 1.4740. The compound formed an insoluble silver salt with alcoholic silver nitrate.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.58; H, 10.84.

The 3,5-dinitrobenzoate prepared in pyridine and recrystallized from 95% ethanol melted at 141°. The yield of this derivative was very small.

Anal. Calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.78. Found: C, 60.01; H, 5.98; N, 8.31.

2,2,6,6-Tetramethyl-1-ethynylcyclohexanol was prepared by the same method as above, b. p. 129.5° (50 mm.), m. p. 36–37°, $n^{30}D$ 1.4775.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.03; H, 11.41.

Preparation of 2,2,6-Trimethyl-1-ethynylcyclohexene-1 (IV) and the Chloro Compound $C_{11}H_{17}Cl$.—To 100 g. of the pure trimethylcarbinol, dissolved in 150 ml. of dry pyridine, was added 71.2 g. of thionyl chloride, purified according to Fieser,[17] dissolved in 150 ml. of dry pyridine, with stirring in the cold (ice-bath) over a period of two hours. The mixture was allowed to react for one further hour and then poured into 2000 ml. of ice water and thoroughly extracted ten times with 200-ml. portions of petroleum ether (b. p. 40–60°). The combined extracts, after washing with sodium carbonate solution, water, saturated sodium chloride solution and drying over anhydrous potassium carbonate, in the presence of traces of hydroquinone, were distilled *in vacuo* through a packed column of ten to twelve theoretical plates. Two main fractions were collected; the hydrocarbon fraction boiled at 69–70° (13 mm.), $n^{20}D$ 1.4915, $n^{25}D$ 1.4892, $\epsilon_{max.}$ 13,000, at $\lambda_{max.}$ 227 mμ. The yield was 13.5 g. or 15%. On standing, the compound polymerized even at ice-box temperature, unless stabilized by hydroquinone. The compound gave a precipitate (silver salt) with alcoholic silver nitrate.

Anal. Calcd. for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.73; H, 11.22.

The second fraction, the chloro compound, boiled at 96° (14 mm.), $n^{20}D$ 1.5030 and amounted to 60 g. (54%).

Anal. Calcd. for $C_{11}H_{17}Cl$: C, 71.53; H, 9.28; Cl, 19.20. Found: C, 72.44; H, 9.73; Cl, 19.00.

By boiling with the stoichiometric amount of silver nitrate in 75% ethanol, four-fifths of the chlorine was removed from this compound and an additional amount of silver nitrate produced the formation of a silver acetylide which was then decomposed by ammonium thiocyanate. In this manner we obtained in one experiment a carbinol of the same elementary composition as the original carbinol, but differing in its physical properties: b. p. 83° (13 mm.), $n^{20}D$ 1.4754.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 80.03; H, 10.94.

1′-Dehydro-β-ionone (V).—To a solution of 0.067 mole of ethylmagnesium bromide in 25 ml. of dry ether was added 10 g. (0.067 mole) of 2,2,6-trimethyl-1-ethynylcyclohexene-1 in 25 ml. of ether over a period of one hour. The mixture was stirred and refluxed for an additional two hours and allowed to stand overnight under nitrogen. The Grignard compound, thus formed, was added with stirring during two hours to a solution of 13.8 g. of acetic anhydride in 40 ml. of dry ether at −70°. The mixture, after reacting another two hours, was decomposed with saturated ammonium chloride solution. The organic layer was then distilled *in vacuo*. The product 6.5 g. (50% yield) was collected boiling at 119–120° (10 mm.), $n^{20}D$ 1.5205, $\lambda_{max.}$ 288 mμ, $\epsilon_{max.}$ 11,800.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.32; H, 9.55.

The semicarbazone prepared in the usual manner and recrystallized from ethanol (platelets) melted at 129.2°; $\lambda_{max.}$ 292 mμ, $\epsilon_{max.}$ 20,800.

(14) Masson, *Compt. rend.*, **154**, 518 (1912).

(15) Cornubert, *Bull. soc. chim.*, **41**, 894 (1927).

(16) K. Campbell, B. Campbell and Eby, THIS JOURNAL, **60**, 2282 (1938).

(17) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 381.

Anal. Calcd. for $C_{14}H_{21}N_3O$: N, 16.99. Found: N, 16.70, 17.01.

From the mother liquors a small amount of a second semicarbazone, fine needles, presumably another form of the former was obtained; m. p. 129–130° (recrystallized from ethanol–water mixture). It showed a marked melting point depression in admixture with the aforementioned semicarbazone. Its ultraviolet absorption spectrum showed $\lambda_{max.}$ 292 mμ, $\epsilon_{max.}$ 16,700.

Anal. Calcd. for $C_{14}H_{21}N_3O$: N, 16.99. Found: N, 17.47.

The 2,4-dinitrophenylhydrazone melted after recrystallization from ethanol at 145–145.2°. It showed in alcohol $\lambda_{max.}$ 372 mμ, $\epsilon_{max.}$ 28,600; in chloroform $\lambda_{max.}$ 380 mμ $\epsilon_{max.}$ 28,800.

Anal. Calcd. for $C_{19}H_{22}N_4O_4$: N, 15.13. Found: N, 15.77.

The ultraviolet absorption spectrum, not previously reported, of the 2,4-dinitrophenylhydrazone of 1-(1′-cyclohexenyl)-butyn-1-one-3[1] showed $\lambda_{max.}$ 372 mμ, $\epsilon_{max.}$ 27,800 in alcohol and $\lambda_{max.}$ 376 mμ, $\epsilon_{max.}$ 28,100 in chloroform.

Tetrahydroionone Semicarbazone.—1′-Dehydro-β-ionone (0.77 g.) was hydrogenated in 50 ml. of ethanol at atmospheric pressure employing 100 mg. of palladium-on-calcium carbonate (5%) as catalyst. Ninety per cent. of the volume of hydrogen required by one double and one triple bond was consumed. The residual oil, after filtration and evaporation of the solvent, was converted into the semicarbazone derivative. Three recrystallizations from 95% ethanol afforded the pure semicarbazone of tetrahydroionone of melting point 179–180°. This derivative showed no depression on admixture with an authentic specimen, m. p. 182°, which had been prepared by the hydrogenation of β-ionone employing the same catalyst as mentioned above; reported m. p. 183–184°,[6] reported m. p. 179–180°.[18]

It had been mentioned that the dehydration of 2,2,6-trimethyl-1-ethynylcyclohexanol over alumina yielded among other products an acetylenic hydrocarbon fraction. The Grignard compound of this acetylene was condensed with acetic anhydride in the same manner as described above. In a run starting with 7.0 g. of hydrocarbon, b. p. 64–66° (14–15 mm.), $n^{20}D$ 1.4771, $\lambda_{max.}$ 227 mμ, $\epsilon_{max.}$ 4000, we obtained 0.8 g. of an impure ketonic fraction, b. p. 123–127° (20 mm.), which after further purification by evaporative distillation showed $n^{22}D$ 1.5055. Its spectrum exhibited two absorption maxima at $\lambda_{max.}$ 224 mμ and $\lambda_{max.}$ 287 mμ with the respective $\epsilon_{max.}$ of 9000 and 5000. The semicarbazone prepared from this fraction and recrystallized from ethanol melted at 112–114°; $\lambda_{max.}$ 265 mμ, $\epsilon_{max.}$ 14,000. We ascribe this semicarbazone to that compound of the ketonic mixture which is responsible for $\lambda_{max.}$ 224 mμ.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.05; H, 9.53. Found: C, 79.12; H, 9.57. Calcd. for $C_{14}H_{21}N_3O$: N, 16.99. Found: N, 16.00.

DL-1′-Dehydro-β-ionol (VI).—The Grignard derivative from 14.8 g. (0.10 mole) of 2,2,6-trimethyl-1-ethynylcyclohexene-1 was prepared as above and 4.4 g. of freshly distilled acetaldehyde in 40 ml. of dry ether was added thereto during one hour at −15°. The mixture was allowed to react for another three hours with stirring at 0° and for a further hour at room temperature. After decomposition with saturated ammonium chloride solution, the organic layer was distilled and 12 g. of product (58% yield) was isolated; b. p. 103–104° (2.4 mm.), 108° (3 mm.); $n^{25}D$ 1.5070, d^{25}_4 0.9355; *MR* calcd. 59.11, found 61.27, exaltation 2.16; $\lambda_{max.}$ 232 mμ, $\epsilon_{max.}$ 13,000.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.49. Found: C, 81.53; H, 10.59.

DL-Tetrahydroionol (*cis*) (VIII).—One and four-tenths of a gram of dehydro-β-ionol was hydrogenated in the presence of platinum oxide at atmospheric pressure in 50 ml. of purified glacial acetic acid as solvent. The theoretical amount of hydrogen was absorbed. The reaction product, after evaporative distillation at 50° (2–3 mm.), amounted to 1.2 g., $n^{20}D$ 1.4700; reported $n^{20}D$ 1.4717,[19a] $n^{20}D$ 1.4770.[19b]

One gram of the above tetrahydroionol was oxidized in 10 ml. of glacial acetic acid by 0.55 g. of chromium trioxide at 80° during one hour. The reaction mixture, diluted with water, was extracted with petroleum ether (b. p. 30–60°). After washing with sodium carbonate solution and drying over sodium sulfate, the product was evaporatively distilled at 38° (3 mm.); yield, 0.74 g., $n^{22}D$ 1.4655. Reported $n^{22}D$ 1.4660 (*cis*)[6]; $n^{22}D$ 1.4634 (*trans*). The semicarbazone prepared from the above ketone and recrystallized from ethanol melted at 179–180° and again showed no melting point depression on admixture with authentic tetrahydroionone semicarbazone.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from methanol, m. p. 118.5–120°, and showed no depression of melting point on admixture with an authentic sample, m. p. 119–120.5°, which had been prepared from the hydrogenation product of β-ionone; reported m. p. 120–120.5°.[19b]

The 4-phenylsemicarbazone was prepared. The melting point rose gradually from 104° for the crude reaction product to 114–115° (clear melt at 118°) on recrystallizations from methanol. Prelog[6] reports m. p. 109–110° for the 4-phenylsemicarbazone of the hydrogenation product of ionone, while he finds 133° for the analogous derivative derived from dihydrocyclocitral to which he ascribes *trans*-substitution on the ring. To our surprise, both the tetrahydroionone obtained by our synthesis and that obtained by the hydrogenation of β-ionone, gives rise to two 4-phenylsemicarbazones melting at 109–110° and 114–115° (clear melt at 118°). These two forms may be obtained alternatively from methanol solution, depending on conditions, not completely understood, as their recrystallization may not always be influenced by seeding with one form. We consider the two forms allomorphs of Prelog's *cis*-form, since we were able to derive each from the other one. No melting point depressions were observed in mixture of the lower or the higher-melting derivatives, prepared from the synthetic and authentic tetrahydroionone. Moreover, mixtures of the lower-melting form and higher-melting form from either source (synthetic and authentic) melted over the intermediate range, showing no depression.

Acknowledgment.—We wish to thank Miss Bernice Hamerman and Mrs. Edith Rosen Kaplan for their able and painstaking assistance.

Summary

1. The preparation of 2,2,6-trimethylcyclohexanone and 2,2,6,6-tetramethylcyclohexanone and of the ethynyl carbinols, derived from them, is described.

2. The dehydration of 2,2,6-trimethyl-1-ethynylcyclohexanol by means of thionyl chloride and pyridine leads to 2,2,6-trimethyl-1-ethynylcyclohexene-1.

3. The acetylenic analogs of β-ionone (1′-dehydro-β-ionone) and of β-ionol were prepared and their structure was confirmed by conversion into the perhydro compounds.

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(18) Ruzicka, Seidel and Pfeiffer, *Helv. Chim. Acta*, **31**, 827 (1948).

(19) (a) Kandel, *Ann. chim.*, **11**, 73 (1939); (b) Naves and Bachman, *Helv. Chim. Acta*, **26**, 2151 (1943).

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

The Partial Reduction of an Enyne System by Lithium Aluminum Hydride

BY J. D. CHANLEY AND HARRY SOBOTKA

We have found that lithium aluminum hydride[1] is effective as a selective reducing agent for the triple bond in the enyne system of 1-(1′-cyclohexenyl)-1-butyn-3-ol (I); the dienol, trisnor-β-ionol (II) was obtained in 70% yield. In contrast, catalytic hydrogenation of this triple bond failed to yield more than spectroscopically detectable traces of the dienol. When the catalytic hydrogenation was interrupted upon absorption of 1 mole of hydrogen, a mixture of saturated or monounsaturated reaction products together with unchanged starting material was found.

Rearrangement, during reduction, of the carbon skeleton or allylic shift of the hydroxyl group was excluded, since complete hydrogenation yielded 1-cyclohexyl-3-butanol (III) and the oxidation of the latter led to the known 1-cyclohexyl-3-butanone (IV). By oxidation according to Oppenauer the alcohol II was, furthermore, converted to the corresponding ketone, 1-(1′-cyclohexenyl)-1-buten-2-one (V), the trisnor analog of β-ionone. After the preparation of this paper, two publications by Heilbron and co-workers[2a,b] have appeared, which describe the preparation of the enynol (I)[2a] by the same method as employed by us, but of the dienone (V)[2b] by two other methods; the physical constants of our compounds and their derivatives agree with those given by Heilbron, *et al.*

The synthesis of trisnor-β-ionone permits the comparative examination of the ultraviolet absorption spectra of this group. Table I gives the absorption maxima and the molecular extinction coefficients for the dienone, its derivatives and precursors, and the same data for the corresponding enynes.[3]

TABLE I

ABSORPTION SPECTRA OF CYCLOHEXENYL ETHYLENES AND ACETYLENES

	$C_6H_9CH{=}CHR$		$C_6H_9C{\equiv}CR$	
R	λ_{max}, mμ	ϵ_{max}	λ_{max}, mμ	ϵ_{max}
-H	230[7]	8,500	223[8]	10,400
-CHOH·CH_3	233.5	24,300	227.5	12,500
-CO·CH_3	280	26,700	274[8]	9,500
-C[:NNHCONH_2]CH_3	290	45,000	285[3]	14,500
-C[:NNH$C_6H_3(NO_2)_2$]CH_3	390	30,000	372[5]	27,800

The λ_{max} of these dienes is regularly 5–7 mμ higher than that of the analogous enynes. As was to be foreseen on the basis of numerous examples adduced by Heilbron and co-workers[4] the extinction was about twice as strong. A comparable difference in λ_{max} of 8 mμ has also been observed for the pair β-ionone and dehydro-β-ionone.[5] This difference in λ_{max} between the spectra of dienes and enynes is not found in open chain compounds[4] such as 2,4-pentadien-1-ol and 2-penten-4-yn-1-ol or 3,5-hexadien-2-ol and 3-hexen-5-yn-2-ol; however, the extinction coefficients in these cases are twice as high in the dienes, compared to the enynes.

Experimental

All reactions were carried out under nitrogen. The ultraviolet absorption spectra were obtained with a Beckman spectrophotometer Model DU in 95% ethanol solutions. All melting points were corrected. The microanalyses were performed by Elek Microanalytical Laboratories, Los Angeles 16, Calif.

DL-1-(1′-Cyclohexenyl)-1-butyn-3-ol (I).—To an ice-cold suspension of 0.65 mole of the Grignard compound of 1-ethynylcyclohexene[3] in one liter of dry ether, 28.6 g. (0.65 mole) acetaldehyde was added during a period of two and one-half hours. The reaction mixture was stirred for additional three hours at room temperature, decomposed with saturated ammonium chloride solution and worked up in the usual manner; yield of carbinol (I): 62 g. (59%), b. p. 99–100° at 3 mm. (distilled and stored in the presence of hydroquinone).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.84; H, 9.42.

DL-1-(1′-Cyclohexenyl)-1-buten-3-ol (II).—Twelve grams of the preceding compound (I) (0.08 mole) in 100 ml. of absolute ether was added over a period of one-half hour to a solution of 1.87 g. (0.05 mole) of lithium aluminum hydride in 250 ml. of absolute ether. A voluminous precipitation occurred; the mixture was then refluxed and stirred for three hours, the precipitate having dissolved at the end of the first hour. After decomposition with water and dilute sulfuric acid, the product was isolated in the customary manner; yield, 8.5 g. (70%); b. p. 98–100° at 3–4 mm. The presence of traces of hydroquinone during distillation is vital for the prevention of polymerization.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.80; H, 10.58. Found: C, 78.92; H, 10.53.

On careful redistillation the physical constants obtained for the two carbinols are:

	Enynol (I)	Dienol (II)
B. p. at 2 mm., °C.	93.5–94	.....
B. p. at 1.5 mm., °C.	.....	90
$n^{25}D$	1.5197	1.5220
d^{25}_4	0.9740	0.9572
MR found	46.84	48.52
MR calcd.	45.25	46.78
Exaltation	1.59	1.74
λ_{max}, mμ	227.5	233.5
ϵ_{max}	12,500	24,300
$\lambda_{infl.}$, mμ	.....	229

The slight increase rather than diminution of the refractive index and of the exaltation of the molecular refraction upon partial reduction is peculiar.[4,6]

(1) Nystrom and Brown, THIS JOURNAL, **69**, 1179, 2548 (1947); **70**, 491 (1948).

(2) (a) Heilbron, Jones, Lewis, Richardson and Weedon, *J. Chem. Soc.*, 742 (1949); (b) Heilbron, Jones, Richardson and Sondheimer, *ibid.*, 737 (1949).

(3) Sobotka and Chanley, THIS JOURNAL, **70**, 3914 (1948).

(4) Heilbron, *et al.*, *J. Chem. Soc.*, **77**, 84 (1945); Heilbron, *et al.*, *ibid.*, 54 (1946); Haynes and Heilbron, *ibid.*, 1585 (1947); Jones and McCombie, *ibid.*, 26 (1943).

(5) Sobotka and Chanley, THIS JOURNAL, **71**, 4136 (1949).

(6) Isler, Huber, Ronco and Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947); Festschrift f. E. Barell, p. 31 (Basle, 1946).

The shift of λ_{max} by 6 mμ toward higher wave lengths in the diene is analogous to the difference between λ_{max} of cyclohexenylacetylene[3] (223 mμ) and that of cyclohexenylethylene[7] (230 mμ), a pair which shows, however, no appreciable difference in extinction.

DL-**1-Cyclohexyl-3-butanol (III).**—Two grams (0.013 mole) of the dienol (II) was hydrogenated completely over 100 mg. of platinum oxide in 100 ml. of ethanol. Hydrogen uptake at 26° and 750 mm.: calculated for two double bonds, 662 ml.; found (corrected for uptake by the catalyst), 622 ml. The saturated product was obtained in the theoretical yield and boiled at 84° at 4 mm.; $n^{25}D$ 1.4670. Oxidation by sodium hypoiodite according to Shriner and Fuson[8] yielded iodoform.

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.91; H, 12.91. Found: C, 77.26; H, 12.57.

1-Cyclohexyl-3-butanone (IV).—A solution of 1.1 g. of cyclohexylbutanol (III) in 10 ml. of glacial acetic acid and 0.82 g. of chromic anhydride was heated gently on the steam-bath for thirty minutes and permitted to stand overnight. The mixture, poured into 50 ml. of water, was extracted with petroleum ether, which was then washed and dried. The residue was evaporatively distilled at 16 mm. and 50° bath temperature; yield, 0.85 g. (76%); $n^{20}D$ 1.4590; reported[9] $n^{20}D$ 1.4586.

The semicarbazone of IV, recrystallized from aqueous methanol, melted at 166–168°; reported[9] m. p. 163°.

The 2,4-dinitrophenylhydrazone of IV, recrystallized from methanol, melted at 106°; reported[9] m. p. 106°.

Trisnor-β-ionone (V).—A mixture of 1.8 g. (0.118 mole) of trisnor-β-ionol (II) and 4.55 g. of aluminum *t*-butoxide in 90 ml. of dry acetone plus 135 ml. of dry benzene were refluxed under nitrogen for forty-eight hours. After decomposition with 150 ml. of 2 *N* sulfuric acid, the reaction product was worked up in the customary manner. According to the spectral data, the crude distillate (1.5 g.) of b. p. 92–95° at 4 mm. consisted of five-sixth ketone and the rest starting material. The ketone was converted into the semicarbazone. After one recrystallization from ethanol, decomposition according to Heilbron[9] and subsequent evaporative distillation at 47° bath temperature and 12 mm. pressure yielded 0.77 g. (43% yield) of the pure ketone; $n^{20}D$ 1.5500, λ_{max} 280 mμ, ϵ_{max} 26,700. The secondary maximum at 234 mμ, due to the presence of the dienol in the crude product was not completely eliminated.

Anal. Calcd. for $C_{10}H_{14}O$: 79.95; H, 9.39. Found: C, 79.57; H, 9.55.

The **semicarbazone,** melting after two recrystallizations at 201–203° (dec.), had a λ_{max} of 290 mμ, ϵ_{max} 45,000; it turns yellow on exposure to light.

Anal. Calcd. for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.58; H, 8.13; N, 19.78.

The **2,4-dinitrophenylhydrazone,** recrystallized three times from absolute ethanol, consisted of garnet-red crystals melting at 199–200° (dec.); λ_{max} 390 mμ, ϵ_{max} 30,000.

The **4-phenylsemicarbazone,** buff-colored platelets recrystallized from ethanol, m. p. 199–200° (dec.).

Catalytic Reduction of the Enynol I.—Various attempts to reduce selectively the triple bond of I with hydrogen over a 0.3% palladium–calcium carbonate catalyst in ethyl acetate yielded mixtures which were subjected to fractional distillation. The lowest boiling fractions, comprising less than 20% of the reduction product, showed, in typical runs, λ_{max} between 231 and 233.5 mμ with ϵ_{max} from 4000 to 6600 and $n^{20}D$ of 1.4960, supposedly a mixture of one-fourth or less (5% of the total yield) of dienol with three-fourths non-conjugated carbinol of low refractive index (either compound III or trisnordihydroionol). The higher fractions, comprising the bulk of the mixture, converged toward λ_{max} 229 mμ with ϵ_{max} up to 11,600 and $n^{20}D$ 1.5086, with starting material predominating. Similar results were obtained with Raney nickel in ethyl acetate, whereas no reduction at all was achieved with copper-zinc in alcohol.

Acknowledgment.—We thank Miss Bernice Hamerman for her able assistance in these experiments.

Summary

Lithium aluminum hydride serves for the partial hydrogenation of the triple bond to a double bond in cyclohexenylbutynol. The resulting trisnor-β-ionol was oxidized to trisnor-β-ionone. The ultraviolet absorption spectra of cyclohexenyl ethylenes and acetylenes are discussed.

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(7) Booker, Evans and Gillam, *J. Chem. Soc.*, 1453 (1940).

(8) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1940, p. 53–54.

(9) Heilbron, E. R. H. Jones and Richardson, *J. Chem. Soc.*, 287 (1949).

[CONTRIBUTION FROM THE WHITMORE LABORATORY OF THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Grignard Reactions. XX.[1] Effect of Cuprous Chloride on the Reaction of *t*-Butylmagnesium Chloride and Trimethylacetyl Chloride

BY NEWELL C. COOK AND WILLIAM C. PERCIVAL

In a continuation of the study of the reaction between acid halides and Grignard reagents we have now found conditions which make it possible to obtain consistently high yields of a highly branched ketone from a reaction which heretofore has given mainly reduction products. In earlier attempts to prepare hexamethylacetone from *t*-butyl Grignard reagent and trimethylacetyl chloride[2] no ketone was formed using a one-to-one ratio of the Grignard reagent and the acid chloride. With a five-to-one ratio of reagents and using reverse addition at −10°, there was obtained a 32% yield. We have now shown that through the use of cuprous chloride with a one to one ratio of reactants, yields of 70 to 80% hexamethylacetone are readily obtained.

The role of cuprous chloride in such reactions was suggested when an 87% yield of 2,4,4-trimethyl-3-hexanone was obtained by treating *t*-amylmagnesium chloride and isobutyryl chloride in a copper reactor.[3] Previously, only 10 to

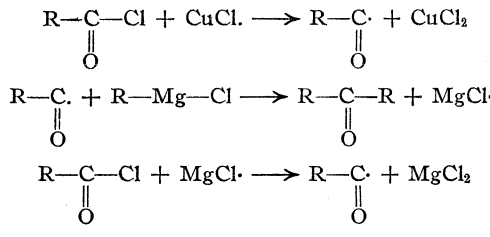
(1) For Paper XIX see Stehman, Cook and Whitmore, THIS JOURNAL, **71**, 1509 (1949).

(2) Whitmore, *Rec. trav. chim.*, **57**, 562 (1938).

(3) In the original note[1] this compound was erroneously reported as 2,4,4-trimethyl-3-pentanone.

15% yields had been realized from these reactions.[4] The reaction of *t*-butylmagnesium chloride and trimethylacetyl chloride, one of the most difficult tests of the beneficial effect of cuprous salts, was found to give hexamethylacetone in yields as high as 80% under cuprous chloride catalysis. We have confirmed our findings in several other syntheses of highly branched ketones to be reported later.

Kharasch[5] has shown that metallic ions such as the cuprous ion give rise to free radicals in Grignard reactions. If such were the case here the following could represent the mechanism by which the cuprous chloride causes the formation of the hexamethylacetone.



The reactions tried to date using straight chain acid chlorides and Grignard reagents show that yields of ketones are improved but not as markedly as with highly branched reactants. It is believed that conditions such as temperature and more effective catalysts can be found which will give more satisfactory results. This work is being continued.

Experimental

The fractionation columns were of the total condensation variable take-off type packed with $^3/_{32}$ in. single turn glass helices. The dimensions (cm.) are for the packed section: column I, 70 × 1.5; column II, 90 × 2.2.

The Grignard reactors were of seven-liter capacity, water jacketed copper vessels (11″ × 8″) stirred with an off-center propeller (4″) driven by a $^1/_4$ hp. motor.

The *t*-butyl Grignard reagent (3.1 moles/l.) used in these reactions was synthesized in a large preparation and stored in a glass carboy under a nitrogen atmosphere. Only clear reagent was used in all runs.

The trimethylacetyl chloride, made by carbonation of *t*-butyl Grignard reagent and subsequent treatment of the trimethylacetic acid with thionyl chloride, had the following properties: b. p. 104°, n^{20}D 1.4123. The ethyl ether used was Mallinckrodt reagent grade.

The runs were either five or three mole reactions. Products from the five mole runs were fractionated in column I while those from the three mole runs were fractionated in column II. From several reactions using a variety of conditions it was established that with cuprous chloride yields of 70–80% hexamethylacetone could be obtained, and that reactions in glass without cuprous chloride gave only 1–2% hexamethylacetone. Even normal addition with cuprous chloride gave a 53% yield of ketone.

Reaction of *t*-Butylmagnesium Chloride and Trimethylacetyl Chloride.—Filtered *t*-butylmagnesium chloride (5 moles, 3 *M* solution) was added at reflux temperature over a one-hour period to 5 moles of trimethylacetyl chloride and 5 g. of cuprous chloride dissolved in 2 l. of anhydrous ethyl ether in a 7-l. Grignard reactor. A take-off condenser was then attached and warm water passed through the jackets of the reactor until the majority of the solvent had been stripped from the reactants. Steam was then passed through the reactor for a period of three days. The reaction mixture was drowned with ice, neutralized and ether extracted. The products were fractionated through a twenty-plate column, giving 1.3% *t*-butyl pivalate (b. p. 135°, n^{20}D 1.3920), 1.0% neopentyl alcohol (b. p. 112°, m. p. 50°), 71.6% hexamethylacetone (b. p. 153°, n^{20}D 1.4392) and 9.8% residue, calculated as trimethylacetyl radical.

Identification of Products.—Hexamethylacetone: by reduction with lithium aluminum hydride to the alcohol which was converted to the phenylurethan, m. p. 120–121°. *t*-Butyl pivalate: by neutral equivalent (4 *N* sodium ethylate), obs. 156, calcd. 158; molecular weight, obs. 146, calcd. 158; trimethylacetic acid from hydrolysis ester, anilide, m. p. 133–134°. Neopentyl pivalate: by hydrolysis and derivative of trimethylacetic acid (anilide m. p. 133–134°) and neopentyl alcohol (m. p. 50°)(phenylurethan m. p. 112–113°). Trimethylacetic acid: as the anilide, m. p. 133–134°. Neopentyl alcohol: as the phenylurethan, m. p. 112–113°.

All derivatives were established by mixed melting points with authentic samples.

Summary

The reaction of *t*-butylmagnesium chloride and trimethylacetyl chloride to form hexamethylacetone has been investigated. With the use of cuprous chloride as a catalyst yields of from 70 to 80% are obtained, using one to one ratios of reactants. The temperature of addition has little effect upon the reaction. Although good yields are obtained using normal addition, reverse addition gives better results. A free radical mechanism is postulated.

STATE COLLEGE, PA. RECEIVED JUNE 21, 1949

(4) Whitmore and co-workers, THIS JOURNAL, **63**, 643 (1941).

(5) Kharasch, Nudenberg and Archer, *ibid.*, **65**, 495 (1943).

NOTES

Cyclopentanes and Petroleum Origin

By Benjamin T. Brooks

Cyclopentanes and cyclopentenes are not found in nature in plants or essential oils and five carbon ring structures are only very rarely found in complex substances such as pyrethrin, jasmone as a minor component in oil of peppermint and in the perfume oil of jasmine, chaulmoogric acid and combined with other ring structures as in a few of the triterpenes and isoprenic steroids. Cyclopentanes are found in the gasoline fractions of all types of petroleums, and in many cases, in substantial proportions. The careful analyses of seven petroleums made by Rossini[1] and his coworkers show the following percentages of cyclopentanes in the gasoline fraction distilling in the range 40–180°.

Crude source	Total cyclopentanes, per cent. by volume
Ponca, Okla.	8.86
East Texas	11.03
Bradford, Pa.	5.49
Greendale, Mich.	3.32
Winkler, Texas	5.46
Midway, Calif.	13.61
Conroe, Texas	5.66

In view of the extreme rarity of the five carbon ring structure in nature, the presence of cyclopentanes in petroleums is certainly not due to degradation of any natural products containing such structures. It is suggested that the cyclopentanes in petroleums have been formed by rearrangement of cyclohexanes. Such rearrangements have been observed experimentally at temperatures as low as 25° by the action of moist aluminum chloride.[2] It is believed that the occurrence of cyclopentanes in petroleums gives support to the theory that active surface minerals act catalytically in forming the wide diversity of hydrocarbons found in petroleums. Other evidence for this has been more fully presented in other papers.[3]

There is no constant relation between the per cent. of cyclohexane and methylcyclopentane and no relation between the ratios of these hydrocarbons and present bottom hole temperatures. The ratios of these two hydrocarbons do not correspond in the case of the gasolines noted, to the calculated thermal equilibrium compositions for any particular small temperature range and the high ratio of methylcyclopentane to cyclohexane found in some cases, 4.03% methylcyclopentane to 2.04% cyclohexane in East Texas gasoline, is far out of line with the equilibrium compositions found experimentally (in the presence of aluminum chloride). At 77.4° the experimental equilibrium mixture contained 25.6% methylcyclopentane and lower percentages at lower temperatures. The lowest ratio of methylcyclopentane to cyclohexane in any of these gasolines was 2.97 to 4.34 in the Conroe, Texas, gasoline, or 39% of the sum of these two hydrocarbons. The composition of gasolines is full of similar inconsistencies when reference is made to calculated thermal equilibrium compositions. One such calculation led to a temperature of petroleum formation within the range of commercial cracking processes, a condition which is clearly precluded by the time element as well as many of the facts as to chemical composition of crude petroleum.

405 Lexington Avenue
New York 17, N. Y. Received September 30, 1949

(1) A. F. Forziati, C. B. Willingham, B. J. Mair and F. D. Rossini, *Refiner*, Nov. (1943).

(2) A. L. Glasebrook and W. G. Lovell, This Journal, **61**, 1717 (1939).

(3) B. T. Brooks, *Am. Assn. Petr. Geol.*, **32**, 2269 (1948); **33**, Sept. (1949).

Enzymatic Hydrolysis of Steroid Hormone Esters by Blood Serum[1]

By Fritz Bischoff, Robert E. Katherman, John J. Moran and Yee Sing Yee

The solubilities of testosterone, progesterone and estradiol in mammalian blood serum are accounted for by the solubilities of these substances in solutions of the serum constituents.[2,3] Testosterone propionate and estradiol benzoate,[4] are much less soluble in solutions of serum constituents than the corresponding free steroids, but the solubilities of these esters in serum on equilibration approach the solubilities of the free parent steroids. These results can be explained only by postulating the existence of a serum steroid hormone esterase.

Proof for this enzymatic hydrolysis by rabbit, bovine and human serum has been established using the Folin–Ciocalteu phenol reaction with estradiol benzoate as substrate. The benzoate ester gives no color with the phenol reagent, while estradiol develops the characteristic blue color, following Beer's law over a wide range. Serum or serum diluted with 6% bovine albumin is incubated with estradiol benzoate (0.2 mg. per cc.), which is added in ethanol so that final ethanol concentration is below 10%. Serum heated for one hour at 63° serves as a control for enzyme activity. Heated and unheated sera without substrate serve as controls for sera constituents reacting with the phenol reagent. The reaction is ended by precipitation at 80 to 90% ethanol concentration, removing the proteins which would react with the phenol reagent.

(1) Aided by a grant from the Donner Foundation, Incorporated.

(2) F. Bischoff and R. E. Katherman, *Am. J. Physiol.*, **152**, 189 (1948).

(3) F. Bischoff and H. R. Pilhorn, *J. Biol. Chem.*, **174**, 663 (1948).

(4) F. Bischoff, R. E. Katherman and J. J. Moran, Abst. 115th Meeting Am. Chem. Soc., 1949, p. 6C.

Any liberated estradiol is recovered (90 ± 5%) in the filtrate. Aliquots of the filtrates are evaporated to dryness *in vacuo* at room temperature, and extracted with chloroform or acetone, which further removes chromogenic substances. After evaporation the residue is ready for the Folin–Ciocalteu reaction. The reaction mixture is taken to *p*H 7.0 before ethanol precipitation in order to prevent appreciable hydrolysis of unchanged estradiol benzoate during processing.

The following are typical results of estradiol liberated for 1 cc. of serum at 37.5°. Rabbit serum, *p*H 7.0 in albumin buffer for thirty minutes: 0.50 mg. estradiol. Control heated rabbit serum: 0.015 mg. estradiol. Human serum, *p*H 7.2 in albumin buffer for six hours: 0.18 mg. estradiol. Control heated human serum: 0.03 mg. estradiol. Bull serum, *p*H 8.3 for thirty minutes: 0.070 mg. estradiol. Control heated bull serum: 0.008 mg. estradiol.

The degree of hydrolysis of solutions of estradiol benzoate in aqueous albumin or sodium lauryl sulfate in the *p*H range and concentration used in the enzymatic reaction is of the low order found for serum heated one hour at 63° or ten minutes at 70°. The marked hydrolytic effect of unheated serum therefore proves the existence of a steroid hormone esterase.

The enzymatic action has also been demonstrated in rat, chicken and pigeon blood, and on the substrates estradiol diproprionate and estrone acetate.

CHEMICAL LABORATORY
SANTA BARBARA COTTAGE HOSPITAL
RESEARCH INSTITUTE
SANTA BARBARA, CALIFORNIA RECEIVED AUGUST 1, 1949

A Hydrogen Transfer Reaction of the Butylenes and Butyl Alcohols in Sulfuric Acid

BY WILLIAM H. CALKINS AND T. D. STEWART

Isobutylene, 2-butene and the four butyl alcohols each react in 96% sulfuric acid at 0° to yield up to 20% isobutane. This reaction was observed by us during a study of the alkylation of isobutane by 2-butene.[1]

We had occasion to introduce 2-butene alone, as a gas, into a flask containing stirred sulfuric acid and nitrogen gas at atmospheric pressure; the reactor was fitted with a mercury manometer. With a rate of introduction of 10 ml./min. the pressure rose immediately to 7–8 mm., remained nearly constant for ten to fifteen minutes, and then started to rise again. When the 2-butene flow was shut off within five minutes the pressure immediately fell to practically its original value; but if it was shut off during the later rise, the pressure fell only 2–3 mm. and then continued to rise for an hour or more without further 2-butene input. The same behavior, and to the same degree, was observed with the rate of input 27 ml./min. The volume of the reactor system was 600 ml.; the sulfuric acid varied from 25–100 ml. The eventual pressure rise for a charge of about 150 ml. of 2-butene was 20–30 mm., which, when corrected to room temperature, corresponded to a 17% yield of gas.

A preliminary examination of the gas formed, by Orsat combustion, indicated butane. This was confirmed by an analysis performed for us by the Shell Development Company, using their Consolidated Mass Spectrometer, which indicated 4% by volume of isobutane, 1% isopentane and traces of possible hexanes, in the nitrogen. Routine analyses were later made by an infrared spectrophotometer (National Technical Laboratories), calibrated at the wave lengths 8.48, 9.78 and 10.2 μ against pure samples of normal butane, isobutane and isopentane, and following the procedure of Brattain, Rasmussen and Cravath.[2]

This isobutane evolution is related to the conversion of the four-carbon alkenes and alcohols to liquid saturated hydrocarbons under similar, but not identical, circumstances.[3] Its uniqueness lies in the high percentage of isobutane, which may be a precursor to the hydrocarbons of higher molecular weight. The reaction is characterized by the presence of an induction period of a few minutes, in the case of 2-butene, and by the fact that rate of gas evolution from any given solution is approximately first order. However, both the rate and amount of gas formation vary somewhat with different amounts of sulfuric acid used. Table I details typical results.

TABLE I

YIELDS OF GAS EVOLVED FROM BUTYLENES AND BUTYL ALCOHOLS IN CONCENTRATED SULFURIC ACID AT 0°

Alkenes	Volume of acid, ml.	Moles of reactant	Pressure increase, mm.	Molal conversion, %
2-Butene	25	0.0059	27	16
2-Butene	50	.0072	37	16
2-Butene	100	.0063	26	13
Isobutylene	25	.0061	32	18
Alcohols				
n-Butyl	25	.0066	15	7.4
t-Butyl	25	.0074	22	10
t-Butyl	100	.0063	30	15
s-Butyl	25	.0033	18	19
s-Butyl	100	.0066	32	14
Isobutyl	25	.0065	48	25
Isobutyl	100	.0065	49	22

In the case of the alcohols, solution was effected slowly at 0° in a small amount of the acid outside the stirred reactor; this solution was then added rapidly to the excess of acid. Gas evolution was followed manometrically and analysis showed it to be almost entirely isobutane.

The induction periods in the case of the alcohols were striking. For *n*-butyl it was seventy-five minutes, for isobutyl thirty minutes, for *s*-butyl five minutes, and for *t*-butyl no induction period was observable. This corresponds to induction periods for 2-butene and isobutylene of a few minutes and none, respectively.

The relative rates of isobutane formation, based upon that from 2-butene as unity and using 25 ml. of sulfuric acid, were approximately as follows: 2-butene, 1; isobutylene, *t*-butyl alcohol and isobutyl alcohol, 0.5; *s*-butyl alcohol, 1.7; *n*-butyl alcohol, 0.2. The half-life of the 2-butene reaction was twenty-five to thirty minutes. It may be noted also that whereas in general the gas evolution from a given solution seemed to be a first-order reaction, that from the tertiary alcohol or isobutylene was distinctly not, the end reaction being very slow.

It is tentatively suggested that this apparent dismutation and rearrangement is based, not upon simple reactions of the original materials, but involves some polymeric material, perhaps through dealkylation; until polymer is formed no isobutane is evolved. The problem then con-

(1) Stewart and Calkins, THIS JOURNAL, **70**, 1006 (1948).

(2) Brattain, Rasmussen and Cravath, *J. Applied Phys.*, **14**, 418 (1943).

(3) Ormandy and Craven, *J. Soc. Chem. Ind.*, **47**, 317T (1928). The conversion of alkenes into alkanes during alkylation and polymerization, usually accompanied by rearrangement, has been observed, for instance by Ipatieff and Pines, *J. Org. Chem.*, **1**, 464 (1936), and McAllister, *et al.*, *ibid.*, **6**, 647 (1941). The polymerization studies have not been concerned with the low-boiling products; in alkylation an alkane–alkene transhydrogenation apparently occurs. In the present case a given alkene or alcohol is the sole initial reactant.

cerns the fundamental stability of alcohols and alkenes in sulfuric acid toward polymerization.

We wish to thank Drs. R. R. Brattain and D. Stevenson of the Shell Development Laboratories for their coöperation.

CHEMICAL LABORATORY
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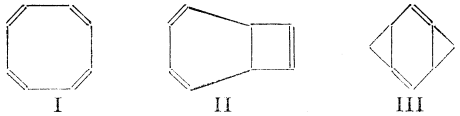
BERKELEY 4, CALIFORNIA RECEIVED JUNE 27, 1949

Some Observations on Certain Cycloöctatetraene Derivatives

BY S. L. FRIESS AND V. BOEKELHEIDE

In a recent publication, Reppe and his co-workers[1] have described the preparation of cycloöctatetraene (C.O.T.) and its conversion to many different derivatives. In attempting to explain the formation of the various reaction products of C.O.T., Reppe, *et al.*, have considered that C.O.T. may react as though it were present as any one of three different forms, I, II and III.

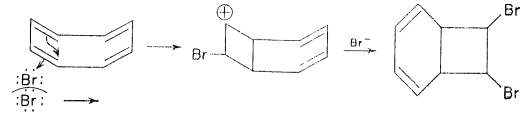


I II III

However, since I, II and III cannot very well be considered to be contributing forms to a resonance hybrid, it would appear desirable that the formation of unusual products from C.O.T. should be explicable on some other basis.

One possible explanation for the formation of certain of these products would be to consider that under attack by a reagent C.O.T. may undergo molecular rearrangement. The reaction of C.O.T. with bromine and with perbenzoic acid has been considered from this viewpoint and the results obtained in the present study are in support of such a postulation.

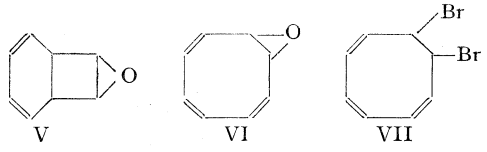
If the assumption is made that the strongest case yet presented for the structure of C.O.T. is the X-ray study[2] pointing to the "tub" or all-*cis* form, then it seems possible to explain certain of the reactions of the compound, and in particular those involving transitions from an initial eight-membered ring to a six–four bicyclic system, by a direct participation of a suitably situated neighboring double bond[3] in these reactions. The bromination process, for example, could be represented by the following scheme, involving the participation of a neighboring double bond in the reaction form presented by the molecule to the attack of a reagent;



IV

This formulation of the bromination of C.O.T. is in accord with the chemical evidence which Reppe, *et al.*,[1] have presented in support of structure IV.

A similar formulation could be postulated for epoxidation, using the electrophilic entity $:\ddot{O}:H^+$ from the perbenzoic acid. The result of participation of the neighboring double bond during epoxidation would be that C.O.T. oxide should be represented by formula V.



V VI VII

In this case, however, Reppe, *et al.*,[1] have assigned structure VI to C.O.T. oxide. A reinvestigation of the oxide has been made and evidence supporting structure V has been found.

The ultraviolet absorption spectrum of C.O.T. oxide in ethanol is shown in Fig. 1. It is seen that the position of the absorption peak for the oxide (λ_{max} = 241 mμ, log ϵ = 3.60) is compatible with a cyclic diene structure, V, as inferred by comparison with the peak of cyclopentadiene[4] in isoöctane (λ_{max} = 241, log ϵ = 3.50). The maximum of the dibromide (λ_{max} = 260, log ϵ = 3.70) is somewhat displaced to longer wave lengths, but is not quite as high as would be expected for the conjugated triene form VII.

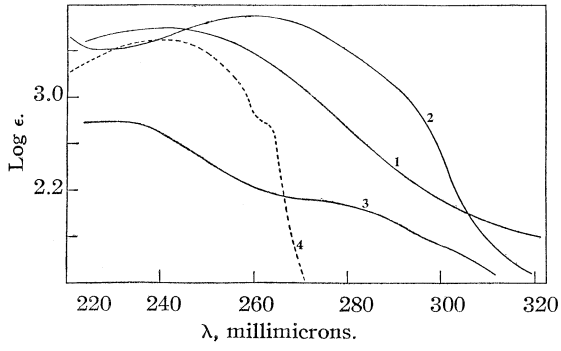


Fig. 1.—Ultraviolet absorption spectra in 95% ethanol of: 1, C. O. T. oxide; 2, C. O. T. dibromide; and 3, C. O. T. oxide hydrogenation product. Curve 4 is for cyclopentadiene in isoöctane.[5]

Further evidence for the diene character of the oxide was obtained from its maleic anhydride adduct. It would be expected that V would yield VIII, whereas structure VI should give IX. When the Diels–Alder reaction was carried out in benzene under anhydrous conditions, an exothermic

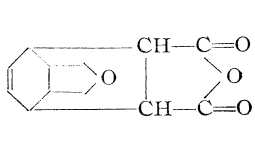
(1) Reppe, Schlichting, Klager and Toepel, *Ann.*, **560**, 1 (1948).

(2) Kaufman, Fankuchen and Mark, *Nature*, **161**, 165 (1948).

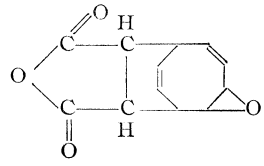
(3) For participation of a neighboring double bond in replacement reactions, see Winstein and Adams, THIS JOURNAL, **70**, 838 (1948).

(4) The ultraviolet absorption spectrum for cyclopentadiene in isoöctane solution is given for illustration since it is recorded in the literature,[9] whereas the complete solution spectrum of 1,3-cyclohexadiene was not available to us. A study of the variation of λ_{max} and log ϵ with increasing ring size in the conjugated cyclic dienes is contemplated.

(5) Data for cyclopentadiene were obtained from Ultraviolet Spectrograms, National Bureau of Standards, A.P.I. Research Project 44, serial no. 53.



VIII



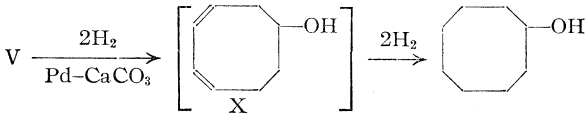
IX

reaction occurred giving an adduct, m. p. 206–207°, which corresponds to that reported by Reppe. Upon catalytic hydrogenation in ethanol with Adams catalyst at one atmosphere pressure, the adduct consumed exactly one mole of hydrogen, would take up no more, and yielded the dihydro compound of m. p. 240–245°, as reported. Upon treatment with perbenzoic acid in chloroform, the adduct consumed exactly one mole of the reagent, indicative again of just one double bond and form VIII as the molecular structure. This affords rather conclusive evidence for V as the structure of the oxide.

Interestingly, when the Diels–Alder reaction on the oxide was carried out under non-anhydrous conditions, a fair proportion of an isomeric adduct of m. p. 147–148° was also obtained. This too consumed exactly one mole of hydrogen, in methanol with platinum catalyst, and also consumed just one mole of perbenzoic acid. In the latter reaction, the product $C_{12}H_{10}O_5$ was isolated as a crystalline material sintering above 300°.

The only important evidence not favoring V as the structure of C.O.T. oxide is the fact that the oxide yields cycloöctanol on hydrogenation. In view of the strain which would be present in a molecule having a fused tricyclic ring system of this type, it seemed possible that cleavage of the fused rings would occur during hydrogenation so that V also would yield cycloöctanol. Evidence for this was obtained as follows.

When C.O.T. oxide in methanol solution was hydrogenated over a palladium-on-calcium carbonate catalyst, and the vigorous hydrogenation process stopped after absorption of just two moles of hydrogen, a colorless liquid fraction was obtained whose ultraviolet absorption spectrum in ethanol (λ_{max} = 230 mμ, log ϵ = 2.79) is also shown in Fig. 1. The position of the peak strongly suggests that a diene structure exists within the molecule. Further, the infrared spectrum of the substance shows a high intensity band at 2.85μ (3509 cm.$^{-1}$), a region characteristic[6] of the OH group vibration. This combination of features makes the formula X for the product most probable, although its homogeneity is not proven, and raises the possibility that in the complete hydrogenation of C.O.T. oxide, an over-all process requiring four moles of hydrogen to cycloöctanol,[1] the ring-fusion and the oxide ring are ruptured first, before the diene system is touched.



Portions of the infrared curves of C.O.T., the oxide and the dibromide are shown in Fig. 2. The oxide and dibromide curves are both quite different from that of C.O.T.

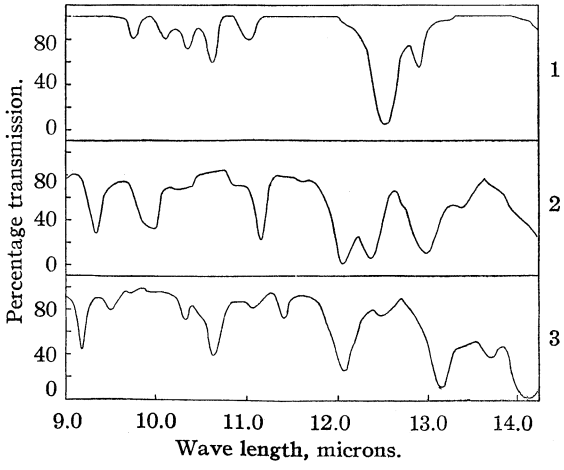


Fig. 2.—Infrared absorption spectra of: cycloöctatetraene (1); C. O. T. oxide (2); and C. O. T. dibromide (3). Data were obtained using 0.025-mm. cell.

Experimental[7]

C.O.T. Oxide.—This compound was prepared essentially according to Reppe's procedure,[1] but in considerably higher yields. In the best run, 5.5 g. of C.O.T. yielded 3.3 g. of oxide; b. p. 68–69° (12 mm.), $n^{21}D$ 1.5397.

C.O.T. Dibromide.—This too was prepared according to Reppe,[1] in comparable yield. The light yellow liquid had the following constants: b. p. 102–103° (5.5 mm.), $n^{21}D$ >1.7.

C.O.T. Oxide Hydrogenation Product (X).—To 25 ml. of methanol containing 1.1 g. of prereduced palladium–calcium carbonate catalyst was added 2.36 g. of C.O.T. oxide. The solution was allowed to absorb two molar equivalents (994 ml.) of hydrogen at atmospheric pressure, the catalyst was filtered off, the methanol removed under reduced pressure, and the residue fractionally distilled. There was collected a 0.76-g. fraction of colorless oil; b. p. 82–83° (16 mm.), $n^{21}D$ 1.4967.

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.27; H, 10.06.

Maleic Anhydride Adducts of the Oxide.—Reppe's procedure was again followed, with strict precautions against moisture. The adduct A crystallized from the benzene solution as white needles, which were filtered, washed with petroleum ether, and air-dried. From 3.3 g. of the oxide there was obtained 4.3 g. of adduct, m. p. 206–207°. In one run, where the drying tube on the reaction flask was eliminated, a benzene-soluble fraction of the adduct was an isomeric product B. This was obtained in 24% yield as white clusters, m. p. 147–148°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.18; H, 4.76.

Per Acid Titration of the Adducts.—A 0.24-g. sample of adduct A was added to a dried standardized chloroform solution of perbenzoic acid, prepared in the customary manner.[8] The per acid was present in excess. Consump-

(6) Barnes, Gore, Liddel and Williams, "Infrared Spectroscopy," Reinhold Publishing Co., New York, N. Y., 1944, p. 19.

(7) Analyses by Mrs. G. L. Sauvage; melting points are uncorrected.

(8) Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 431.

tion of per acid was checked by titration[9] of aliquots at timed intervals. At the end of 111.7 hours at room temperature the adduct had consumed exactly one molar equivalent of per acid, and would take up no more.

Per acid titration of a 0.246-g. sample of B was carried out in the same manner. During the course of the reaction, the product crystallized from solution. Exactly one molar equivalent of per acid had been consumed when the reaction stopped, 125.9 hours after mixing. The crystalline product was filtered, washed, and purified by sublimation under high vacuum. The product sintered above 300°.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.68; H, 4.28.

Hydrogenation of the Adducts.—To 0.10 g. of Adams catalyst prereduced in 10 ml. of ethanol was added 0.400 g. of adduct A dissolved in 40 ml. of alcohol. Hydrogenation at atmospheric pressure and room temperature progressed to the absorption of one molar equivalent of hydrogen (45 ml.) in the course of five and one-half hours, and stopped. After removal of catalyst and solvent, the crude dihydro product melted at 240–245° as reported by Reppe.

A similar hydrogenation of 0.30 g. of B in methanol likewise progressed to the extent of exactly one mole up take (37 ml.) of hydrogen in one hour and stopped.

Acknowledgment.—We gratefully acknowledge receipt of several samples of purified cycloöctatetraene from General Aniline and Film Corp., Easton, Pa.

(9) See ref. 7, p. 434.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER 3, NEW YORK RECEIVED APRIL 28, 1949

The Anion-exchange Separation of Zirconium and Hafnium[1]

BY E. H. HUFFMAN AND R. C. LILLY

An effective separation of zirconium and hafnium as negative fluo-ions has been obtained by using one of the strongly basic anion exchange resins recently developed, although earlier attempts using the weakly basic resins first available were unsuccessful.

Twenty milligrams of zirconium and 10 mg. of hafnium, as oxides, were added to zirconium and hafnium tracers in a small amount of hydrofluoric and nitric acids, warmed until dissolved, and fumed with 0.5 ml. of sulfuric acid. The residue was dissolved in water and the hydroxides precipitated with ammonium hydroxide. The precipitate was centrifuged, washed with water, dissolved in 5 ml. of 0.64 *M* hydrofluoric acid and diluted to 10 ml. with water. Six hundred milligrams of 200–325 mesh Amberlite IRA-400 resin, in its original chloride form, was added to the sample and the mixture shaken for three hours. The resin was separated from the solution and washed well with 10 ml. of water. Tracer count of the solution and washings indicated that 96% adsorption had taken place. This portion of resin was slurried onto the top of a column of the same resin 30 cm. in length and 0.78 sq. cm. in cross section. Elution with a solution of 0.2 *M* hydrochloric acid and 0.01 *M* hydrofluoric acid at the rate of 6 ml. per hour gave the results shown in Fig. 1. The solid parts of the curve were obtained by counting Zr^{95} and Hf^{181} tracers and the dotted parts by spectrographic analysis. The order of elution of the two elements is the reverse of that obtained by cation-exchange.[2]

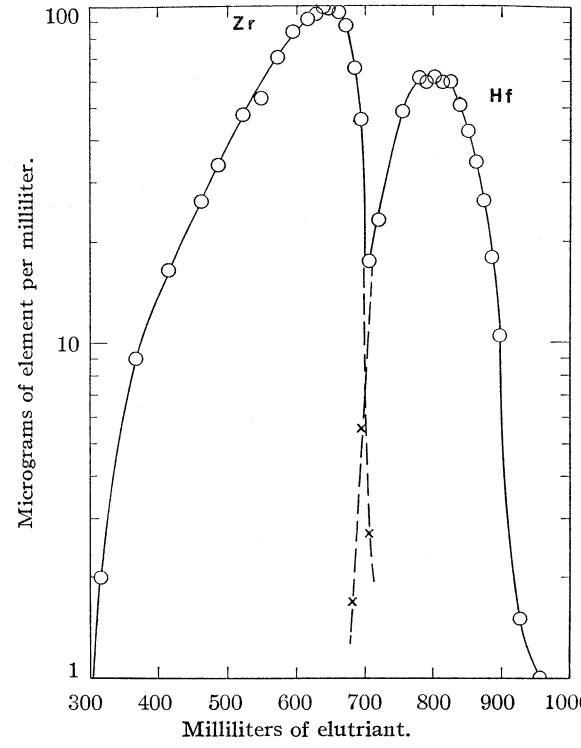


Fig. 1.—Elution of fluozirconate and fluohafniate with 0.2 *M* hydrochloric acid and 0.01 *M* hydrofluoric acid.

Combined fractions of elutriant from 300 ml. to 653 ml., containing 13.8 mg. of zirconium or 69% of the starting material, were found to contain no hafnium detectable by spectrographic analysis. The portion from 300 ml. to 686 ml., containing 17.0 mg. of zirconium or 85% of the starting material, was found to contain 0.04% hafnium. Spectrographic analysis of the 752–1020-ml. portion showed 0.02% zirconium in the 6.9 mg. of hafnium (69% of the starting material). Similarly, 0.03% zirconium was found in the 704–1020-ml. portion containing 8.3 mg. of hafnium (83% of the starting material). The amounts of the major constituents in these portions were determined from the curves.

This work was done under the auspices of the Atomic Energy Commission.

(2) Kenneth Street, Jr., and G. T. Seaborg, THIS JOURNAL, **70**, 4268 (1948).

RADIATION LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA RECEIVED OCTOBER 7, 1949

Derivatives of 5,6-Dihydrophenanthridine

BY CHARLES P. HUTTRER[1]

In the course of studies concerned with antihistaminic substances a number of derivatives of 5,6-dihydrophenanthridine[2] have been prepared in which the hydrogen in position 5 is

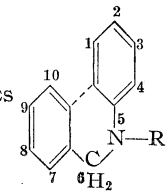
(1) While official declassification of this paper was being awaited, a communication on a similar separation appeared by Kraus and Moore, THIS JOURNAL, **71**, 3263 (1949). The separation reported here uses a different resin, a much shorter column, a more dilute eluting solution and macro quantities of zirconium and hafnium instead of micro quantities.

(1) Present address: National Research Council, Washington, D. C.

(2) Nomenclature according to: "Naming and Indexing of Chemical Compounds," *C. A.*, **39**, 5867 (1945).

TABLE I

BASICALLY SUBSTITUTED 5,6-DIHYDROPHENANTHRIDINES



No.	R	Yield, %	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	$-CH_2CH_2N(CH_3)_2$[a]	50	179 (Dimaleate)	$C_{25}H_{28}N_2O_8$	61.98	61.99	5.82	5.63	5.78	5.69
1	$-CH_2CH_2N(CH_3)_2$	50	183–184 (Dipicrate)	$C_{29}H_{26}N_8O_{14}$	49.02	49.01	3.68	3.66		
2	$-CH_2CH_2N(C_2H_5)_2$	55	158–159 (Dipicrate)	$C_{31}H_{30}N_8O_{14}$	50.41	50.29	4.09	4.04	15.16	14.96
3	$-CH_2CH_2NC_5H_{10}$	45	236–238 (Dihydrochloride)	$C_{20}H_{26}N_2Cl_2$[b]					7.66	7.62
3	$-CH_2CH_2NC_5H_{10}$	45	157–158 (Dimaleate)	$C_{28}H_{23}N_2O_8$	64.11	64.34	6.15	5.85	5.34	5.06
4	$-CH_2CH_2NC_4H_8O$	58	189–191 (Monohydrochloride)	$C_{19}H_{23}N_2OCl$	68.98	68.84	7.00	6.86	8.46	8.41
4	$-CH_2CH_2NC_4H_8O$	58	248 (Dihydrochloride)	$C_{19}H_{24}N_2OCl_2$[c]	62.13	61.98	6.59	6.77	7.63	7.62

[a] This compound has been reported by VIAUD, without any chemical data, *Prod. Pharmac.*, **2**, 53 (1947), to have no antihistaminic activity *in vitro* or *in vivo*. [b] Calcd.: Cl, 19.42. Found: Cl, 19.41. [c] Calcd.: Cl, 19.87. Found: Cl, 19.81.

replaced by a dialkylaminoalkyl group (see Table I).

5,6-Dihydrophenanthridine, the starting material, was prepared according to Ritchie[3] by reduction of phenanthridine with tin and concentrated hydrochloric acid and also (for the first time) by catalytic reduction using Raney nickel in dry ethanol. The latter method gave quantitative yields. 5,6-Dihydrophenanthridine as well as a number of substituted 5,6-dihydrophenanthridines were condensed with different substituted aminoethyl halides in the presence of sodamide using toluene as the solvent to give the desired compounds. The reaction mixtures were worked up according to the method previously described.[4]

The following four compounds (Table I) are reported at the present time. Compounds, 1, 3 and 4 have been tested in our Pharmacology Department (Dr. N. Ercoli, director) for their inhibitory action on contractions of the isolated guinea pig intestine induced by histamine. Compounds 1 and 4 were found to be completely inactive while compound 3 had very slight activity. (The doses required for inhibition were higher than 20 gamma/cc.)

Inspection of the generic structure of these compounds (Table I) reveals that they differ from the Antergan type only in the existence of the linkage represented by the dotted line. Whereas ring closures of this type can result in compounds of increased activity in the field of antispasmodics (*e. g.*, β-diethylaminoethyl diphenylacetate, Trasentine → β-diethylaminoethyl fluorene-9-carboxylate, Pavatrine[5]), it would seem that the same does *not* hold true in the case of antihistaminics. The loss of activity which occurs if the diphenylmethyl group of Benadryl is replaced by 9-fluorenyl[6] could be mentioned as an additional example.

The compounds, 1, 3 and 4 were also found to have no trypanocidal activity when tested in maximum tolerated dosage against *Trypanosoma equiperdum* in mice.

The author wishes to thank Dr. H. M. Wuest for his interest and encouragement.

(3) Ritchie, *J. Proc. Royal Soc. N. S. Wales*, **78**, 182 (1945).

(4) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

(5) Burtner and Cusic, *ibid.*, **65**, 262, 1582 (1943).

(6) Rieveschl, A. A. A. S. Symposium on Histamine Antagonists, Gibson Island, Md., 1945.

WARNER INSTITUTE FOR THERAPEUTIC RESEARCH
NEW YORK, N. Y. RECEIVED JULY 13, 1949

Some Reactions of the Trifluoromethyl Group in the Benzotrifluoride Series. I. Hydrolysis

BY GENE M. LE FAVE[1]

The inertness of the trifluoromethyl (CF_3–) group in benzotrifluoride and many of its derivatives is well-known.[2] However, it has also been observed that concentrated hydrobromic acid,[3] sodium hydroxide,[4] and 60–80% sulfuric acid[5,6] can bring about the hydrolysis of this group in benzotrifluoride or certain of its derivatives.

While attempting to sulfonate benzotrifluoride with concentrated sulfuric acid, hydrolysis occurred resulting in excellent yields of benzoic acid rather than the expected *m*-sulfonic acid of benzotrifluoride. In order to ascertain the applicability of this reaction, the substituted benzoic acids listed in Table I were prepared from the corresponding benzotrifluorides by treatment with approximately 100% sulfuric acid followed by hydrolysis of the reaction product.

(1) J. I. Holcomb Research Fellow, 1948–1950.

(2) See, for example, Swarts, *Bull. acad. roy. med. Belg.*, **8**, 343 (1922).

(3) Swarts, *ibid.*, **6**, 389 (1920).

(4) Jones, THIS JOURNAL, **69**, 2346 (1947).

(5) McBee and Frederick, *ibid.*, **71**, 1490 (1949).

(6) E. Wertyporoch, *Ann.*, **493**, 1536 (1932).

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR SUBSTITUTED BENZOIC ACIDS

R	M. p., °C.[a]	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
H-	120–121	94.0	68.85	68.65	4.90	4.88
p-Chloro-	237–238	93.9	53.79	53.66	3.19	3.41
m-Chloro-	154–156	95.6	53.79	53.70	3.19	3.29
o-Chloro-	140–141	95.0	53.79	53.73	3.19	3.32
m-Nitro-	139–140	70.6	50.33	50.39	3.01	3.23
m-Amino-	173–174	72.2	61.32	61.41	5.15	5.01
m-Hydroxy-	Ca. 200	79.2	60.81	60.69	4.03	3.81
2-Chloro-5-nitro-	165–166	83.0	41.52	41.71	1.99	2.11
3-Nitro-4-chloro-	180–182	87.3	41.52	41.80	1.99	2.17

[a] All melting points are uncorrected.

Trifluoromethylaryls.—With the exception of *m*-hydroxybenzotrifluoride, all trifluoromethylaryls were obtained through the courtesy of the Hooker Electrochemical Company and were used without further purification. The *m*-hydroxybenzotrifluoride was easily prepared by conversion of *m*-aminobenzotrifluoride through the diazonium transformation.

Hydrolysis of Benzotrifluoride.—A mixture of 36.5 g. (0.25 mole) of benzotrifluoride and 28 g. of 100% sulfuric acid was heated cautiously until the evolution of hydrogen fluoride began as could be detected by its etching of the glass walls of the reaction vessel. The heat source then was withdrawn and reapplied intermittently until the benzotrifluoride layer disappeared. After the evolution of hydrogen fluoride had ceased, the reaction mixture was poured, with stirring, into 1 l. of ice-water, the resultant precipitate sucked dry, and finally washed thoroughly with cold water. The crude product was purified through its sodium salt using Norit, and the free acid was recrystallized from hot water.[7] This procedure is typical for the series investigated.

Using 80% sulfuric acid the starting material is recovered unchanged after refluxing for several hours, while with 20–30% fuming sulfuric acid small amounts of sulfones and sulfonic acids are formed. Prolonged or excessive heating gives rise to tars. Occasionally it is difficult to initiate the reaction. In these cases, the addition of small amounts of 20–30% oleum portionwise is effective. *m*-Nitrobenzotrifluoride in particular is subject to this difficulty and with it 15% oleum must be used for the reaction to take place.

Since 65% fuming sulfuric acid is required to effect satisfactory sulfonation of trifluoromethylaryls,[8] probably because of the strong inductive effect of the meta-directing CF_3– group, it is apparent that the rate of sulfonation is far slower than attack of the CF_3– group. This competitive situation accounts for the appearance of sulfur-containing by-products only at the higher concentrations of sulfur trioxide.

Acknowledgments.—The author expresses appreciation to Dr. K. M. Seymour and Mr. P. G. Scheurer for their helpful suggestions.

(7) Only traces of fluorine and no sulfur or chlorine could be detected by the usual qualitative tests.

(8) Zitscher, U. S. Patent 2,141,893 (Dec. 27, 1938).

J. I. HOLCOMB RESEARCH LABORATORIES
AND THE CHEMISTRY DEPARTMENT OF
BUTLER UNIVERSITY
INDIANAPOLIS, INDIANA RECEIVED JUNE 6, 1949

Steroidal Sapogenins. 174. 17-Hydroxy-20-ketopregnanes from Steroidal Sapogenins

BY RUSSELL E. MARKER[1]

In the synthesis of cortisone and its analogs the introduction of a hydroxyl group on the C-17 carbon of the pregnanes is quite complicated and involved leading to low yields. A new and very simple reaction has now been found in which this can be accomplished in high yield from naturally occurring steroidal sapogenins containing ketonic groups on C-12. As sapogenins occur widely distributed in nature, they now present a large potential source of material for this synthesis.

Treatment of the oxidation product of the diacetate of pseudobotogenin with a dilute methanolic solution of potassium carbonate gives an immediate precipitation of the acetate of 16-dehydropregnen-5-ol-3-dione-12,20 removing it from further action with the alkaline solution.[2] A small amount of a secondary product resulting from this reaction was further studied. It has now been found that this new material is the major product of the hydrolysis if alcoholic potassium hydroxide is employed instead of dilute methanolic potassium carbonate. In this case the product does not precipitate during the reaction. The same product was obtained when 16-dehydropregnen-5-ol-3-dione-12,20 acetate was treated with alcoholic potassium hydroxide. The new product analyzes for a pregnendioldione, containing two hydroxyl groups, only one of which acetylates with boiling acetic anhydride. It is recovered unchanged when shaken with hydrogen and palladium catalyst, showing that it does not contain the conjugated double bond system. These reactions indicate that the new hydroxyl group was introduced in the 17-position as a tertiary carbinol. A secondary hydroxyl group on C-16 would readily form an acetate under the conditions employed. Whether the formation of a 17-hydroxyl group in the conjugated ketone system by alkali is characteristic only of pregnenes containing a ketone group in the beta-position at C-12 has not been determined but present indications are that the addition of water to the 16-double bond is influenced by the presence of a C-12 ketone in the molecule. In the strong alkaline hydrolysis of the oxidation product, the first product formed is probably the expected 16-dehydropregnene which then hydrates under the influence of alkali to give the 17-hydroxy compound.

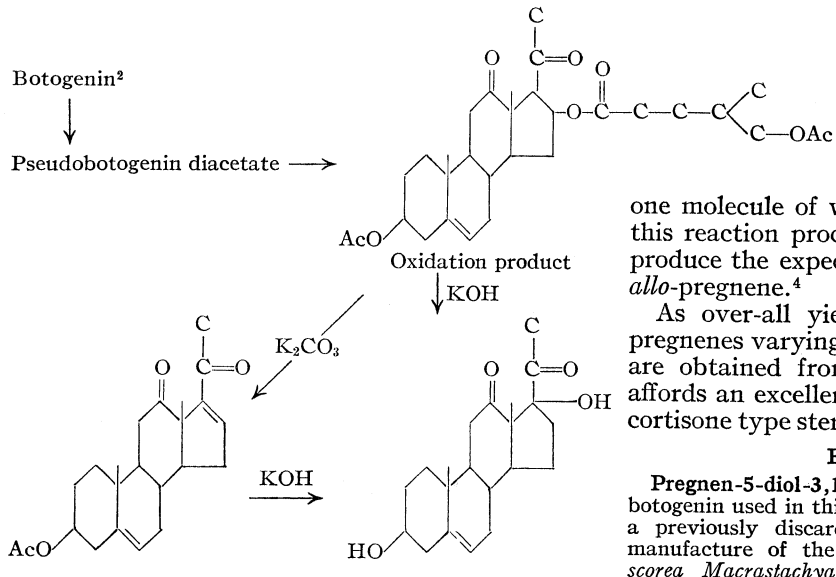
Because of the significance of this reaction in the preparation of cortisone or its analogs from steroidal sapogenins, it has been applied to kammogenin, another possible starting material for the antiarthritic hormone. This sapogenin is now known to occur in many plants and new sources for it and the other steroidal sapogenins will be reported at a later date.

Pseudokammogenin triacetate[3] was oxidized as described for pseudobotogenin diacetate.[2] Treatment of the oxidation product with alcoholic potassium hydroxide gave a diketopregnene containing three hydroxyl groups, only two of which are acetylatable. The product cannot be

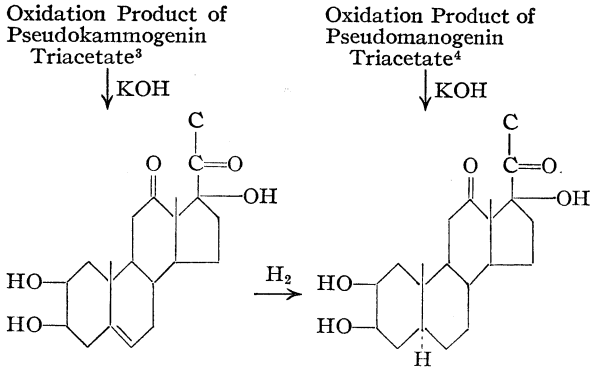
(1) Present address: Hotel Geneve, Mexico City, Mexico.

(2) Marker, THIS JOURNAL, **71**, 2656 (1949).

(3) Marker and Lopez, *ibid.*, **69**, 2373, 2375 (1947).



reduced by hydrogen using palladium catalyst, indicating absence of the C-16 double bond and that a new hydroxyl group was introduced as described above to form pregnen-5-triol-2,3,17-dione-12,20. Mild catalytic reduction using hydrogen and platinum oxide catalyst saturated the double bond in the 5-position. This product was identical with the product obtained by the alkali treatment of the oxidation product of the triacetate of pseudomanogenin followed by acetylation, which also contains a hydroxyl group that does not form an acetate.



It was previously reported[2] that *allo*-pregnantrione-3,12,20 was formed by the reduction of pregnen-5-ol-3-dione-12,20 (erroneously this should have read *16-dehydro*-pregnen-5-ol-3-dione-12,20) followed by mild oxidation.[2] The material actually used was the alcoholic potassium hydroxide hydrolysis product of the acetate of 16-dehydropregnen-5-ol-3-dione-12,20, which has now been shown to give the 17-hydroxypregnene instead of the expected 16-dehydropregnene. Analysis of the triketone produced in this reaction shows it to be 17-hydroxy-*allo*-pregnantrione-3,12,20 containing a tertiary hydroxyl group which does not acetylate. This product is identical with the triketone produced from the oxidation product of pseudohecogenin followed by strong alkaline hydrolysis. Previously it was assumed from the analysis that this was a triketone containing one molecule of water of crystallization and that this reaction proceeded in its normal manner to produce the expected 16-dehydro-3,12,20-triketo-*allo*-pregnene.[4]

As over-all yields of the 17-hydroxy-20-keto-pregnenes varying from 40–55% on a weight basis are obtained from the 12-keto-sapogenins, this affords an excellent method for the production of cortisone type steroids.

Experimental Part

Pregnen-5-diol-3,17-dione-12,20 from Botogenin.—The botogenin used in this work was prepared from ricogenin,[5] a previously discarded by-product in the commercial manufacture of the steroidal sex hormones from *Dioscorea Macrastachya* in Mexico. The crude oxidation product of pseudobotogenin diacetate, prepared from 5 g. of botogenin acetate[2] was refluxed for thirty minutes with 500 cc. of 3% alcoholic potassium hydroxide. Water was added and the product was extracted with a large volume of ether. Upon concentration to a small volume the material crystallized. It was recrystallized from ether, m. p. 258–260°; yield 2.7 g.

Acetylation with boiling acetic anhydride followed by crystallization from ether gave a mono-acetate, m. p. 232–234°. Mixed with the acetate of 16-dehydro-pregnen-5-ol-3-dione-12,20 it gave a depression of 15–22°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.1; H, 8.3. Found: C, 71.4; H, 8.7.

Hydrolysis of the acetate with alcoholic potassium hydroxide followed by crystallization from ether gave the above unacetylated product, m. p. and mixed m. p. 258–260°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.8; H, 8.8. Found: C, 72.6; H, 8.7.

A solution of 1 g. of the acetate of 16-dehydro-pregnen-5-ol-3-dione-12,20 in 100 cc. of 3% alcoholic potassium hydroxide was refluxed for one hour. The product was crystallized from ether to give pregnen-5-diol-3,17-dione-12,20, m. p. and mixed m. p. with the above product, 258–260°. Acetylation of this product followed by crystallization from ether gave the 3-acetate of pregnen-5-diol-3,17-dione-12,20, m. p. and mixed m. p. with the above mono-acetate, 232–234°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.1; H, 8.3. Found: C, 71.4; H, 8.5.

***allo*-Pregnanol-17-trione-3,12,20.**—The preparation of this product was previously reported[2] but erroneously the starting material used in the experiment should have read *16-dehydro*-pregnen-5-ol-3-dione-12,20. This was prepared by alcoholic potassium hydroxide hydrolysis of the acetate of 16-dehydro-pregnen-5-ol-3-dione-12,20 which has now been shown to add water to its 16-double bond to form a new C-17 tertiary hydroxyl group. It melted at 262–264° and gave no depression in melting point when mixed with the same product prepared by alcoholic potassium hydroxide hydrolysis of the oxidation product of pseudohecogenin as previously described.[4] It is unaffected by boiling acetic anhydride.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.8; H, 8.8. Found: C, 72.8; H, 8.6.

Pregnen-5-triol-2,3,17-dione-12,20 from Kammogenin.—To a solution of 2 g. of pseudokammogenin triacetate[3]

(4) Marker and co-workers, THIS JOURNAL, 69, 2167 (1947).
(5) Marker, *ibid.*, 71, 3856 (1949).

in 100 cc. of glacial acetic acid was added a solution of 800 mg. of chromic anhydride in 10 cc. of 90% acetic acid keeping the temperature at 20°. After standing thirty minutes water was added and the product was extracted with ether. The solvent was removed and the residue was refluxed for thirty minutes with 100 cc. of 3% alcoholic potassium hydroxide. Water was added, the solution was neutralized and the product was filtered and washed with water. It was recrystallized from ether, m. p. 275–278°, yield 0.9 g.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.6; H, 8.4. Found: C, 70.0; H, 8.6.

Acetylation with boiling acetic anhydride followed by crystallization from ether gave a diacetate, m. p. 264–265°. Upon shaking with hydrogen and palladium catalyst in ethyl acetate the product was recovered unchanged.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.1; H, 7.7. Found: C, 67.4; H, 7.8.

A solution of 200 mg. of the above diacetate in 25 cc. of acetic acid containing 100 mg. of platinum oxide catalyst was shaken with hydrogen at 40 pounds pressure for fifteen minutes. After filtration, water was added and the product was extracted and crystallized from ether, m. p. 265–267°. It gave no depression in melting point when mixed with the 2,3-diacetate of *allo*-pregnantriol-2,3,17-dione-12,20 prepared from the potassium hydroxide hydrolysis of the oxidation product of pseudomanogenin triacetate followed by acetylation. Mixtures of both products with the unreduced diacetate from kammogenin gave depressions in melting point of 12–18°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.8; H, 8.1. Found: C, 67.0; H, 8.4.

BOTANICA-MEX., S. A.[6]
TEXCOCO, MEXICO
MEXICO CITY, D. F.

RECEIVED OCTOBER 26, 1949

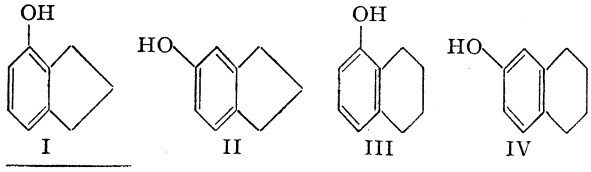
(6) Now with Hormosynth, S. A., Cervantes Saavedra, No. 5, Mexico City.

Partition Studies on Phenols. III. Steric Effects

BY MILTON ORCHIN[1] AND CALVIN GOLUMBIC[1]

It has been previously suggested that the partition coefficient of a phenol between water and an organic phase provides a sensitive index of the degree of steric hindrance around the phenolic group.[2] This arises from the fact that an important factor affecting the solubility of a phenol in the aqueous phase often is the degree of hydrogen bonding between the phenol and the water molecules; if the approach to the phenolic group is sterically inhibited, hydrogen bonding and, hence, solubility in water is reduced.

Arnold and co-workers have shown in a series of papers[3] that the relative steric influence of methylene groups in six-membered rings is greater than that of five-membered rings. In the course of our investigations on partition coefficients, we have obtained information on the same subject.



I II III IV

The partition coefficients of the indanols, I and II, and the tetrahydronaphthols, III and IV, were determined in the system cyclohexane–water (Table I). The partition coefficient (k) of 5-hydroxy-1,2,3,4-tetrahydronaphthalene, III, is 5.6 times that of 4-indanol, I. It would be expected, of course, that III would have less solubility in water than I solely on the basis of its greater molecular weight, but that III's high partition coefficient is due mainly to steric inhibition of hydrogen bonding is shown by comparison with its isomer IV, the hydroxyl group of which is unhindered. The ratio of partition coefficients of IV/I is only 1.9 as compared to III/I of 5.6. These results agree with Arnold's contention that methylene groups in five-membered rings offer less steric hindrance than those in six-membered rings. Further evidence of the correctness of this view is provided by the infrared specta of I and III in the hydroxyl group region. The spectrum of I shows a rather broad band at 2.93μ, while that of III shows only a weak shoulder at 2.91μ. This significant difference between the two spectra indicates the greater association through hydrogen bonding in the case of 4-indanol.[4] The slightly higher k value of I as compared to II indicates some steric interference of hydrogen bonding by the five-membered ring. This is consistent with the fact that I is the lower boiling of the two isomers.

TABLE I

PARTITION COEFFICIENTS AND IONIZATION CONSTANTS OF PHENOLS[a]

Compound	$k(H_2O)$	m	pK
4-Indanol (I)	4.5	0.98	10.2
5-Indanol (II)	3.7	1.03	10.2
5-Hydroxy-1,2,3,4-tetrahydronaphthalene (III)	25.3	1.04	10.1
6-Hydroxy-1,2,3,4-tetrahydronaphthalene (IV)	8.6	1.08	9.9

[a] Measurements at 25°.

Table I also lists the pK values of the four phenolic compounds calculated from observed partition coefficients at various pH values in the manner previously described.[2] The slopes (m) of the straight lines obtained by plotting the logarithms of the observed partition coefficients against pH are also listed in Table I. These values are in good agreement with the theoretical slope of one for monobasic phenols.

Experimental[5]

4-Indanol (I) was isolated by Dr. E. O. Woolfolk from the products of the hydrogenation of coal at the Bureau of Mines. It had a melting point of 47–48°.

(1) Organic Chemist, Bureau of Mines, Research and Development Branch, Office of Synthetic Liquid Fuels, Pittsburgh, Pa.

(2) Golumbic, Orchin and Weller, THIS JOURNAL, **71**, 2624 (1949).

(3) For the most recent paper in this series see Arnold and Richter, *ibid.*, **70**, 3505 (1948).

(4) We wish to thank Dr. R. A. Friedel, Lois Harnack and Marion Springer for the spectral data. Both spectra were determined in a 7% carbon disulfide solution and will be published in greater detail with other material in another article. We are indebted to George Goldbach for assistance with the experimental work.

(5) All melting points corrected.

5-Indanol (II) was also isolated by Dr. Woolfolk from coal-hydrogenation oils. It had a melting point of 52.4–53.8°.

5-Hydroxy-1,2,3,4-tetrahydronaphthalene (III) was prepared from pure 1-naphthol by hydrogenation.[6] Repeated crystallization gave a spectroscopically pure sample, m. p. 67.8–69.0°.

6-Hydroxy-1,2,3,4-tetrahydronaphthalene (IV) was prepared by the hydrogenation of 2-naphthol according to the directions of Stork.[7] We experienced considerable difficulty in freeing the tetrahydro compound from its aromatic precursor. Purification was achieved by distributing the mixture between cyclohexane and an aqueous alkaline buffered (*p*H 12.5) solution. In such a system all the 2-naphthol and a portion of the tetrahydronaphthol is retained in the aqueous phase and the organic phase contains pure tetrahydronaphthol. The tetrahydro compound was recovered from the organic phase by distillation and recrystallization. The pure material had a melting point of 57.2–58.4° and its ultraviolet absorption spectrum indicated the absence of naphthol.

Partition Experiments.—The phenols were dissolved in 20 ml. of spectrographic grade cyclohexane (0.5 mg. per ml.) and shaken with an equal volume of water for two minutes. After phase separation, the concentration of the phenol in the organic phase was determined by ultraviolet spectrophotometry in the usual way.[4]

(6) Musser and Adkins, THIS JOURNAL, **60**, 664 (1938).

(7) Stork, *ibid.*, **69**, 576 (1947).

CENTRAL EXPERIMENTAL STATION
U. S. BUREAU OF MINES
PITTSBURGH 13, PA.

RECEIVED JUNE 29, 1949

The Reaction of Sodium Hypobromite with Arylcyanopyruvic Esters

BY SIGVARD WIDEQVIST

The appearance of a paper on the bromination of esters of arylcyanopyruvic acid[1] has prompted us to report some experiments, carried out some years ago, on the reaction between sodium hypobromite and certain organic compounds having labile hydrogen atoms. One of these was ethyl phenylcyanopyruvate. It was found that a cleavage of the ester took place with the production of phenylbromoacetonitrile, probably according to the equation

$$C_6H_5—CH(CN)—COCOOC_2H_5 + NaOBr \longrightarrow C_6H_5—CH(CN)Br + NaOCOCOOC_2H_5$$

This reaction was later used for synthetic purposes.

Treatment of an alkaline solution of ethyl phenylcyanopyruvate with an iodine–potassium iodide solution yielded a crystalline iodo compound, presumably phenyliodoacetonitrile, which, however, was very unstable and decomposed with the liberation of iodine. Ethyl α-naphthylcyanopyruvate was also cleaved in the same manner.

Phenylbromoacetonitrile.—Twenty-one and seven-tenths grams (0.1 mole) of ethyl phenylcyanopyruvate was dissolved in 200 cc. of water containing 5 g. of sodium hydroxide. The solution was cooled to 0°, and an ice-cold mixture of 16 g. of bromine, 9 g. of sodium hydroxide and 100 cc. of water was added. Phenylbromoacetonitrile immediately separated as a heavy, lemon-yellow oil; yield 16 g. (82%). It was converted into diphenylacetonitrile by the Friedel–Crafts reaction.

α-Naphthylbromoacetonitrile.—Ethyl α-naphthylcyanopyruvate (m. p. 114–115°, prepared from α-naphthylacetonitrile and diethyl oxalate; yield 73%) 5.0 g. (0.019 mole) was dissolved in 35 cc. of 2 *N* sodium hydroxide solution and cooled to 0°. A cold mixture of 5 g. of bromine and 40 cc. of 2 *N* sodium hydroxide was added. α-Naphthylbromoacetonitrile immediately separated as an orange-yellow oil which solidified in a few minutes; yield 4 g. (87%). It was recrystallized from hot alcohol (m. p. 101–102°).

Anal. Calcd for $C_{12}H_8NBr$: C, 58.54; H, 3.28; N, 5.69; Br, 32.49. Found: C, 58.80; H, 3.42; N, 5.59; Br, 32.92.

CHEMICAL INSTITUTE
DEPARTMENT OF ORGANIC CHEMISTRY
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UPPSALA, SWEDEN

RECEIVED JULY 11, 1949

(1) Skinner, Kleibacker, Rosenberg, Gladner and Reed, THIS JOURNAL, **70**, 4011 (1948).

The Synthesis of 2-Fluoro-4- and 2-Fluoro-6-pyridinecarboxylic Acid and Derivatives

BY ARTHUR ROE, P. H. CHEEK AND G. F. HAWKINS[1]

The synthesis of 2-fluoronicotinamide,[2] 5-fluoronicotinamide[3] and 6-fluoronicotinamide[2] has been reported; preliminary reports indicate that at least one of them acts as a growth inhibitor for some microörganisms. It was therefore of interest to prepare some fluorinated isomers of nicotinic acid; this note reports the preparation of 2-fluoro-4-pyridinecarboxylic acid and 2-fluoro-6-pyridinecarboxylic acid together with their methyl esters and amides. The synthesis involved preparation of 2-fluoro-4-methylpyridine and 2-fluoro-6-methylpyridine followed by oxidation to the fluoro acids.

The authors are indebted to Eli Lilly and Company for generous support of this and related projects.

Experimental

The preparation of the fluoromethylpyridines and fluoro acids was carried out as described[2,3] for the fluoronicotinic acids, except that the water solubility of the 2-fluoro-6-pyridinecarboxylic acid made it necessary to remove the water from the acidified oxidation concentrate; this was accomplished by addition of ethanol and benzene, with subsequent distillation, in a manner somewhat similar to that reported by Black, Depp and Corson.[4] The acid was extracted from the inorganic material with benzene–alcohol. The methyl esters were obtained by allowing the acids to react with diazomethane[3]; the amides were prepared by the reaction of the methyl esters with 1:1 methanol–liquid ammonia mixture. The properties and analyses of the compounds prepared are given in Table I.

(1) Present address: Tennessee Eastman Corporation, Kingsport, Tennessee.

(2) Minor, Hawkins, VanderWerf and Roe, THIS JOURNAL, **71**, 1125 (1949).

(3) Hawkins and Roe, *J. Org. Chem.*, **14**, 328 (1949).

(4) Black, Depp and Corson, *ibid.*, **14**, 14 (1949).

TABLE I

Compound	M. p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
2-Fluoro-4-methylpyridine	[a]	36	C_6H_6NF	12.6	12.8
2-Fluoro-6-methylpyridine	[b]	34	C_6H_6NF	12.6	12.8
2-Fluoro-4-pyridinecarboxylic acid	195–197[c]	34	$C_6H_4O_2NF$	9.93	9.69, 9.88
2-Fluoro-6-pyridinecarboxylic acid	135–137	50	$C_6H_4O_2NF$	9.93	9.77, 9.86
Methyl 2-fluoro-4-pyridinecarboxylate	[d]	84	$C_7H_6O_2NF$	9.03	8.93
Methyl 2-fluoro-6-pyridinecarboxylate	53–54.5	76	$C_7H_6O_2NF$	9.03	9.05
2-Fluoro-4-pyridinecarboxamide	173–174	100	$C_6H_5ON_2F$	20.00	20.14
2-Fluoro-6-pyridinecarboxamide	134–135	100	$C_6H_5ON_2F$	20.00	19.83, 19.81

[a] Liquid, b. p. 157°; $n^{25}D$ 1.4690; d^{25}_4 1.0805. [b] Liquid, b. p. 142°; $n^{25}D$ 1.4673; d^{25}_4 1.0762. [c] Taken in the usual manner, the material contracted sharply at 188°, but no definite transition to the liquid state was observed upon further heating. If the bath were pre-heated to 195–197° the material when inserted melted quickly to a liquid, but re-solidified at once. [d] Liquid, b. p. 91° at 13 mm.; $n^{25}D$ 1.4843.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, N. C. RECEIVED JUNE 11, 1949

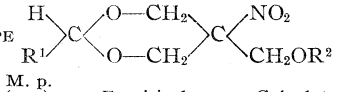
Some Cyclic Acetals of Tris-(hydroxymethyl)-nitromethane and their Derivatives

BY ALLEN SCATTERGOOD AND ALAN L. MACLEAN[1]

The cyclic acetals derived from tris-(hydroxymethyl)-nitromethane and five different aldehydes have been reported by Senkus[2] who prepared them by the azeotropic removal of water from equimolar quantities of the nitro triol and the aldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid. These cyclic acetals are the 5-nitro-5-(hydroxymethyl)-2-alkyl-1,3-dioxanes and should theoretically be capable of existing in both *cis* and *trans* forms. Although *cis–trans* isomers of cyclic acetals of tris-(hydroxymethyl)-nitromethane have never been obtained, Senkus[3] has prepared two sets of *cis–trans* isomers of cyclic acetals of a nitro glycol.

It seemed possible that tris-(hydroxymethyl)-nitromethane might serve as a model polyol useful in exploring conditions that could be employed in the acid catalyzed formation of cyclic acetals of carbohydrates or their derivatives in aqueous solution. Accordingly this triol was allowed to react with several aldehydes in an aqueous medium that was two molar in both reactants and also in hydrochloric acid. Three of the aldehydes formed crystalline acetals under these conditions. Two of these crystalline acetals were derived from aldehydes previously employed by Senkus. However, these acetals melted at higher temperatures than the acetals obtained by Senkus. It is probable that the compounds isolated by Senkus are *cis–trans* isomers of the ones prepared by us. We have demonstrated the presence of a free hydroxyl group in all of our acetals by the formation of their crystalline benzoates. We have also secured one *p*-toluenesulfonate and a cyanoethylation product. The properties of the new compounds are given in Table I.

TABLE I

SOME ACETALS OF THE TYPE 

R^1	R^2	Yield, %	Solvent	M. p. (cor.), °C.	Empirical formula	Calculated, % C	H	N	Analyzed, %[c] C	H	N
C_6H_5	H	74	Ethanol–water	124.8	$C_{11}H_{13}O_5N$	55.2	5.44	5.85	55.19	5.48	6.04
C_6H_5	C_6H_5CO	90	Isobutyl alcohol	116.2	$C_{18}H_{17}O_6N$	63.1	4.96	4.08	63.11	4.96	4.25
C_6H_5	$SO_2C_6H_4CH_3$	90	Isobutyl alcohol	143.3	$C_{18}H_{19}O_7NS$	54.9	4.83	3.56	54.61	4.96	3.68[d]
n-C_3H_7	H	81	*n*-Hexane	100.2[a]	$C_8H_{15}O_5N$	46.8	7.31	6.82	46.93	7.47	6.83
n-C_3H_7	C_6H_5CO	..	Isobutyl alcohol	107.0	$C_{15}H_{19}O_6N$	58.2	6.15	4.53	57.94	6.14	4.59
$(C_2H_5)_2CH$	H	65	*n*-Hexane	81.2[b]	$C_{10}H_{19}O_5N$	51.5	8.15	6.01	51.5	8.21	6.28
$(C_2H_5)_2CH$	C_6H_5CO	..	*n*-Hexane	63.1	$C_{17}H_{23}O_6N$	60.5	6.82	4.15	60.40	6.88	4.26
C_6H_5	CH_2CH_2CN	..	*n*-Hexane	77.7	$C_{14}H_{16}O_5N_2$	57.5	5.48	9.6	58.5	5.47	9.60

[a] Senkus[2] reported a melting point of 69.8° for the acetal prepared by his method. [b] Senkus[2] reported a melting point of 70.3° for the acetal prepared by his method. [c] The microanalyses were performed by Mr. S. M. Nagy and Mrs. Louise W. Spencer. [d] Calcd. for $C_{18}H_{19}O_7NS$: S, 8.14. Found: S, 8.19.

Experimental

Cyclic Acetals of Tris-(hydroxymethyl)-nitromethane.—One-tenth mole (15.1 g.) of tris-(hydroxymethyl)-nitromethane (supplied by the Commercial Solvents Corporation, Terre Haute, Indiana), 10 cc. of water, 8 cc. (0.1 mole) of concentrated hydrochloric acid and 10 cc. of methyl cellosolve (to act as a mutual solvent, omitted in the case of *n*-butyraldehyde) and 0.1 mole of the aldehyde were mixed, and the volume of the mixture (which may be two phase) was made up to 50 ml. with water. Thus the mixture was two molar in each of the reactants and also in hydrochloric acid. Homogeneous mixtures were allowed

(1) The material in this note is taken in part from a thesis submitted to the Massachusetts Institute of Technology by Alan L. MacLean in partial fulfillment of the requirements for the degree of Bachelor of Science in Chemical Engineering.

(2) Senkus, THIS JOURNAL, **63**, 2635 (1941).

(3) Senkus, *ibid.*, **65**, 1658 (1943).

to stand at room temperature until the bulk of the product had crystallized, while two phase mixtures were shaken by machine at room temperature until formation of product was complete. After several days at room temperature, the solid product was filtered off, washed with water until neutral, and air-dried. The solid products were recrystallized to constant melting point. The solvent, melting point and analytical data for each acetal are given in Table I. No solid acetals were obtained from the reaction of tris-(hydroxymethyl)-nitromethane and the following aldehydes under our conditions: propionaldehyde, isobutyraldehyde, α-ethyl-*n*-hexaldehyde, *n*-heptaldehyde and α-ethyl-β-*n*-propyl-acrolein.

Benzoates and Tosylates of Cyclic Acetals of Tris-(hydroxymethyl)-nitromethane.—One-tenth mole of each acetal was dissolved or suspended in 0.2 mole of purified pyridine and 0.1 mole of benzoyl chloride or *p*-toluenesulfonyl chloride was added all at once. If the temperature went above 50° the reaction mixture was cooled until the temperature had gone below this figure. After twenty-four hours at room temperature, the reaction mixtures were poured into water, and the solid products were removed by filtration and washed with additional water. The solvents used in recrystallization together with the melting points and analytical data are listed in Table I.

2-Phenyl-5-nitro-5-(β-cyanoethoxymethyl)-1,3-dioxane.—One-tenth mole of the benzaldehyde acetal of tris-(hydroxymethyl)-nitromethane was dissolved in 65 cc. of dioxane containing 5.3 g. (0.1 mole) of acrylonitrile, and 0.4 g. of sodium hydroxide dissolved in a little water was added. After standing overnight, the solution was concentrated and the viscous residue was extracted with hot *n*-hexane. After recrystallization from *n*-hexane the substance melted at 77.7°. The analytical data are recorded in Table I.

SUGAR RESEARCH FOUNDATION LABORATORY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASS. RECEIVED APRIL 12, 1949

Side Reaction in the Hydrogenation of 4-Nitro-2-chlorobenzoic Acid and Its Esters

BY ANNA WEIZMANN

In attempts to prepare diethylaminoethyl 4-amino-2-chlorobenzoate,[1] the catalytic hydrogenation of the corresponding 4-nitro-acid, its ethyl and its β-diethylaminoethyl ester was studied. A number of side reactions were observed which made the method impractical from a preparative point of view.

In some cases, incomplete reduction resulted, leading to hydroxylamino- and azoxybenzene derivatives, in others the chlorine atom was lost—this occurred in hydroxylic solvents, not in ethyl acetate. Sometimes, β-diethylaminoethyl 4-nitro-2-chlorobenzoate suffered hydrogenolysis to give *ethyl* esters; in one case even a *methyl* ester was formed, before the nitro group was attacked. These hydrogenolytic reactions are somewhat unusual; they recall similar, very recent observations of Metayer.[2]

Experimental

4-Nitro-2-chlorobenzoic acid is best prepared by the method of Cohen and McCandlish[3] with some modifications: a mixture of 2 kg. of 4-nitro-2-chlorotoluene and 6 liters of 33.5% nitric acid (1.32) is heated (autoclave) at 120° for eight hours. While 1010 g. of the starting material remains unattacked, 1090 g. of the desired acid is obtained; m. p. 138–139°; conversion, 49.5%; yield, 93.6%. *Ethyl ester*, b. p. 188° (24 mm.); 145–147° (3 mm.); 122–123° (0.2 mm.).

Diethylaminoethyl 4-Nitro-2-chlorobenzoate.—A mixture of 23 g. of ethyl 4-nitro-2-chlorobenzoate and 26.4 g. of diethylaminoethanol was heated for six hours at 140–150° and the reaction product treated with water and ether and fractionated; b. p. 162–163° (0.18 mm.); 140° (0.02 mm.); yield, 16 g. (52%).

Anal. Calcd. for $C_{13}H_{17}O_4N_2Cl$: C, 52.0; H, 5.7; N, 9.3. Found: C, 51.8; H, 5.5; N, 9.0.

Hydrochloride from ethyl acetate, white needles, m. p. 144°.

Anal. Calcd. for $C_{13}H_{18}O_4N_2Cl_2$: C, 46.3; H, 5.3; N, 8.3; Cl, 21.1. Found: C, 46.6; H, 5.2; N, 8.2; Cl, 21.5.

Approximately the same yield (50%) was obtained when the reaction was carried out under reflux in dioxane as solvent (six hours, bath temperature 120°); *trans*-esterification in presence of toluene and aluminum isopropoxide as catalyst (150°, five hours, with continuous removal of the ethyl alcohol formed) gave a yield of 37.5%.[4]

Diethylaminoethyl Acetate.—Azeotropic esterification of 160 g. of ethylene chlorohydrin and 120 g. of acetic acid in 100 cc. of benzene took five hours, when 10 cc. of concentrated sulfuric acid was employed as catalyst. The resulting solution was washed with sodium carbonate and dried and the β-chloroethyl acetate purified by fractionation; b. p. 145–147° (760 mm.); 50° (18 mm.); yield, almost quantitative.[5] The ester obtained (200 g.) was refluxed with an excess of diethylamine (250 g.) for eight hours, and after addition of another 125 g. of diethylamine for the same period again. The filtered solution was fractionated; b. p. 147°; yield, 130 g.

Hydrogenation of Diethylaminoethyl 4-Nitro-2-chlorobenzoate.—Three representative experiments are reported: (a) A solution of 9 g. (0.03 mole) of the nitro-ester in 50 cc. of anhydrous ethyl alcohol absorbed, at room temperature and in presence of 1 g. of palladium–barium sulfate catalyst, 2010 cc. of hydrogen (0.09 mole) within five and one-half hours. The oily residue of the filtered solution crystallized partly; trituration with cold chloroform gave a white solid which was recrystallized from butyl acetate and melted at 135°. Analysis and reducing properties pointed to the formation of **diethylaminoethyl 4-hydroxylamino-2-chlorobenzoate**, $HONH{\cdot}C_6H_3(Cl){\cdot}COO{\cdot}CH_2CH_2N(C_2H_5)_2$.

Anal. Calcd. for $C_{13}H_{19}O_3N_2Cl$: C, 54.5; H, 6.6; N, 9.8; Cl, 12.2. Found: C, 54.3, 54.7; H, 6.9, 7.1; N, 9.8; Cl, 12.4.

Evaporation of the chloroform solution left a strongly basic oil of anesthetic properties which boiled at 130–135° (0.05 mm.) and gave, with alcoholic hydrogen chloride, crystals of ethyl 4-aminobenzoate hydrochloride, m. p. 210°, which were identified by analysis and mixed m. p.

Anal. Calcd. for $C_9H_{12}O_2NCl$: C, 53.7; H, 6.0. Found: C, 53.8; H, 5.9.

(b) When a solution of 6 g. (0.02 mole) of the nitro-ester in 30 cc. of diethylaminoethyl acetate was hydrogenated at room temperature in presence of 0.5 g. of the palladium catalyst, a thick precipitate appeared after the absorption of 500 cc. of hydrogen (0.02 mole), and no further absorption took place. Extraction of the solid phase with butyl acetate gave 2 g. of the above hydroxylamino-compound, m. p. 135°, while the liquid phase contained 3 g. of an oil which crystallized partly on standing. Recrystallization from methanol gave **ethyl 4-amino-2-chlorobenzoate** of m. p. 110°.[1]

(1) Rubin, Marks, Wishinsky and Lanzilotti, THIS JOURNAL, **68**, 623 (1946).

(2) Metayer, *Bull. soc. chim.*, 1093 (1948).

(3) Cohen and McCandlish, *J. Chem. Soc.*, **87**, 1271 (1905).

(4) For a similar method, see Alix, French Patent 841,343; *C. A.*, **34**, 4077 (1940).

(5) For the usual acetylation of ethylene chlorohydrin, see "Beilstein," Vol. II, p. 128; 2nd suppl. Vol. II, p. 136.

In another experiment, the liquid phase gave, upon trituration with petroleum ether, a solid which crystallized from methyl alcohol and melted at 77–78°. Analysis and comparison with an authentic specimen prepared from 4-nitro-2-chlorobenzoic acid (3 g.) and methyl alcohol (20 cc.) in presence of concentrated sulfuric acid (6 drops) indicated that methyl 4-nitro-2-chlorobenzoate had formed.

Anal. Calcd. for $C_8H_6O_4NCl$: C, 44.7; H, 2.8; N, 6.5; Cl, 16.3. Found: C, 45.0; H, 2.8; N, 6.4; Cl, 16.1.

In addition, a small amount of an unidentified substance was formed which crystallized from butyl alcohol or isobutyl acetate in slightly yellowish leaflets of m. p. 152°.

(c) A solution of 15 g. of diethylaminoethyl 4-nitro-2-chlorobenzoate (0.05 mole) in 105 cc. of ethyl acetate absorbed in presence of palladium–barium sulfate catalyst, 3850 cc. of hydrogen (3.44 moles) at room temperature in three hours. The residue of the filtered solution crystallized upon standing. After trituration with methanol and recrystallization from methanol or petroleum ether, the substance melted at 92°. It is characterized by the formation of dimorphous crystals: yellow needles and orange-red prisms. Analysis proved the formula of diethyl 3,3′-dichloro-azoxybenzene-4,4′-dicarboxylate.

Anal. Calcd. for $C_{18}H_{16}O_5N_2Cl_2$: C, 52.6; H, 3.9; N, 6.8; Cl, 17.3; mol. wt., 411. Found: C, 52.6; H, 3.9; N, 7.2; Cl, 17.0; 17.1; mol. wt. (in camphor), 396.

3,3′-Dichloroazoxybenzene-4,4′-dicarboxylic acid was isolated in one experiment, in which 5 g. of 4-nitro-2-chlorobenzoic acid was hydrogenated in 30 cc. of isopropyl alcohol at room temperature and the reaction came to a standstill after the absorption of 1.9 moles of hydrogen. Recrystallization from butyl alcohol gave short needles, m. p. 320°.

Anal. Calcd. for $C_{14}H_8O_5N_2Cl_2$: C, 47.3; H, 2.3. Found: C, 47.5; H, 2.6.

The hydrogenation experiments with 4-nitro-2-chlorobenzoic acid and its ethyl ester were carried out at room temperature and atmospheric pressure, in approximately 10% solutions, using palladium-on-barium sulfate (5%) as catalyst. In ethyl acetate, the acid and the ethyl ester absorbed 3 moles of hydrogen in twenty-four and three hours, respectively, and gave 4-amino-2-chlorobenzoic acid (from toluene, m. p. 213°)[6] and ethyl 4-amino-2-chlorobenzoate (from methanol, m. p. 110°) in quantitative yield. In isopropyl alcohol as solvent, 4 moles of hydrogen were absorbed in sixteen and five hours, respectively, without any break in the rate of absorption. The products isolated were 4-aminobenzoic acid (m. p. 187°; yield, 90%) and the hydrochloride of ethyl 4-aminobenzoate (m. p. 211°, from ethyl acetate; yield, quantitative). Also an aqueous solution of sodium 4-nitro-2-chlorobenzoate absorbed 4 moles of hydrogen (in eight hours) and gave 4-aminobenzoic acid (in 90% yield).

(6) Tiemann, *Ber.*, **24**, 708 (1891).

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REHOVOTH, ISRAEL

RECEIVED APRIL 11, 1947

Irreversible Decolorization of Pinacyanol Chloride in the Presence of Paraffin-Chain Salts[1]

BY ANNA MAE TIMBERS AND E. C. LINGAFELTER

In using pinacyanol chloride as a means of determining the critical concentration of paraffin-chain salts,[2] we have observed that the color fades upon standing. Since we do not plan to pursue this investigation, we wish at this time to report some preliminary observations on the factors which affect the rate of disappearance of the color.

1. The disappearance of color is not due to the familiar effect of hydrogen ion, since it is not reversed by the addition of hydroxide ion.

2. The disappearance of color is due to an oxidation, since the rate is decreased by removing oxygen (either by passing nitrogen through the solution or by adding hydroquinone) and is increased by the addition of hydrogen peroxide. The oxidation of pinacyanol chloride to colorless products by nitric acid and by alkaline potassium ferricyanide has been reported previously.[3]

3. The reaction is photosensitive, the rate being markedly increased by exposure to intense illumination. For example, a solution containing 10^{-5} *M* pinacyanol chloride, 0.27 *M* hydrogen peroxide, and 0.01 *M* sodium decanesulfonate showed no loss of color after several days in the dark, but was completely decolorized after ninety-five minutes in daylight or after eight minutes of exposure to a Cenco mercury arc.

4. The rate of decolorization is independent of the concentration of added sodium chloride but is markedly affected by the presence of paraffin-chain salts. The results of three sets of experiments using sodium decanesulfonate (critical concentration, 0.04 *M*) are shown in Fig. 1. Similar results were obtained with other concentrations of hydrogen peroxide and also with sodium octane-

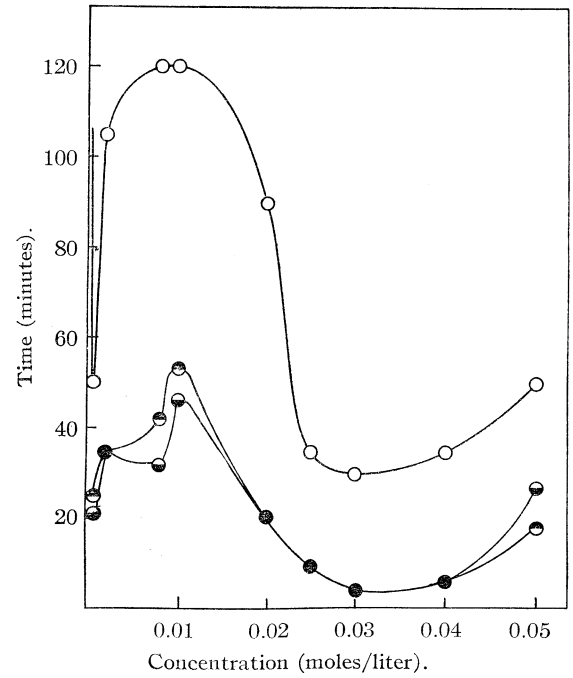

Fig. 1.—Time for complete decolorization of 10^{-5} *M* pinacyanol chloride as a function of concentration of sodium 1-decanesulfonate: ○, 0.03 *M* H_2O_2; ◓, 0.35 *M* H_2O_2; ◒, 0.53 *M* H_2O_2.

(1) Taken from a thesis submitted by A. M. Timbers in partial fulfillment of the requirements for the M.S. degree, June, 1947.

(2) Corrin, Klevens and Harkins, *J. Chem. Phys.*, **14**, 487 (1946).

(3) Mills and Hamer, *J. Chem. Soc.*, **117**, 1550 (1920).

sulfonate and sodium dodecyl sulfate as the paraffin-chain salts.

We have no explanation to offer at the present time for the effect of concentration of paraffin-chain salt, although the phenomenon is not surprising in view of the profound effect of paraffin-chain salts upon the absorption spectrum of the dye.

CONTRIBUTION FROM THE
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WASHINGTON
SEATTLE 5, WASHINGTON

RECEIVED JUNE 28, 1949

NEW COMPOUNDS

p,p'-Dichlorobenzhydryl-β-cyanoethyl Ether

Ten grams (0.04 mole) of *p,p'*-dichlorobenzhydrol[1] (m. p. 88–89°) and 1.0 ml. of phenyltrimethylammonium hydroxide (Monsanto, 20% aqueous solution) were dissolved in 40 ml. of purified dioxane. A solution of 2.3 g. (0.04 mole) of redistilled acrylonitrile in 10 ml. of dioxane was added dropwise with stirring. After pouring into 200 ml. of water, the oil layer was separated. On standing overnight 11 g. (91%) of solid melting 52–66° formed. Crystallization from 50 ml. of 95% ethanol gave 7.6 g. (67%) melting 74–76°.[2] For analysis a sample was recrystallized; m. p. 75–76.5°.

Anal. Calcd. for $C_{16}H_{13}OCl_2N$: Cl, 23.2; N, 4.58. Found: Cl, 22.45; N, 4.43.

Attempts to hydrolyze this cyanide in alkaline solution to β-(*p,p'*-dichlorobenzhydroxy)-propionic acid unexpectedly cleaved the ether linkage with the formation of *p,p'*-dichlorobenzhydrol. Five grams (0.016 mole) of the ether and 50 ml. of 15% aqueous sodium hydroxide were refluxed for twenty-four hours. At the end of this time the evolution of ammonia had practically ceased. After cooling and filtering 2.5 g. of solid, m. p. 83–85°, was collected. A mixed melting point with authentic *p,p'*-dichlorobenzhydrol was 84–88°. Acidification of the filtrate gave no precipitate. With 50 ml. of 25% sodium hydroxide solution and four hours of refluxing, the yield of alcohol was 97% of the theoretical.

(1) Montagne, *Rec. trav. chim.*, **24**, 120 (1905).

(2) This is essentially the procedure used by Bruson, THIS JOURNAL, **64**, 2457 (1942), and subsequent papers, to prepare many cyanoethyl ethers.

SHERWIN–WILLIAMS LABORATORY
WESTERN RESERVE UNIVERSITY
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OLIVER GRUMMITT
DEAN MARSH

RECEIVED AUGUST 15, 1949

Derivatives of Di-(*p*-chlorophenyl)-acetic Acid

Di-(*p*-chlorophenyl)-acetic acid, m. p. 164–166°, was made by the alkaline hydrolysis of DDT.[1]

Methyl Di-(*p*-chlorophenyl)-acetate.—From 16.9 g. (0.06 mole) of di-(*p*-chlorophenyl)-acetic acid, 20 ml. (14.2 g., 0.44 mole) of methanol and 1 ml. of concentrated sulfuric acid reacted at reflux for four hours there was obtained 9 g. (54%) of ester boiling at 208–212° (5–6 mm.). On standing overnight the product crystallized; m. p. 37–39° (see Table I for analysis).

Phenacyl Di-(*p*-chlorophenyl)-acetate.—From 8 g. (0.03 mole) of acid as the salt and 6.23 g. (0.032 mole) of phenacyl bromide reacted in the usual way at reflux for two hours 8.0 g. (71%), m. p. 129–130°, of ester formed.[2] A sample purified by crystallization from benzene melted 132–133°.

Di-(*p*-chlorophenyl)-acetic Anhydride.—A mixture of 20 g. (0.07 mole) of acid and 15.7 g. (0.15 mole) of reagent grade acetic anhydride was refluxed gently for two hours. Distillation at 0.5 mm. gave 2.1 g. at 135–165°, 14.7 g. at 165–195°, 0.2 g. at 195–260° and 2 g. of black residue. Redistillation of the 165–195° fraction gave 11.6 g. at 180–190° (0.5 mm.). Addition of ether precipitated 8.9 g. of yellow solid melting 82–123°. Crystallization from 12 ml. of dry chloroform gave 2.6 g., m. p. 158–163°; a mixed melting point with di-(*p*-chlorophenyl)-acetic acid gave 159–164°. Repeated crystallizations of the chloroform-soluble portion from benzene–petroleum ether (b. p. 60–70°) (1/2 by volume) finally gave 2.6 g. of faintly yellow needles melting 104–105.5°.

Hydrolysis of 0.5 g. of the anhydride by refluxing with 10 ml. of 10% sodium hydroxide solution gave 0.4 g. of di-(*p*-chlorophenyl)-acetic acid, m. p. 163–165°; mixed m. p. 163–165°.

2-(*p,p'*-Dichlorobenzhydryl)-benzimidazole.—From 8 g. (0.028 mole) of acid and 3.2 g. (0.03 mole) of freshly crystallized *o*-phenylenediamine reacted in the usual way there was obtained 5.0 g., 50%, melting 246–248°, after crystallization from 1/1 alcohol–benzene.[3]

Di-(*p*-chlorophenyl)-acetyl Chloride.—A mixture of 8 g. (0.029 mole) of acid and 11 g. (0.09 mole) of purified thionyl chloride was refluxed for four hours. Removal of the excess chloride gave 8.5 g. (95%) of a brown oil which decomposed on vacuum distillation at 3–4 mm. Attempted crystallization from petroleum ether (b. p. 60–70°) gave an oil which did not crystallize at 0°. Hydrolysis of 2.0 g. of the acid chloride with ice yielded 1.7 g. of di-(*p*-chlorophenyl)-acetic acid, m. p. 158–162°, mixed melting point, 159–163°.

Di-(*p*-chlorophenyl)-acetamide.—Seven grams (0.023 mole) of the acid chloride and 12 ml. (0.092 mole) of ice cold concentrated ammonium hydroxide gave 5.5 g., (85%) of crude amide melting 136–138° dec. Several crystallizations from 95% ethanol gave a product melting 152–154°.

Di-(*p*-chlorophenyl)-acetanilide.—A mixture of 8 g. (0.03 mole) of the acid chloride, 5.5 g. (0.06 mole) of redistilled aniline and 100 ml. of benzene was refluxed for one-half hour. The benzene layer was decanted from the aniline hydrochloride, washed with water, 5% sodium carbonate solution, 10% hydrochloric acid, and water, and evaporated to give 1.2 g. melting 205–206°. Extraction of the aniline hydrochloride with benzene in a Soxhlet extractor gave 5.8 g., m. p. 203–206°, for a total yield of 7.0 g., 75%. Crystallization from 1/1 benzene–pyridine gave a product melting 205–206°.

Di-(*p*-chlorophenyl)-aceto-4-chloranilide.—Prepared as the acetanilide from 9.5 g. (0.034 mole) of acid chloride, 8.9 g. (0.07 mole) of *p*-chloroaniline and 50 ml. of benzene with two and one-half hours' reflux. The crude product, 9.5 g., 72% melting 220–240° dec. was crystallized from benzene: m. p. 258–260°.

***p,p'*-Dichlorobenzhydryl Phenyl Ketone.**—A Friedel–Crafts reaction of 9.4 g. (0.088 mole) of aluminum chloride in 50 ml. of reagent grade benzene with 18.2 g. (0.06 mole) of di-(*p*-chlorophenyl)-acetyl chloride in 100 ml. of benzene at 0–10° for one hour gave 19.5 g. (94%) of crude ketone melting 81–86°. Crystallization from 80 ml. of 95% ethanol gave 14.0 g. (67%), m. p. 90–91°.

Di-(*p*-chlorophenyl)-acetonitrile.—A mixture of 5.0 g. (0.018 mole) of di-(*p*-chlorophenyl)-acetamide and 9.5 g. (0.08 mole) of freshly purified thionyl chloride was refluxed for four hours, cooled, and poured onto 200 g. of ice. After extraction with ether the crude nitrile was vacuum distilled at 2 mm. but decomposition was apparent. Another portion of the ether extract on standing

(1) Grummitt, Buck and Egan, *Org. Syn.*, **26**, 21 (1946).

(2) Shriner and Fuson, "Identification of Organic Compounds," 3rd edition, John Wiley & Sons, New York, N. Y., 1948, p. 157.

(3) Pool, Harwood and Ralston, THIS JOURNAL, **59**, 178 (1937).

TABLE I

DI-(*p*-CHLOROPHENYL)-ACETIC ACID DERIVATIVES

	Compound	M. p., °C.[c,d]	Formula	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Mol. wt. Calcd.	Mol. wt. Found
1	Methyl di-(*p*-chlorophenyl)-acetate	37–39	$C_{15}H_{12}Cl_2O$	24.6	24.2			295	295[f]
2	Phenacyl di-(*p*-chlorophenyl)-acetate	132–133	$C_{22}H_{16}Cl_2O_3$	17.8	17.9			399	378[g]
3	Di-(*p*-chlorophenyl)-acetic anhydride	104–105.5	$C_{28}H_{18}Cl_4O_3$	26.1	26.3			544	548[g]
4	2-(*p,p'*-Dichlorobenzhydryl)-benzimidazole	246–248	$C_{20}H_{13}Cl_2N_2$	20.1	19.4	7.95	7.81		
5	Di-(*p*-chlorophenyl)-acetyl chloride	Oil	$C_{14}H_9Cl_3O$	35.4	34.9				
6	Di-(*p*-chlorophenyl)-acetamide	152–154	$C_{14}H_{11}Cl_2NO$	25.3	25.0	5.00	4.60		
7	Di-(*p*-chlorophenyl)-acetanilide[a]	205–206	$C_{20}H_{15}Cl_2NO$	19.9	19.9	3.93	4.03		
8	Di-(*p*-chlorophenyl)-aceto-4-chloroanilide	258–260	$C_{20}H_{14}Cl_3NO$	27.2	27.3	3.59	3.65		
9	*p,p'*-Dichlorobenzhydryl phenyl ketone	90–91	$C_{20}H_{14}Cl_2O$	20.9	20.9			341	353[h]
10	Di-(*p*-chlorophenyl)-acetonitrile[b]	85–86	$C_{14}H_9Cl_2N$	27.1	25.8	5.34	5.62		

[a] Described by Gatzi and Stammbach, *Helv. Chim. Acta*, **29**, 563 (1946), as melting 202–204° in a paper published after our synthesis had been done. [b] Despite the sharp m. p., analysis shows that this compound is not pure. [c] These m. p.'s are uncorrected. [d] The m. p.'s of the corresponding diphenylacetic acid (m. p. 148–149°) derivatives were taken from the literature for comparison; they are 1, 60°; 3, 98°; 5, 56–57°; 6, 167–168°; 7, 180–181°; 9, 136–137°. In these examples the diphenylacetic acid derivatives frequently are higher melting. [e] Saponification values of this ester ran 75–100% over the calculated, probably as the result of a secondary reaction of phenacyl alcohol with alkali. Boiling point rise molecular weights in benzene gave high values, indicative of association. This value was found by the Rast camphor method. [f] By saponification equivalent. [g] By neutral equivalent. [h] By b. p. rise in benzene.

partially crystallized to give 1.5 g. of solid melting 83–85°. Crystallization from 10 ml. of 95% ethanol gave 1.0 g. (18%) melting 85–86°. Despite the sharp melting point, analysis indicated an impure compound.

SHERWIN–WILLIAMS LABORATORY
WESTERN RESERVE UNIVERSITY OLIVER GRUMMITT
CLEVELAND 6, OHIO DEAN MARSH

RECEIVED AUGUST 15, 1949

COMMUNICATIONS TO THE EDITOR

GEOMETRIC ISOMERS OF 1-PHENYL-1,3-BUTADIENE

Sir:

1-Phenyl-1,3-butadiene made by the hydrolysis of the cinnamaldehyde–methylmagnesium bromide addition compound in 30% sulfuric acid[1] has been shown to be the pure *trans* isomer by its quantitative Diels–Alder reaction with maleic anhydride.[2] Varying the conditions of hydrolysis does not, as previously reported,[3] give the *cis* and *trans* forms but only the *trans* is obtained.

cis-1-Phenyl-1,3-butadiene has been made by ultraviolet irradiation of the *trans* isomer. The *cis* compound does not react with maleic anhydride at room temperature. Irradiation of the *cis* compound isomerizes it partially to the *trans*. The two isomers differ markedly in physical properties:

	Dist. temp., °C.	Mm.	F. p., °C.	d^{25}_4	$n^{25}D$	Molar ref.[a]
cis	71	11	−56.99 ± 0.04	0.9197	1.5822	47.25
trans	83	11	4.52 ± .04	.9232	1.6089	48.82

[a] The molar refraction calculated from the Lorentz–Lorenz equation is 43.85.

The boiling point, density and refractive index are usually greater for the *cis* form of olefinic hydrocarbons. This is also true of piperylene.[2] The exceptional behavior of the phenylbutadienes is noteworthy.

In ultraviolet absorption spectra the *cis* form shows a maximum at 265–269 mμ, molar extinction 184 × 10^2, and the *trans* at 280 mμ, molar extinction 298 × 10^2. An outstanding difference in infrared absorption spectra is the 14.20-μ band for the *cis* and the 10.56-μ band for the *trans* which are unique for each isomer.

Neither geometric isomer adds sulfur dioxide to give a cyclic sulfone.

MORLEY CHEMICAL LABORATORY
WESTERN RESERVE UNIVERSITY OLIVER GRUMMITT
CLEVELAND 6, OHIO FRANK J. CHRISTOPH

RECEIVED OCTOBER 13, 1949

(1) Grummitt and Becker, THIS JOURNAL, **70**, 149 (1948).

(2) Robey, Morrell and Wiese, *ibid.*, **63**, 627 (1941) and Craig, *ibid.*, **65**, 1006 (1943) differentiated *cis* and *trans* piperylenes by the greater reactivity of the *trans* isomer to maleic anhydride.

(3) Muskat and Herrman, *ibid.*, **53**, 252 (1931).

THE PREPARATION OF HAFNIUM-FREE ZIRCONIUM

Sir:

We have recently performed a series of experiments which indicate that silica gel strongly and preferentially adsorbs hafnium compounds from a zirconium–hafnium compound mixture in certain organic solvents, and that this fact provides a new, simple, and effective means of preparing hafnium-free zirconium.

A solution of 455 g. of zirconium tetrachloride dissolved in 2275 ml. of anhydrous methanol was allowed to stand for three hours and filtered. The filtered solution contained 106 mg. total oxide per ml. A column 30″ in length × 27 mm. in diameter was packed with 290 g. of 28 to 120 mesh silica gel which had been purified by elution with 1:1 nitric acid and activated four hours at 300°. The column was prepared by sludging silica gel and methanol, and hence initially contained approximately 200 ml. of methanol; 1800 ml. of the above solution was then fed into the column, the flow being from bottom to top at a rate of 200 ml./hr. The effluent was collected in approximately 200-ml. batches and the total oxides in 5-ml. aliquots of each batch precipitated and analyzed spectrographically. The results were as shown (weights refer to ignited oxide, analyses to per cent. hafnium in sample).

TABLE I

COMPOSITION OF SUCCESSIVE BATCHES

No.	1	2	3	4	5	6	7	8	9
Wt. g.	7	18.2	21.5	22.5	22.9	25.0	24.7	18.5	22.1
% Hf	[a]	0.00	0.03	0.15	0.38	0.66	0.80	0.93	1.10

[a] Analysis uncertain due to large Fe and Ti content. The $ZrCl_4$ used contained approximately 0.13% $FeCl_3$ and 0.53% $TiCl_4$.

The column was then stripped with one liter of methanol made 1.2 *M* in anhydrous hydrochloric acid, the eluant being collected in four fractions. Analyses over 15% Hf are rough spectrographic estimates since the method has not yet been extended to this region.

TABLE II

COMPOSITION OF FRACTIONS OF ELUANT

No.	1	2	3	4
Wt. g.	9.0	2.5	0.68	0.48
% Hf	1.8	15	60	40

Similar, but not quite so striking results have been obtained using acetone instead of methanol as solvent; the degradation of acetone by zirconium tetrachloride tends to cause tars and clogging in the column which causes some inconvenience.

To summarize: Hafnium in zirconium may be reduced to less than 0.1% by passing a 1:5 solution of the chlorides in methanol through a silica gel column; 290 g. silica gel will furnish 60 g. purified oxide; the column can be stripped with 1 *M* anhydrous hydrochloric acid in methanol and re-used. By feeding in an oxide equivalent of approximately 65 g., in this case, the purified oxide yield would be about 90%.

Work on the mechanism of this and similar processes is being continued and will be reported at a later date.

We are indebted to V. A. Fassel and C. H. Anderson for spectrographic analyses.

INSTITUTE FOR ATOMIC RESEARCH AND
DEPARTMENT OF CHEMISTRY ROBERT S. HANSEN
IOWA STATE COLLEGE, AMES, IOWA

WORK PERFORMED IN THE AMES LABORATORY
ATOMIC ENERGY COMMISSION KEITH GUNNAR

RECEIVED OCTOBER 8, 1949

THE METAL ION CATALYZED DECARBOXYLATION OF DIMETHYLOXALOACETIC ACID

Sir:

Recent investigations[1] of the metal ion catalysis of the enzymatic and non-enzymatic decarboxylation of oxaloacetic acid have prompted us to make a detailed study of the mechanism of the decarboxylation of α,α-dimethyloxaloacetic acid and of its monoethyl ester. The synthesis of these compounds is outlined below.

$$C_2H_5O_2CCO_2C_2H_5 + (CH_3)_2CHCO_2C(CH_3)_3 \xrightarrow{(C_6H_5)_3CNa} C_2H_5O_2CCOC(CH_3)_2CO_2C(CH_3)_3 \xrightarrow[HOAc]{HBr}$$

(A)

$$C_2H_5O_2CCOC(CH_3)_2CO_2H \xrightarrow[H_2O]{HCl} HO_2CCOC(CH_3)_2CO_2H$$

(B) (C)

The condensation was carried out by Hauser's method,[2] the cleavage of the *t*-butyl ester, A, by a method based on the work of Tronow,[3] and the hydrolysis of the ethyl ester, B, by a method based on the work of Michael.[4]

Anal. Calcd. for diester, A, (b. p. 107–111° (7 mm.)): C, 59.0; H, 8.20. Found: C, 58.7; H, 8.21. Calcd. for monoester, B, (m. p. 38–39°): C, 51.0; H, 6.43. Found: C, 50.8; H, 6.44. Calcd. for diacid, C, (m. p. 105.5–106.5°): C, 45.0; H, 5.03. Found: C, 45.1; H, 5.18.

Both the monoester and the diacid decarboxylated smoothly at 25° in aqueous solutions of *p*H between 2 and 7 to form the expected products. (The 2,4-dinitrophenylhydrazone of α-keto-β-methylbutyric acid melted[5] at 194–194.5°; the

(1) L. Krampitz and C. Werkman, *Biochem. J.*, **35**, 595 (1941); H. Krebs, *ibid.*, **36**, 303 (1942); A. Kornberg, S. Ochoa and A. Mehler, *J. Biol. Chem.*, **174**, 159 (1948); J. Speck, *ibid.*, **178**, 315 (1949); P. Nossal, *Australian J. Exptl. Biol. Med. Sci.*, **27**, 143 (1949).

(2) B. Hudson, Jr., and C. Hauser, THIS JOURNAL, **63**, 3156 (1941).

(3) B. Tronow and N. Ssibgatullin, *Ber.*, **62B**, 2850 (1929).

(4) A. Michael and J. Bucher, *ibid.*, **29**, 1792 (1896).

(5) G. Ramage and J. Simonsen, *J. Chem. Soc.*, 532 (1935).

2,4-dinitrophenylhydrazone of the ethyl ester (from B) melted at 171.5–172°. *Anal.* Calcd. for $C_{13}H_{16}O_6N_4$: C, 48.2; H, 4.97; N, 17.3. Found: C, 48.0; H, 4.80; N, 17.0). Some first order rates of decarboxylation, determined manometrically near *p*H 5 in the presence and absence of metal ions, are shown in the table below.

Metal ion	Monoester B Concn. of metal ion, m./l.	Monoester B k, min.$^{-1}$	Diacid C Concn. of metal ion, m./l.	Diacid C k, min.$^{-1}$
None		0.075		0.0032
Cu^{++}			0.001	.14
	0.01	.069	.01	*ca.* 1.6
Al^{+++}	.01	.070	.001	0.13
Ni^{++}	.01	.075	.01	.022
Mn^{++}	.01	.066	.01	.0046

Thus metal salts strongly catalyze the decarboxylation of the diacid, C, but do not affect the rate of decarboxylation of the monoester, B. Since no enol form of α,α-dimethyloxaloacetic acid is possible, it is clear that the *keto* acid (like dimethylacetoacetic acid[6]) undergoes decarboxylation. Further, these experiments show that the metal ion catalysis of the decarboxylation of dimethyloxaloacetic acid requires the formation of a complex between the metal ion and the carboxyl group gamma to the one lost; presumably the metal ion is also coördinated with the carbonyl oxygen atom. By analogy, these conclusions also apply to the decarboxylation of oxaloacetic acid itself.

The investigation of these reactions is continuing.

(6) K. Pedersen, THIS JOURNAL, **51**, 2098 (1929); **58**, 240 (1936).

THE GEORGE HERBERT JONES LABORATORY
UNIVERSITY OF CHICAGO RUDOLPH STEINBERGER
CHICAGO 37, ILL. F. H. WESTHEIMER

RECEIVED NOVEMBER 12, 1949

DEGRADATION PRODUCTS OF PSEUDOHECOGENIN

Sir:

It has been shown that "*allo*-pregnan-3,12,20-trione" from pseudohecogenin does not agree in properties with *allo*-pregnan-3,12,20-trione prepared from 12(α)-acetoxyprogesterone.[1] We have now reinvestigated "16-*allo*-pregnen-3,12,20-trione" from pseudohecogenin. From its method of synthesis and analysis, it was assumed to be an α,β-unsaturated triketone containing a molecule of water of crystallization.[2] However, we find that this material does not show an absorption maximum in the ultraviolet typical for α,β-unsaturated ketones, that it is unchanged by conditions of hydrogenation with palladium catalyst and that *it is actually identical with the compound designated as "allo-pregnan-3,12,20-trione,"* also assumed to contain a molecule of water of crystallization. It is not changed by hot acetic anhydride and pyridine, which suggests that the "molecule of water" might be a tertiary hydroxyl group at C-17. Mild chromic acid oxidation gives impure starting material in agreement with the results of Reichstein and Gatzi[3] for this ketol system. It is noteworthy that mild oxidation of the isomeric D-homo derivative is reported to give an acidic product.[4]

Hydroxyl groups in steroids have been associated with infrared absorption maxima at 3570 to 3620 cm.$^{-1}$ along with a carbonyl harmonic band at 3300 to 3475 cm.$^{-1}$ if a ketone group is also present.[5] It was hoped that such data (Fig. 1) would support the assignment of a hydroxyl group to this substance; however, the results are inconclusive. A scarcity of material has curtailed further work.

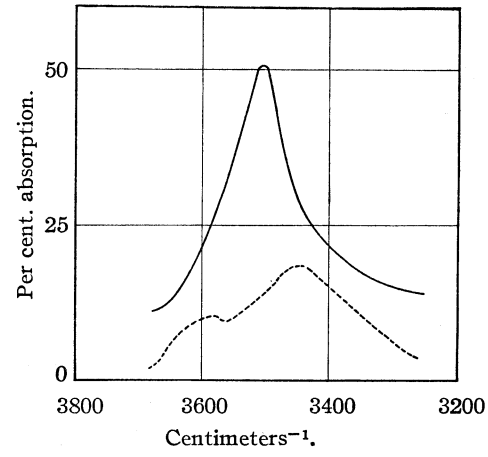


Fig. 1.—Infrared absorption spectra in carbon disulfide solution: ...., 17(α)-hydroxyprogesterone; ——, degradation product from pseudohecogenin.

Although it is not possible to state definitely the structure for this product, it becomes clear that the non-identity of it with *allo*-pregnan-3,12,20-trione is not necessarily due to an incorrect assignment of the C-12 oxygen in hecogenin and botogenin.[6]

We thank Parke, Davis and Company for their help.

WHITMORE LABORATORIES
SCHOOL OF CHEMISTRY AND PHYSICS R. B. WAGNER
THE PENNSYLVANIA STATE COLLEGE JAMES A. MOORE
STATE COLLEGE, PENNSYLVANIA ROBERT F. FORKER

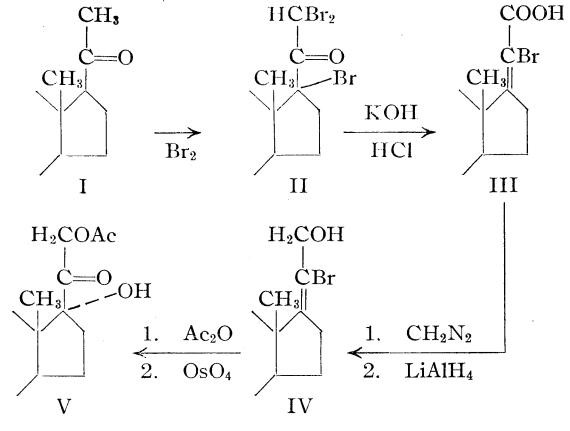
RECEIVED NOVEMBER 1, 1949

(1) Wagner, Moore and Forker, THIS JOURNAL, **71**, 3856 (1949).
(2) Marker, Wagner and co-workers, *ibid.*, **69**, 2167 (1947).
(3) Reichstein and Gatzi, *Helv. Chim. Acta*, **21**, 1497 (1938).
(4) Ruzicka, Gatzi and Reichstein, *ibid.*, **22**, 637 (1939).
(5) Jones, *et al.*, THIS JOURNAL, **70**, 2024 (1948).
(6) At the time that this communication was in preparation, Marker, *ibid.*, **71**, 3856 (1949), presented further evidence that the degradation of pseudobotogenin diacetate can lead to a 17-hydroxy steroid.

A NEW ROUTE TO THE CORTICAL SIDE CHAIN

Sir:

The conversion of the readily available bromopregnanolones to compounds of the cortical series having a dihydroxyacetone side chain has been achieved. The key steps involve a rearrangement of a tribromoketone and subsequent reduction of the product.



Bromination of pregnan-3(β)-ol-20-one acetate (I) with three moles of bromine yields the 17,21, 21-tribromo derivative (II), m. p. 196° (dec.), $[\alpha]^{25}D$ −3.4° (chloroform). Calcd. for $C_{23}H_{33}O_3Br_3$: Br, 40.1. Found: Br, 40.3. Rearrangement with alcoholic potash yields 17-pregnen-3(β)-ol-20-bromo-21-oic acid (III), m. p. 273° (dec.), $[\alpha]^{25}D$ + 41° (dioxane). Calcd. for $C_{21}H_{31}O_3Br$: C, 61.4; H, 7.6; Br, 19.4. Found: C, 62.0; H, 7.7; Br, 19.1. Reduction of the bromo acid with hydrogen and platinum catalyst gives pregnan-3(β)-ol-21-oic acid, m. p. and mixed m. p., 220°.[1] Lithium aluminum hydride reduction of the methyl ester of III yields the unsaturated 20-bromo-21-ol (IV), m. p. 253° (dec), $[\alpha]^{25}D$ +53° (dioxane). Calcd. for $C_{21}H_{33}O_2Br$: C, 63.5; H, 8.4. Found: C, 63.4; H, 8.5. Treatment of the diacetate of IV with osmium tetroxide in ether yields pregnan-3(β),17(α),21-triol-20-one diacetate (V), m. p. 153°, $[\alpha]^{28}D$ +49° (dioxane). Calcd. for $C_{25}H_{38}O_6$: C, 69.1; H, 8.8. Found: C, 68.8; H, 8.8. Hydrogenation of V gives the same tetrol obtained by the lithium aluminum hydride reduction of methyl 17-pregnen-3(β)-ol-21-oate with subsequent hydroxylation (OsO_4), isolated as the triacetate, m. p. and mixed m. p. 184°, $[\alpha]^{28}D$ +55° (chloroform). Calcd. for $C_{27}H_{42}O_7$: C, 67.8; H, 8.9. Found: C, 67.4; H, 8.9.

We thank Parke, Davis and Company for their help.

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STATE COLLEGE, PENNSYLVANIA
R. B. WAGNER
JAMES A. MOORE

RECEIVED NOVEMBER 19, 1949

(1) Marker, Crooks and Wagner, THIS JOURNAL, **64**, 817 (1942).

HOMOLOGATION OF ALCOHOLS

Sir:

The conversion of an alcohol to the primary alcohol containing one carbon atom more than the original is usually a tedious procedure. We wish to report a simple one-step homologation reaction. The process consists in treating the alcohol with synthesis gas (carbon monoxide and hydrogen) in the presence of a cobalt catalyst under conditions resembling those employed in the oxo reaction.

The oxo or hydroformylation reaction consists of the conversion, by means of synthesis gas, of an olefin to a mixture of aldehydes containing one carbon atom more than the starting material.

$$R{-}CH{=}CH_2 + CO + H_2 \xrightarrow{Co} R{-}CH_2{-}CH_2{-}CHO + R{-}CH(CH_3)CHO$$

As developed in Germany, a mixture of olefins secured from the Fischer–Tropsch reaction was usually used as the starting material. The aldehydes resulting from the oxo reaction were then converted in a separate step, to a mixture of alcohols which were of value for detergent manufacture. It has been reported recently[1] that olefins may be converted in one step directly to the alcohol if the usual oxo reaction is operated at slightly higher temperatures. That our homologation reaction need not proceed *via* an olefin intermediate followed by a one-step hydroformylation–hydrogenation is shown by the fact that benzyl alcohol is converted to β-phenylethyl alcohol under our conditions: $PhCH_2OH + 2H_2 + CO \rightarrow PhCH_2CH_2OH$. Other conversions we wish to report consist of the formation of *n*-butyl alcohol and of isobutyl alcohol from isopropyl alcohol and of isoamyl alcohol from *t*-butyl alcohol. *n*-Propyl alcohol gave a mixture of *n*-butyl and isobutyl alcohols but the reaction proceeded so slowly at 180° that part of the initial products was transformed by further homologation to higher alcohols.

We are inclined to believe that the homologation reaction is an acid ($HCoCO_4$) catalyzed reaction that proceeds *via* a carbonium ion according to a mechanism that will be discussed in detail later.

In a typical experiment, *t*-butyl alcohol (86 g., 1.3 moles) and cobaltous acetate (7.0 g., 0.03 mole) were placed in an 0.5-liter stainless steel autoclave and heated with synthesis gas (3200 p. s. i., $1H_2$:1CO) at 160–180° for one and one-half hours Gas absorption was 89% of the theoretical according to the equation

$$\begin{array}{l} CH_3 \\ CH_3{-}C{-}OH + 2H_2 + CO \longrightarrow \\ CH_3 \end{array} \qquad \begin{array}{l} \\ CH_3{-}CH{-}CH_2{-}CH_2OH + H_2O \\ CH_3 \end{array}$$

There was obtained a 63% yield of isoamyl alco-

(1) Wender, Levine and Orchin, Abstracts of the Atlantic City meeting of the American Chemical Society, September 19–23, 1949

hol; α-naphthylurethan, m. p. 65.6–66.3°; mono ester with 3-nitrophthalic anhydride, m. p. 165.3–166.4°. Somewhat better results were obtained with cobaltous oxide as catalyst.

Benzyl alcohol gave toluene (49%) and β-phenylethyl alcohol (26%); α-naphthylurethan, m. p. 117.5–118.5°. Distillation of the alcohol from molten potassium hydroxide gave an 86% yield of styrene, identified through its dibromide.

Isopropyl alcohol gave 11% of a mixture of *n*-butyl and isobutyl alcohol; the former was identified by its infrared spectrum and the latter by its phenylurethan, m. p. 84.6–85.5°. *n*-Propyl alcohol reacted slowly at 180° to give a mixture of butyl, isobutyl, isoamyl and *n*-amyl alcohols, identified by their infrared absorption spectra.

U. S. BUREAU OF MINES
PITTSBURGH 13, PA.
DEPARTMENT OF CHEMISTRY — IRVING WENDER
THE UNIVERSITY OF PITTSBURGH — ROBERT LEVINE
PITTSBURGH, PA. — MILTON ORCHIN

RECEIVED OCTOBER 10, 1949

NEW BOOKS

Radioactive Indicators. Their Application in Biochemistry, Animal Physiology, and Pathology. By GEORGE HEVESY, Institute for Research in Organic Chemistry, University of Stockholm, Sweden; Institute for Theoretical Physics, University of Copenhagen, Denmark. Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y., 1948. xvi + 556 pp. Illustrated. 16 × 24 cm. Price, $10.00.

Thirty-six years ago the first paper on the use of radioactive indicators was published by Paneth and Hevesy. They first determined the solubility of some lead compounds and for several years were the only research workers applying this new tool. Ten years later, in 1923, Hevesy reported the first biological application of radioactive indicators: a study of the absorption and translocation of lead in plants. The present book is the most recent of a long series of publications by this pioneer in applied radiochemistry.

Chemists not primarily concerned with life science research will find little of direct interest in this book since it is a reference book written as a very extensive review article of the applications of radioactive indicators in biochemistry, animal physiology and pathology.

The first three chapters cover the production, availability and measurement of radioactive tracers. These chapters and the next two on atomic interchange and applications in chemical analysis do not fall within the province of the author's major interests and suffer as a consequence thereof. They represent an uncritical compilation of some of the literature and include such items as a copy of the 1947 catalog and price list of radioisotopes available from the U. S. A. E. C. Three long tables showing the decay of Na^{24}, K^{42} and P^{32} also seem unnecessary in a book of this type. The remaining eighty per cent. of the book is a substantial contribution to the literature of radioactive indicators, representing as it does a review of thirteen years of intensive work by many investigators in a very active field of research.

This section follows a logical pattern, starting with the general considerations of absorption, distribution and excretion of more than twenty-five elements, as simple inorganic species, in the whole animal organism. This is followed by a discussion of the problems associated with the transport of ions and compounds across the many types of membranes in living systems. Metabolic studies, including intermediary metabolism, are treated next. This section closes with a survey of the new information obtained from radioactive indicator studies of the special organs; the skeleton and red cells. The shortcomings of radioactive indicators in biology treated in the final chapter provide a timely warning for overenthusiastic readers.

Throughout the book many of the data from the original articles are reproduced in tables and graphs and detailed references are given. A Segre chart is included in an attached envelope in the back of the book. The author index and subject index are both excellent as they should be for this type of reference book.

Since the use of radioactive indicators in the fields of biochemistry, animal physiology and pathology is increasing so rapidly, Hevesy's "Radioactive Indicators" may be the last complete review of these fields. It will serve well as a point of departure for subsequent reviews of the accumulating knowledge, during the next few years.

JOHN W. IRVINE, JR.

Chemistry of Specific, Selective and Sensitive Reactions. By FRITZ FEIGL, Eng., Dr. Sc., Laboratory of Mineral Products, Ministry of Agriculture, Rio de Janeiro, Brazil; formerly Professor of Analytical and Inorganic Chemistry at the University of Vienna. Translated by Ralph E. Oesper, Professor of Chemistry, University of Cincinnati, Ohio. Academic Press, Inc., New York, N. Y., 1949. xiv + 740 pp. 15 × 23 cm. Price $13.50.

Perhaps few books have been written under greater hardships and handicaps than this one. The author began the laborious task of collecting and preparing material long before World War II but this was all lost during his flight from Europe and he had to make a new start after getting relocated in Brazil. The manuscript was written in German and translated into English by Professor R. E. Oesper, to whom the author pays especial thanks for his technical advice, patience ("even with last minute changes"), and deep understanding of the aims of the work. The "earmarks" of a translation, so often evident in English translations of technical books, are pleasingly missing and the reviewer found no serious typographical errors while reading the book from cover to cover.

The contents of the book and the method of presentation were chosen with three groups of readers in mind: (1) "those who wish to know the chemical basis of many modern analytical procedures," (2) "those who are actively engaged in research in analytical chemistry or in related fields," and (3) "those interested in experimental chemistry as a part of science which is still a fertile field for the trained and alert investigator." This was indeed an ambitious undertaking and no one is better qualified for such a task than Fritz Feigl who for more than a quarter of a century has made outstanding contributions to the

chemistry of specific, selective and sensitive reactions. He is the originator of modern spot test analysis to which he and his students have added many new and novel techniques in the field of qualitative and quantitative analysis.

The book contains twelve chapters which deal with the following topics: General comments on the analytical usefulness of chemical reactions (Chapter I, 5 pages); characterization of chemical tests and the role of reaction conditions (Chapter II, 16 pages); complex and coördinating compounds (Chapter III, 44 pages); masking and demasking of reactions (Chapter IV, 42 pages); enhancement of reactivity of compounds and reaction systems (Chapter V, 57 pages); effect of certain atomic groupings on the specific and selective activity of compounds in inorganic analysis (Chapter VI, 202 pages) and in organic analysis (Chapter VII, 13 pages); regularities and anomalies in the solution of materials in indifferent solvents (Chapter VIII, 28 pages); influence of size and weighting effects on solubility and salt-forming ability (Chapter IX, 21 pages); surface effects in analytical chemistry (Chapter X, 180 pages); genetic formation of materials and topochemical reactions (Chapter XI, 58 pages); and analytical uses of fluorescence effects and photochemical reactions (Chapter XII, 23 pages).

Hundreds of references to the original literature are given throughout the book as well as many previously unpublished observations by the author and his co-workers. A valuable feature of the book is the many suggestions for future research problems. There is hardly a page from which one does not glean valued suggestions for future work. Another feature of the book is the large number of critical remarks (frequently given as footnotes in smaller type) pertinent to the subject. The reviewer regrets that most of the footnotes were not incorporated in the main text; reading would have been much easier because of less frequent interruption. A hasty count revealed that 190 pages have a footnote, some fairly long, and that about 40 pages have two or more footnotes. This is not intended as a serious criticism but only a suggestion for a future edition; indeed, some readers may prefer the frequent use of footnotes in a work of this type.

The book has both an author and a subject index, many useful tables (29), and makes liberal use of structural formulas. Printing, paper and binding are good.

Dr. Feigl deserves congratulations and much praise for making such a noteworthy contribution to the "chemistry of specific, selective and sensitive reactions."

JOHN H. YOE

BOOKS RECEIVED

October 10, 1949–November 10, 1949

M. A. BRAVAIS. "On the Systems Formed by Points Regularly Distributed on a Plane or in Space." Translated by Amos J. Shaler. Published by the Crystallographic Society of America. Printed by the Book Concern, Hancock, Michigan. 1949. 113 pp. $3.40 (members), $3.90 (non-members).

JOHN W. COPENHAVER AND MAURICE H. BIGELOW. "Acetylene and Carbon Monoxide Chemistry." Reinhold Publishing Corporation, 330 West 42nd St., New York, N. Y. 1949. 357 pp. $10.00.

R. LEMBERG AND J. W. LEGGE. "Hematin Compounds and Bile Pigments." Interscience Publishers, Inc., 215 Fourth Ave., New York 3, N. Y. 1949. 749 pp. $15.00.

PETER PRINGSHEIM. "Fluorescence and Phosphorescence." Interscience Publishers, Inc., 215 Fourth Ave., New York 3, N. Y. 1949. 794 pp. $15.00.

WILLIAM E. SIRI. "Isotopic Tracers and Nuclear Radiations with Applications to Biology and Medicine." McGraw-Hill Book Co., Inc., 332 West 42nd St., New York, N. Y. 1949. 653 pp. $12.50.

A. E. VAN ARKEL. "Molecules and Crystals." Translated by J. C. Swallow. Interscience Publishers, Inc., 215 Fourth Ave., New York 3, N. Y. 1949. 234 pp. $3.85.

Additions and Corrections

NOTICE TO READERS.—For the convenience of those who wish to cut out the corrections and attach them to the margins of the articles corrected, they have been printed upon one side of the page only.

1941, VOL. 63

F. H. MacDougall. A Study of the Vapor of Propionic Acid at 45, 50, 55, 60 and 65°.

Page 3423. In column 1, the equation following line 5, the second line should read "$- (5K_2^3 - 5K_2K_3 + K_4)p^4$." Then four lines lower, Equation (7) should read "$K_2' = K_2 + 2K_3p + 3K_4p^2 + (2K_3^2 - 2K_2K_4 + 4K_5)p^3$."—F. H. MACDOUGALL.

1946, VOL. 68

Henry Gilman, C. G. Stuckwisch and J. F. Nobis. Pyrryl Derivatives of Pyridine, Quinoline and Acridine.

Page 326. In Table I, entry 6, the Calcd. and Found values for nitrogen should read "11.14" and "11.21," respectively, instead of "5.75" and "5.72."—HENRY GILMAN.

1947, VOL. 69

Alice T. Merrill, W. T. Haskins, Raymond M. Hann and C. S. Hudson. L-Gulo-D-*talo*-heptitol (β-Sedoheptitol) and its Enantiomorph.

Page 72. In col. 2, line 6 above the Summary, for "volemitol (*syn.*, D-manno-L-*talo*-heptitol)" read "volemitol (*syn.*, D-manno-D-*talo*-heptitol)."—C. S. HUDSON.

Webster B. Kay. Vapor Pressures and Saturated Liquid and Vapor Densities of Cyclopentane, Methylcyclopentane, Ethylcyclopentane and Methylcyclohexane.

Page 1276. In Table II, last line, last column, for "0.285" read "0.266" g./cc.—W. B. KAY.

Charles H. Tilford, M. G. Van Campen, Jr., and Robert S. Shelton. Aminoesters of Substituted Alicyclic Carboxylic Acids.

Page 2905. In Table II, the eleventh compound, for "3-methylcyclobutyl" read "3-methyl-1-phenylcyclobutyl."—CHARLES H. TILFORD.

1948, VOL. 70

R. G. Bates. Determination of the Product of the Constants for the Overlapping Dissociation of Weak Acids by Electromotive Force Methods.

Page 1580. The coefficient 2 has been omitted from the last term of equation (11). Consequently equation (20a) should also be amended by insertion of the coefficient 2 before m_A in the numerator and by adding $+m_A$ within the parentheses in the denominator. On page 1582, 2 should be inserted before m_A on the left side of equation (34) and, on the right side, 2 should be replaced by 4. The coefficient 2.5 should be dropped from (37d).—R. G. BATES.

Percy L. Julian, Arthur Magnani, Edwin W. Meyer and Wayne Cole. Sterols. V. The *i*-Cholesterylamines.

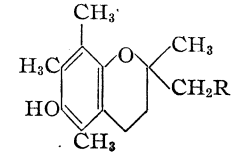
Page 1836. In column 1, following line 47, insert:

"*Anal.* Calcd. for $C_{34}H_{53}N\cdot HCl$: N, 2.73; Cl, 6.93. Found: N, 2.99; Cl, 6.81, 6.97.

"The pure hydrochloride was converted to the base, benzyl-*i*-cholesterylamine, by treatment with 5% sodium hydroxide solution in the presence of alcohol-free ether. Concentration of the washed and dried ether solution gave a colorless, viscous oil which could not be crystallized. For analysis this material was dried well *in vacuo:* $(\alpha)^{30}D$ +12° (138.8 mg. made up to 5 ml. with chloroform, α +0.34°, *l*, 1 dcm.)."—WAYNE COLE.

Lee Irvin Smith and Gerald A. Boyack. Vitamin E. XLVII. The Coumaran Isomer of α-Tocopherol.

Page 2690. In col. 1, formula II should be



.—GERALD BOYACK.

R. Christian Anderson and Everett S. Wallis. The Catalytic Hydrogenation of Polyhydric Phenols. I. The Synthesis of *meso*-Inositol, Scyllitol and a New Isomeric Cyclitol.

Page 2931 ff. The authors write: "In a recent publication, we refer to Burton, *et al.*, in their discussion of a previous observation that *meso*-inositol and "α"-hexachlorocyclohexane can be linked structurally on biological evidence. Reference to an article by Kirkwood and Phillips, *J. Biol. Chem.*, **163**, 251 (1946), was omitted."—R. C. ANDERSON AND E. S. WALLIS.

Herbert E. Ungnade and Edward C. Hendley. The Bitter Principle of *Helenium Tenuifolium.*

Page 3922. In the legend of Fig. 1 insert "this curve in plotting was displaced upward by one unit of log ε. Its ordinates, therefore, should be read as one unit less than is indicated by the scale." after tenulin, m. p. 194–196°.—HERBERT E. UNGNADE.

W. W. Binkley and M. L. Wolfrom. Acetylation of D-Psicose.

Page 3940. In Col. 1, line 5 of the article, for "D-erythrohexulose" read "D-ribohexulose."—M. L. WOLFROM.

Murray Halwer. Light Scattering by Sucrose Solution at High Concentrations.

Page 3985. In col. 2, the equation near the end of the column, the last term under the line should read "0.02831 c^2".—MURRAY HALWER.

Charles H. Tilford, Robert S. Shelton and M. G. Van Campen, Jr. Histamine Antagonists. Basically Substituted Pyridine Derivatives.

Page 4005. In col. 1, line 11, after the word procedure, insert "using acetophenone."

Page 4006. In Table II, compound 32, the halogen values should read: "calcd. 21.5. Found: 21.2."

Page 4007. In the continuation of Table II, compound 63, the free base melting point should be "59–61."—CHARLES H. TILFORD.

Roger Adams and J. J. Tjepkema. Restricted Rotation in Substituted Aromatic Amines. VI. Stereoisomers of N,N′-Dialkyl-N,N′-dibenzenesulfonyldiaminomesitylene.

Page 4204. Ref. 1, beginning of line 2, should read "THIS JOURNAL, **70**, 4202 (1948)."

Page 4205. Formula V should have a CH_3 group in place of C_2H_5 attached to right hand side of benzene ring: Formula IX should have a RO_2CH_2C- group attached to left hand nitrogen atom in place of RO_2CH_2O-: Formulas XI and XII should have CH_3 in place of CH_2 attached to benzene rings.—ROGER ADAMS.

1949, VOL. 71

W. B. Wheatley, L. C. Cheney and S. B. Binkley. β-Dimethylaminoethyl Ethers of Substituted 2-Benzylphenols.

Page 65. In col. 2, text line 9 should have at the end "^{9}" instead of "^{2}".—WILLIAM B. WHEATLEY.

M. L. Wolfrom, L. W. Georges and I. L. Miller. Crystalline Derivatives of Isomaltose.

Page 126. In line 3 of the experimental portion, reference 19 should read 19a which latter should be inserted as follows: (19a) G. L. Stahly, U. S. Patent 2,310,263 (1943).—M. L. WOLFROM.

Kenneth W. Doak and Alsoph H. Corwin. Kinetics of Pyrrole Substitutions. The Iodination Reaction.

Page 163. Regarding Fig. 3, the authors write: "The ordinate top left point is 0.021 and the asymptote of the lower curve is 0.000."—ALSOPH H. CORWIN.

H. R. Snyder and James H. Brewster. The Stereochemical Course of Amine Replacement Reactions.

Pages 292 and 293. The Authors write: "The rotations of the pure liquids are *observed* values, not specific rotations. In the preparation of the manuscript brackets were erroneously inserted and should be deleted from the letter α associated with each of the following figures: page 292, column 1; line 23, +36.24; line 24, +36.60; line 26, +37.70; line 28, +38.73; line 32, +61.76; page 292, column 2; line 33, +36.24 and +36.60; line 43, +61.76; page 293, column 1; line 39, −112; line 54, +59.04; column 2; line 49, +19.06.—H. R. SNYDER.

George H. Hitchings and Gertrude B. Elion. Isomeric Dihydroxanthopterins.

Pages 470–471–472. In the legends for Figs. 5–11, read "—, at *p*H 11.0; - - -, at *p*H 1.0."—G. H. HITCHINGS.

Gertrude B. Elion, Amos E. Light and George H. Hitchings. The Preparation of Xanthopterin.

Page 741. In col. 1, text line 4 from the end, for "0.01 *M*" read "0.1 *M*."—G. H. HITCHINGS.

Frederick C. Uhle. The Synthesis of 5-Keto-1,3,4,5-tetrahydrobenz(cd)indole. A Synthesis of 4-Substituted Indoles.

Page 763. In the graph of ultraviolet absorption spectra cruves, for XX read VIII, for XXI read IX, for XXII read XVI, for XXIII read XVII, for XXIV read XVIII.—FREDERICK C. UHLE.

W. D. Schaeffer, W. R. Smith and C. B. Wendell. The Adsorption of Helium on Carbon Black at Liquid Helium Temperatures.

Page 864. In Fig. 2, change places with the O and ●. In Table I, col. 5, each value should be multiplied by 2.3.

Page 865. In col. 1, line 42, for "interatomic" read "interplanar." In line 46, for "nearly identical to" read "somewhat less than."—W. D. SCHAEFFER.

Fred. K. Kirchner, John Hays Bailey and Chester J. Cavallito. Ring Substituted Benzoylacrylic Acids as Antibacterial Agents.

Page 1212. In Table I, in the major heading for the last columns, and in footnote *b*, for "moles" read "millimoles."—FRED. K. KIRCHNER.

Roger G. Bates and Gladys D. Pinching. Resolution of the Dissociation Constants of Citric Acid at 0 to 50°. and Determination of Certain Related Thermodynamic Functions.

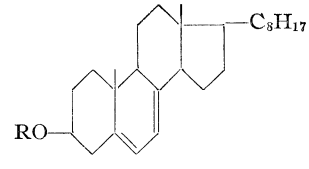
Page 1276. The coefficient 2 should be inserted before m_{Ci} in equation (9) and on the left side of equation (10). On the right side, 2 should be replaced by 4. The coefficient 2.5 should be dropped from equation (14). These corrections alter the limiting value of $^1/_2 \log (K_1K_2)$ computed by equation (9) by about 0.001.—R. G. BATES.

Thomas L. Jacobs and William Penn Tuttle, Jr. Acetylenic Ethers. V. The Polymerization of Phenoxyacetylene.

Page 1316. In Fig. 4 the ordinate legend should be "log ε" and the abscissa should have "2200 2400 2600 2800" on the central coördinate divisions, and the legend "Wave length, Å."—T. L. JACOBS.

Albert E. Sobel, Phyllis S. Owades and Joseph L. Owades. Sulfate Esters as Intermediates in the Formation of 7-Dehydrocholesterol and Dicholesteryl Ether.

Page 1488. Formula III should be



.—ALBERT E. SOBEL.

Charles E. Becker and Clarence E. May. Concerning the Structure of *d*-Glucosone.

Page 1492. In col. 1, line 9, for "positive" read "negative."—CLARENCE E. MAY.

Ellis K. Fields. Benzamidine Derivatives.

Page 1495. Col. 1, lines 18 and 19 from the end should read "2-Para-cyanostyrylpyridine, the corresponding imino-ethyl ester and amidine dihydrochloride have been made by Gregory, Holt and Slack (*J. Chem. Soc.*, 89 (1947)). Except for these, the compounds described in Table I have not previously appeared in the literature."—ELLIS K. FIELDS.

Alf W. Swenson and George Glockler. The Polarographic Reduction of Praseodymium.

Page 1641. The authors write: "Due to an oversight we failed to mention Dr. T. L. Moeller's work, "The Hydrolysis of Praseodymium Salts," *J. Phys. Chem.*, **50**, 242 (1946). It is gratifying to note that his earlier work is checked by our later results.—ALF W. SWENSEN AND GEO. GLOCKLER.

Charles H. Tilford, Lewis A. Doerle, M. G. Van Campen, Jr., and Robert S. Shelton. Aminoesters of 1-Substituted Alicyclic Carboxylic Acids.

Page 1706. In col. 1, 10th text line, and in col. 2, 10th text line from the end, for superscript [1] read [2].

Chas. T. Lester and John R. Proffitt, Jr. 3-Methyl-3-ethyl-2-hexanone.

Page 1878. In footnote (6) the authors should be Gilman and Nelson.—CHAS. T. LESTER.

F. T. Jones and K. J. Palmer. Optical, Crystallographic and X-Ray Diffraction Data for Limonin and Some of its Solvates.

Page 1937. In col. 2, lines 16 and 15 from the end should read "nin has one carbonyl group, two lactone groups and two (and probably." In line 3 from the end, for "carboxyl" read "carbonyl."—FRANCIS T. JONES.

Charles C. Templeton. The Distribution of Rare Earth Nitrates between Water and *n*-Hexyl Alcohol at 25°.

Page 2188. In Table I, the oxides referred to in the first two columns are, respectively, La_2O_3, CeO_2, Pr_6O_{11}, Nd_2O_3 and Sm_2O_3. Equations (1) and (2) are thus not applicable to the cases of cerous and praseodymium nitrates, and the mole-fractions given for these two salts are in error. The correct mole-fractions, as calculated from suitable modifications of equations (1) and (2), are:

Weight % oxide			
Aqueous phase	Alcohol phase	$X'_{R^{3+}}$	$X''_{[R(NO_3)_3]}$
	Cerous Nitrate, C. P.		
30.3[a]	2.87	0.0574	0.0176
29.57	2.34	.0548	.0143
28.5	1.70	.0515	.0103
27.57	1.28	.0485	.0077
26.2	0.85	.0446	.0051
24.47	.57	.0400	.0034
22.83	.34	.0361	.0020
21.5	.26	.0330	.0015
	Praseodymium Nitrate, C. P.		
28.75[a]	2.71	0.0533	0.0168
28.7[a]	2.68	.0533	.0166
28.4[a]	2.36	.0517	.0146
26.05	1.43	.0452	.0087
25.4	1.09	.0432	.0066
25.35[a]	0.99	.0431	.0060
23.9	.74	.0393	.0044
22.6	.51	.0361	.0031
21.3	.35	.0329	.0021
20.25	.25	.0308	.0015

Page 2189. In Fig. 1, the corrected data raise the cerium line slightly above the lanthanum line, and the praseodymium line up nearer to the neodymium line. This makes the order of increasing extractability into the alcohol the same as that of the atomic numbers, and *invalidates the contention that cerium is in an anomalous position*. The only part of the Discussion affected is the material in the first two paragraphs, ending with line 16, first column, page 2189.

Page 2190. Summary, paragraph 2, should read: For all the rare earth nitrates investigated there is an increased extractability into *n*-hexyl alcohol from aqueous solution with increasing atomic number.—CHARLES C. TEMPLETON.

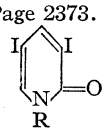
Ralph G. Pearson. The Alkylation of Malonic Ester.

Page 2212. In col. 1, line 4 of Experimental, for "0.9982" read "1.0012."

Page 2214. In col. 2, line 9, after "ethyl" insert "> benzyl."—RALPH G. PEARSON.

Erwin Klingsberg and Domenick Papa. An Unusual Formation of a Disulfide from a Sulfide.

Page 2373. In col. 1, the formula for IV-V-VI should be



.—D. PAPA.

George Richard Hill. The Kinetics of the Oxidation of Cobaltous Ion by Ozone.

Page 2434. In Fig. 1, the abscissa units are (HAc) × 10^4.—GEORGE RICHARD HILL.

James S. Fritz, F. Wm. Cagle, Jr., and G. Frederick Smith. The Determination of the Decomposition Pressures of Certain 1,10-Phenanthroline Hydrates.

Page 2480. Values of bond strengths given in the introduction, discussion, and summary are in kcal.

Page 2481. In the section on results, under the reaction $C_{12}H_8N_2{\cdot}H_2O(s) = C_{12}H_8N_2(s) + H_2O(g)$ read $\Delta S = 37.1$ cal./mole-deg. for $\Delta S - 37.1$ cal./mole/deg.

Page 2481. In the equation three lines below Fig. 2 read $\log_D P$ for $\log_{10} P$.

Page 2483. In footnote (10), third line from the end, read "The value of $\delta\Delta H_f$ is 200 cal./g. mole . . . . ."—G. FREDERICK SMITH.

Q. Van Winkle, R. G. Larson and Leonard I. Katzin. The Half-Life of Protactinium (Pa^{231}).

Page 2586. In col. 1, the very last line should be transposed to the top of the column.

Shigeto Yamaguchi and Tominosuke Katsurai. A New Method of Synthesis of Hydrogen Cyanide by the Reaction between Coal and Ammonium Alum.

Page 2591. The received date of this Communication was May 9, 1949.

Edward W. Hughes and Walter J. Moore. The Crystal Structure of β-Glycylglycine.

Page 2619. In col. 1, line 9 from the end, for "thirty-six" read "twenty-seven."

Pages 2622 and 2623. In all occurrence throughout, read "08" for "02."—E. W. HUGHES.

Stanley J. Cristol and Donald L. Harms. Some Positional Isomers of DDT Analogs.

Page 2875. In col. 2, 6th line from the end, for "Chlorophenylcarbinol" read "bromophenylcarbinol."

Page 2876. In col. 1, first line, for "(0.25 mole)" read "(0.025 mole)."—STANLEY J. CRISTOL.

William S. Johnson and Walter E. Heinz. The Acid-Catalyzed Decarboxylation of Cinnamic Acids.

Page 2915. In line 3 of footnote (11) insert superscript 12 at the end, since footnote (12) is the source of the statement in footnote (11).

Page 2916. In col. 1, line 8, change [12] to [13] and in line 10 change [13] to [14].—WILLIAM S. JOHNSON.

D. I. Weisblat and D. A. Lyttle. The Chemistry of Nitroacetic Acid and its Esters. II. The Synthesis of Ethyl α-Nitro-β-(3-indole)-propionate from Gramine and Ethyl Nitromalonate.

Page 3080. In col. 2, lines 25 and 23 from the end, exchange places with "43.3" and "51.3."—DAVID I. WEISBLAT AND DOUGLAS A. LYTTLE.

Carl B. Kretschmer and Richard Wiebe. Liquid–Vapor Equilibrium of Ethanol–Methylcyclohexane Solutions.

Pages 3177 and 3178. The authors write: "The designations of the vertical axes of Figs. 1 and 3 are interchanged. In Fig. 1 the ordinate should be marked $\alpha(x + C)(1 - 2C + Cx)$, and the numbers reading up should be 0, 0.5, 1.0 and 1.5. In Fig. 3, the ordinate should be labelled Calories/mole, and the numbers reading up should be -200, -100, 0, 100, 200, 300 and 400."—CARL B. KRETSCHMER.

Yoshiro Ogata and Masaya Okano. Nucleophilic Substitution in Aromatic Ethers. I. Kinetics of the Methanolysis of 2,4-Dinitrodiphenyl Ethers.

Page 3213. In the last line of the Summary, for "σ" read "ρ."—YOSHIRO OGATA.

Louis Meites. Polarographic Studies of Metal Complexes. I. The Copper(II) Tartrates.

Page 3271. The abscissa legend of Fig. 7 should read "Moles KHTart/mole Cu."—LOUIS MEITES.

Marvin D. Armstrong. The Relationship between Homoserine and its Lactone.

Page 3400. In the equations the vertical arrow reading $\uparrow OH^-$ should read $\uparrow H_2O$ and the arrow reading $\swarrow H_2O$ should read $\nwarrow OH^-$.—M. D. ARMSTRONG.

J. R. Dice, L. E. Loveless, Jr., and H. L. Cates, Jr. Some 1,2-Dialkylcyclohexanes.

Page 3547. In col. 2, line 7 from the end, for "1,2-dialkylcyclohexanones" read "1,2-dialkylcyclohexanols."

Page 3548. In col. 1, line 18, for "cyclohexenes" read "cyclohexanes."—JOHN R. DICE.

W. A. Mosher (reviewer). Elsevier's Encyclopedia of Organic Chemistry.

Page 3579. In line 2 of the heading, for "13A" read "12A."

David Fielding Marsh and Robert A. Woodbury. Chemotherapeutic Agents from Heterocyclic Amines. I. Amide Arsenicals.

Page 3748. In the main title after I., the word "Amine" should be "Amide."

Author Index to Volume LXXI, 1949

ABBOTT, R. K., JR. See Gilman, H.
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ACKERMAN, J. F. See Campbell, K. N.
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ADAMS, R., AND CAMPBELL, J. B. 2-Triphenylmethylaminopyridine 3539
ADAMS, R., AND GARBER, J. D. Amine bisulfites (II) use as resolving agents for aldehydes and ketones 522
ADAMS, R., AND GOVINDACHARI, T. R. Senecio alkaloids: alkaloids of *Senecio douglasii, carthamoides, eremophilus, ampullaceus* and *parksii*, 1956; α- and β-longilobine from *Senecio longilobus*, 1180; isolation of senecionine from *Senecio cineraria* and some observations on structure of senecionine 1953
ADAMS, R., HARFENIST, M., AND LOEWE, S. New analogs of tetrahydrocannabinol (XIX) 1624
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ADAMS, R., AND JONES, V. V. Addn. and condensation reacns. of 2-pyridone 3826
ADAMS, R., AND LIPSCOMB, R. D. Amine bisulfite addn. products of aldehydes and ketones (I) 519
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